Neudorff North America · 10555 West Saanich Road · V8L 5L6 Sidney B.C.

Robert Pooler
USDA/AMS/TM/NOP
1400 Independence Avenue SW
Room 4008-S Ag Stop 0268
Washington, DC 20250

May 1, 2003

Re: Submission of Petition for Inclusion of Ferric Phosphate on the NOSB List Under the Category: Synthetic substance allowed for use in organic crop production.

Dear Mr. Pooler;

Please accept this as a cover letter to W. Neudorff GmbH KG's submission of our organic petition for the technical active ingredient, ferric phosphate. We are petitioning for the inclusion of ferric phosphate on the NOSB list under the category: "Synthetic substance allowed for use in organic crop production", subsection (h) of 7 CFR §205.601, as an acceptable synthetic substance for use as a slug and snail bait in organic crop production.

Enclosed are 2 copies of our petition. One copy is a CBI Copy, which reveals confidential business information (CBI) in Section 5, as well as in Appendix A of the petition. Each page containing confidential information has been labeled "CBI Copy" in the upper right hand corner, with this phrase also highlighted in green. All CBI within the text is outlined in the right margin with a bracket, followed by "CBI". This CBI Copy is not suitable for inspection by members of the public, or anyone else who does not require access to it. The information in the CBI sections is highly confidential, containing production processes and trade secrets. This information was released by W. Neudorff GmbH KG under the condition that all who view it hold it under strict confidence.

The second copy is a "CBI-deleted" copy. In this copy, the upper right-hand corners on each page in the CBI sections have been labeled "CBI-deleted", with this phrase highlighted in green. All CBI within the text is deleted. In the right hand margin, where the CBI text would have appeared, is a bracket, followed by

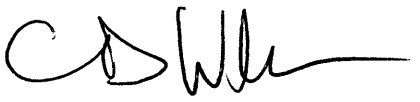
"CBI-deleted". In some cases, entire pages of text contained CBI. In these cases, we chose to simply state one phrase on the page, such as "the contents of page X have been CBI-deleted", instead of using the bracket and "CBI-deleted" method. This copy of the petition is suitable for inspection by members of the public.

We hope we have clearly conveyed to you the difference between the two copies (which are also clearly labeled) and the importance of maintaining confidentiality. We strictly followed the Commercial Confidential Information Section (13) in the Proposed Rule for the Department of Agriculture, 7 CFR Part 205 in the Federal Register, Vol. 65, No. 135, Thursday, July 13, 2000.

If you have any questions, problems, or require more information at any time throughout the review process, please do not hesitate to get in touch with the petition contact, Ms. Laura Kline, via one of the means outlined on page 1 of the petition.

I thank you for your time and look forward to future communication with you.

Sincerely,



Cameron D. Wilson
Operations Manager
Neudorff North America

Ferric Phosphate Organic Petition

Petitioner: W. Neudorff GmbH KG

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SUITABLE FOR PUBLIC INSPECTION

ORGANIC PETITION

FERRIC PHOSPHATE
TECHNICAL ACTIVE INGREDIENT

Petitioner: W. Neudorff GmbH KG
Postfach 1209
An der Mühle 3
D-31860 Emmerthal
Germany

Contact: Laura Kline
Neudorff North America
10555 West Saanich Rd.
Sidney, BC, V8L 5L6
Canada
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Petition for inclusion of ferric phosphate on the NOSB list under the category:

(1) Synthetic substance allowed for use in organic crop production
Subsection (h) of 7 CFR §205.601, as an acceptable synthetic substance for use as a slug and snail bait in organic crop production.

ORGANIC PETITION
FERRIC PHOSPHATE
TECHNICAL ACTIVE INGREDIENT

PART I - DETAILED INFORMATION

1. SUBSTANCE NAME

Ferric Phosphate (Ferric Orthophosphate, Iron Phosphate, Iron Orthophosphate) - CAS # 10045-86-0; EINECS # 233-149-7

2. MANUFACTURER'S NAME, ADDRESS AND TELEPHONE NUMBER

Dr. Paul Lohmann GmbH KG
Hauptstraße 2
D-31857 Emmerthal / Germany
Telephone: 5155 63 0

3. AREA OF CURRENT AND INTENDED USE

Pesticide (Molluscicide, as a slug and snail bait specifically)

4. LIST OF THE CROPS FOR WHICH THE SUBSTANCE WILL BE USED, APPLICATION METHOD AND APPLICATION RATE

Vegetables including (but not limited to): artichokes, asparagus, beans, beets, blackeyed peas, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, corn, cucumbers, eggplants, garlic, lettuce, onions, peas, peppers, potatoes, radishes, rutabagas, spinach, squash, Swiss chard, tomatoes and turnips.

Fruits Including Citrus, including (but not limited to): apples, avocados, apricots, cherries, grapes, melons, peaches, plums, nectarines, citrus, and pears.

Berries, including (but not limited to): strawberries, blackberries, blueberries, boysenberries, loganberries, raspberries.

Field Crops, including (but not limited to): artichokes, beans, field corn, sweet corn, soybeans, sugar beets, sugar cane, asparagus, beets, broccoli, Brussels sprouts, cabbage, carrots, cauliflower, cucumbers lettuce, onions, peas, peppers, potatoes, radishes, strawberries, tomatoes, turnips and wheat.

Outdoor Ornamentals

Greenhouses

Outdoor Container-Grown Nursery Plants

Lawns and Grass Grown for Seed Production

The end-use product, NEU1165M Slug and Snail bait can be applied by hand or by using standard broadcast or granular spreaders.

The rate of application for commercial agriculture uses in vegetables, fruits including citrus, berries, field crops, outdoor container-grown nursery plants, lawns and grass grown for seed production is 24-44 lbs/acre. Lower rates are used for less severe slug and snail problems. For greenhouses, or container-grown plants, ½ teaspoon of bait can be applied in or around each 9-inch pot.

On March 7, 2003, an amendment to the master label of NEU1165M Slug and Snail Bait was submitted to the US Environmental Protection Agency, where the rates for commercial application of the end-use product were revised to reflect recent efficacy tests on certain use sites. The new rates will not appear on the label until approval is received from the US EPA. Once approved, the new rates will be: 20-44 lbs/acre in vegetables (except artichokes), fruits including citrus, berries, and field crops (except artichokes and wheat), and 10-44 lbs/acre in artichokes, grass grown for seed production, and wheat.

In the home and garden market, the end-use product, NEU1165M Slug and Snail Bait is applied at a rate of 1 lb per 1000 square feet, or 1 level teaspoon per square yard. The bait can be used on vegetables, fruits including citrus, berries, outdoor ornamentals, and lawns. In greenhouses, ½ teaspoon of bait is applied in or around each 9-inch pot.

5. SOURCES

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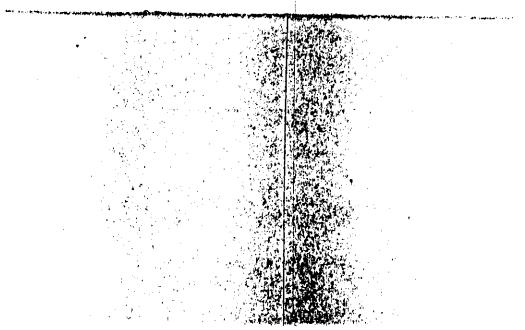

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Availability of a Mined Ferric Phosphate Source

The reason for utilizing ferric phosphate obtained from a synthetic manufacturing process is due to the fact that there are no sources of ferric phosphate that could be economically mined for industrial uses.

W. Neudorff GmbH KG employed a consultant, Mr. John Wohler of Root and Leaf Co., who did an extensive search into finding a viable source of a natural, mined ferric phosphate. The following are his findings on this extensive search, in his report dated March 22, 2001 (also see Appendix B for copies of the report and correspondence he had in regards to this issue):

"I used a three-pronged approach to research and prepare this report. I searched the World Wide Web, contacted commodity companies trading in

agricultural minerals and phosphates and talked with the United States Geological Survey (USGS) offices. This gave me the greatest chance to find an industrial source of ferric phosphate.

All three of these avenues gave the same result. Either they could not find or did not know of any large-scale sources or indicated by their knowledge of phosphate chemistry and geology that deposits large enough to economically develop were not possible.

The Web

A search of the World Wide Web gives information on many minerals that contain iron and phosphate most of these listings are for collectors and dealers of minerals and crystals. I spoke with Tony Nikischer[1] of Excalibur Mineral Company. He indicates that ferric phosphate does not occur in large quantities. It accumulates in small voids where the crystals of the ferric phosphate develop. Strengite is the crystal of ferric phosphate. It is listed on the Web and as a rare mineral. Tony Nikischer said that even Beraunite, which is a combination of ferric and ferrous phosphate, which is more common than Strengite, would not be found in quantities large enough to mine on an industrial scale.

The USGS

I contacted the USGS through a number of different avenues. I sent emails to the general information line as well as directly contacting Steve Jasinski[2] the phosphate rock & peat commodity specialist. All attempts to contact the USGS directed me back to Mr. Jasinski. He stated, "Iron phosphate is not mined because there are no deposits that would be economically feasible to develop." He also suggested that I contact the Florida Institute of Phosphate Research[3]. I contacted Karen Stuart at the FIPS. She gave me several contacts to follow up with. The ones that I was able to contact had no knowledge of any mines for ferric phosphate.

Phosphate & Agricultural Mineral Trading Companies

I contacted IMC Global the largest phosphate supplier in North America. Dennis Michalski[4] returned my faxed request for information. He indicated, "To the best of my knowledge, there are no large scale deposits of ferric phosphate." He also directed me back to the Florida Institute of Phosphate Research.

I spoke to three different mineral trading companies Frit Industries[5], Universal Minerals[6] and North Pacific Trading[7]. None of these companies could locate a mined source of ferric phosphate.

South America

A person at OMRI had indicated that they believed there was a ferric phosphate source in Brazil. I contacted the Institute for Technological Research in Brazil. They are the foremost technical research institutes in Latin America. I was put in contact with Mr. Edson Monte of their geology department. He did not know of

any sources of ferric phosphate nor did any of the other specialists at IPT. He checked with his contacts at other companies in Latin America, none of them knew of a source.

Conclusion

There is no sources ferric phosphate that could be economically mined for industrial uses.

References to John Wohler's Report

1. Mr. Tony Nikischer Owner
Excalibur Mineral Company
1000 N. Division St
Peekskill, NY 10655 USA
www.excaliburmineral.com

2. Stephen M. Jasinski
Commodity Specialist-Phosphate Rock & Peat
USGS
983 National Center
Reston, VA 20192
Phone: 703-648-7711
FAX: 703-648-7722
email: sjasinsk@usgs.gov
Web: minerals.usgs.gov/minerals

3. Florida Institute of Phosphate Research
1855 West Main Street
Bartow, FL 33830
Telephone: (863) 534-7160
FAX: (863) 534-7165
Karen Stewart – Librarian

4. Dennis Michalski
DHMichalski@imcglobal.com

5. Universal Mineral
dans@universalmineral.com

6. North Pacific Trading Co
Darren MacFarlane
dmcfarl@north-pacific.com

7. Frit Industries, Inc
P.O. Box 1589
Ozark, Alabama 36361-1589
Jimmy Wyatt
jwyatt@fritinc.com

8. Institutes for Technological Research
São Paulo, Brazil
sac@ipt.br
www.ipt.br"

6. SUMMARY OF PREVIOUS REVIEWS

No submission has been presented to any organic certification programs. In telephone discussions with Brian Baker of the Organic Materials Review Institute (OMRI), we were advised to first obtain approval for inclusion of ferric phosphate on the NOSB list of synthetic substances allowed for use in organic crop production.

PART II - REGULATORY INFORMATION

7. REGISTRATION INFORMATION

EPA Registration
The registration was received on the end-use product, NEU1165M, on August 14, 1997.
US EPA Registration #67702-3

Food and Drug Administration Registration

Ferric phosphate is a GRAS substance listed in 21 CFR §184.1301.

State Regulatory Authority Registration

The end-use product, NEU1165M, is registered in the state of California.
Registration #67702-3-AA

8. CHEMICAL ABSTRACT SERVICE (CAS) NUMBER AND LABELS

CAS# 10045-86-0

Labels

Both the master label and a sample of distributor labels for the master product, NEU1165M Slug and Snail Bait (all of which contain ferric phosphate), can be found in Appendix C.

PART III-SUPPLEMENTARY INFORMATION

9.1 DETAILED FINDINGS

a) Detrimental Chemical Interactions with Other Materials

Ferric phosphate is a stable substance that is virtually insoluble in water. It is very unlikely that it would react with any other products used in organic farming. It may break down to iron and phosphate ions at an acidic pH. Both of these ions will react with substances in the soil to form compounds that commonly occur in the soil, e.g. iron oxides, various mineral phosphates. These compounds are not detrimental to the environment. Therefore no detrimental chemical interactions would occur with other materials used in organic farming.

b) Toxicity and Persistence in the Environment

Ferric phosphate does not pose a hazard to the environment. This conclusion is based on: a) the natural occurrence of ferric phosphate in the soil, b) the insolubility and stability of ferric phosphate, c) the low rate of application, d) the use pattern of the end-use product, NEU1165M, that does not include marine or any other aquatic uses, e) the lack of toxicity to animals, of NEU1165M, f) the use of ferric phosphate as a nutrient and dietary supplement in foods, g) ferric phosphate (or degradates) may already be present in the food/nutrient sources of plants, wild birds and other animals, and h) the inherent function (as essential nutrients) of the components of ferric phosphate in the metabolic pathways of animals and plants.

Ferric phosphate occurs naturally in the soil and as a consequence its activity in the soil is known. Because of the different mineral constituents of different soils no standard values of the content of iron and phosphate in the soil can be stated. Ferric phosphate occurs as the minerals Strengite, Metastrengite, Vivianite, and Dufrenite. "Iron salts are normally present in the environment. Iron is the fourth most abundant element and the second most abundant metal in the earth's crystal rocks. Iron occurs in a wide variety of minerals, and is present in foods naturally and through added ingredients."[a] "In summary, the fate and transport of Fe(II) and Fe(III) salts in the environment is dominated by three major processes: (1) the pH-redox potential dependent oxidation of Fe(II) to Fe(III); (2) the formation of insoluble oxides and hydroxides that are also well known components of soils; and (3) the distinct surface chemistry of the oxides and hydroxides of iron that control the adsorption of anions, cations and organic material or the adsorption of iron species onto the surfaces of mineral and organic components of soils, contributing to the aggregation of soil particles into larger units."[a]

The insolubility of ferric phosphate ensures that breakdown is a slow process. Although the solubility of ferric phosphate increases with water temperature, 0.67 g/100 cc of 100°C water, at normal soil temperatures it is practically insoluble. The product is not intended for use in an aquatic environment but it should be noted that ferric phosphate's insolubility in water combined with its ready adsorption to the soil render it immobile. As a consequence it is unlikely that the ferric phosphate would migrate from the area of application into aquatic systems. In addition, ferric phosphate is a highly stable compound that does not break down in sunlight, and is a non-volatile solid that would not be mobile in the air.

There are natural mechanisms whereby soil microorganisms and plant rootlets, aided by carbon dioxide and other root exudates, will transform the insoluble ferric phosphate into forms that are usable by plants. Both the iron and the phosphate components are then used to meet the nutritional requirements of the plant. Iron is a plant micronutrient and phosphorus is a macronutrient, both of which are essential to plant growth and development. Iron is required for chloroplast development and is a component of cytochromes. Phosphorous is required for formation of "high-energy" phosphate compounds (ATP and ADP) and is a component of nucleic acids and of several essential coenzymes (Curtis, 1979). The transformation of ferric phosphate is a very slow process which becomes slower with time because by "processes of aging, phosphate availability is reduced."[b] Soils high in organic matter are more effective in releasing the iron and phosphorous so that plants can utilize them. (Brady, 1974.) As a matter of fact, due to the lack of availability of iron and phosphorous in soils, both often need to be added to soils as fertilizers.

The amount of iron and phosphorus added to the soil through the use of the end use product, NEU1165M, is negligible compared to the amounts the soil already contains. Soils contain a range of iron from 5,000 to 50,000 ppm (0.5 to 5%) and a range of phosphorus from 0.01 to 0.20%. (Brady, 1974) The content of these nutrients in soils is not solely dependent on soil type. Tested soil values of P average 83.7 mg/l and of Fe average 262 mg/l, on soils in Belgium that are predominantly silty loams. For this same soil type in Argentina the average P value is 24 mg/l and the average Fe value is 207 mg/l. For tested, predominantly clay, soils of Lebanon the average value for P is 42.5 mg/l and for Fe is 140 mg/l. For this same soil type in Egypt the average value for P is 18.7 mg/l and for Fe is 195 mg/l. (Sillanpää, 1982) The application of NEU1165M to the soil as a slug bait would add 0.014 g iron and 0.036 g phosphate or 0.008 g phosphorus per square meter. Using weight values of an 18 cm depth of different soils from Klingman, 1975, this equates to approximately:

Soil Type	Wt. Soil (g)		Wt.	% Iron		ppb	
	to 18cm		Iron (g)				
Sand	291600		0,014	0,0000048011		4,801	
Loam	233280	277020	0,014	0,0000060014	0,0000050538	6,001	5,054
Clay or Silt	189540	233280	0,014	0,0000073863	0,0000060014	7,386	6,001
Muck	116640		0,014	0,0000120027		12,003	
Peat	58320		0,014	0,0000240055		24,005	
Soil Type	**Wt. Soil (g)**		**Wt.**	**% Phosphor.**		**ppb**	
	to 18cm		**Phos. (g)**				
Sand	291600		0,012	0,0000040286		4,029	
Loam	233280	277020	0,012	0,0000050357	0,0000042406	5,036	4,241
Clay or Silt	189540	233280	0,012	0,0000061978	0,0000050357	6,198	5,036
Muck	116640		0,012	0,0000100715		10,071	
Peat	58320		0,012	0,0000201429		20,143	

NEU1165M adds between 6,000 and 300,000 times less iron and between 800 and 80,000 times less phosphorus to the soil than already exists in it.

The amounts of iron and phosphate that are applied to the soil in fertilizers are also far greater than the amounts added with the use of NEU1165M. To see the effects of fertilizer application approximately 0.65 g iron/m^2 and 2.0 g phosphate/m^2 are required. These amounts are 13 times greater for the iron and 100 times greater for the phosphate when compared to the amounts added with the slug bait.

It should also be noted that ferric phosphate is an iron salt. In their Reregistration Eligibility Document (RED) on Iron Salts, page 12, the US EPA exempts iron salts from environmental chemistry and fate requirements. Their conclusion is based on the use of iron salts as herbicides or fertilizers. The use of iron salts as herbicides or fertilizers "is not expected to contribute significantly to the chemistry and fate of the compounds existing naturally in the environment."[a] It should be noted that iron from iron sulfate fertilizers (which are used in agriculture) is applied at the rate of 0.67 g/m^2 whereas the iron from the end-use product, NEU1165M, is applied at the rate of 0.014 g/m^2. In addition iron sulfate is more soluble than ferric phosphate.

The end-use product, NEU1165M, is registered as a domestic molluscicide in the United States. The conclusion drawn in the US EPA's decision memorandum was that "no unreasonable adverse ecological or environmental fate effects were identified."[c]

Ferric phosphate is included in the Food Chem Codex where it is recognized as a food additive: nutrient and dietary supplement. "Further,

the iron salts are generally recognized as safe (GRAS) by the [US] Food and Drug Administration for use as flavoring agent and nutrient supplement in foods (please see 40 CFR 180.2(a))."[a] Iron phosphate is listed specifically at 21 CFR §182.5301 and §184.1301. As a matter of fact both the iron and the phosphate ions occur in foods naturally because they are an inherent part of plant and animal metabolism, as discussed below. The flour and sugar inert ingredients in NEU1165M together comprise 97.95% of the product and both are common foods.

In plants and animals iron is important for a) oxygen transport, b) electron transfer, c) DNA synthesis and d) many other cellular functions. Phosphorous is a component of ATP and ADP, which are the cell's primary energy sources, nucleic acids and several essential coenzymes. Both the ferric and phosphate ions of ferric phosphate are, therefore, essential in plant and animal metabolism.

c) Environmental Contamination Resulting From Use and Manufacture

The environment would not be contaminated as a result of the use of ferric phosphate in the slug bait end-use product (See Section 9.1.b).

Care is taken in the manufacture of ferric phosphate and the only by-products of the manufacturing process are Na_2SO_4 (sodium sulfate), and H_2O. The Na_2SO_4 is precipitated with lime and is used as a secondary raw material. The wastewater, which in this case contains only water, is purified and prepared in a separate process so that it can be released into a wastewater clarification plant.

Sodium sulfate "occurs in nature as the minerals *mirabilite, thenardite.*" (Merck Index, 1996) Sulfur is essential to the growth of plants. In fact it is a macronutrient required in large quantities by plants. However excesses of sodium salts in the soil are detrimental to plant growth. (Brady, 1974)

d) Effects on Human Health

Ferric phosphate is of low risk to human health. It is found naturally in the environment and is used as an additive in foods.

Both iron and phosphorous are minerals that are essential to the metabolism of plants and animals. Iron is involved in oxygen transport, electron transfer, DNA synthesis and many other cellular functions. Phosphorous is a component of ATP and ADP (which are the cell's primary energy sources), nucleic acids and several essential coenzymes. As

humans cannot easily metabolize iron from food sources, and iron deficiency is a common disease, iron supplementation of food often occurs.

Ferric phosphate is widely accepted for use as a nutrient/dietary supplement in food. The United States Food and Drug Agency accepts ferric phosphate as a GRAS (Generally Recognized As Safe) direct food substance (21 CFR §184.1301). The Food and Agriculture Organization of the United Nations has evaluated ferric phosphate and set an Acceptable Daily Intake for it of 70 mg/kg body weight (FAO, 1994). On the average, humans consume 10-15 mg of iron a day (US EPA, 1997). However, ferric phosphate is not widely used as a source of iron in foods because it has a poor bioavailability compared to other iron sources. On a comparative scale of bioavailability of 0 - 100 (where ferrous sulfate is 100), ferric phosphate was found to have an average relative bioavailability, to man, of 25-32 (Hurrell, 1997).

Many toxicity summaries of iron compounds indicate that inorganic compounds of iron have low acute toxicity by oral exposure, whether from single, acute exposure or from repeated, chronic exposure (Stokinger, 1981). Moreover, the water insoluble forms that have been tested have even lower toxicity because they are less likely to be absorbed from the gastrointestinal tract. Because of its very low solubility, iron phosphate is expected to be poorly absorbed from the gastrointestinal tract into the systemic circulation. However, in the acidic regions of the stomach slight solubility of ferric phosphate will occur resulting in a low bioavailability. This is verified by the calculations of the relative bioavailability of ferric phosphate (Hurrell, 1997). Ferric phosphate has one quarter to one third the bioavailability of ferrous sulfate. In the case of massive acute overexposure (by the oral route) all iron salts, perhaps even ferric phosphate, may be lethally toxic because they can corrode the mucosal lining of the stomach and intestinal tract. This facilitates absorption of massive amounts of solubilized iron salts directly into the circulation. However, for a massive acute overdose of ferric phosphate to occur a very large quantity of ferric phosphate would have to be consumed. Based on the assumption that "severe iron toxicity and death are associated with doses of 200 - 300 mg/kg of iron" (US EPA, 1997), a minimum of 714 - 1071 mg $FePO_4$/kg body weight ($FePO_4$ contains ~28% iron) would need to be ingested for a severe toxic reaction. However, in an acute oral toxicological test on rats with ferric phosphate, the LD50 was determined to be greater than 5000-mg/kg-body weight. In fact no mortality occurred at the dose of 5000 mg/kg. Accidental poisoning is unlikely. Consequently, it may be concluded that iron phosphate will have low single, second single and repeated dose toxicity (oral route).

As iron salts, including ferric phosphate, have been used as food additives over many generations without exhibiting adverse effects, it can also be concluded that chronic toxicity via ingestion, would not occur.

The soluble iron salts $FeCl_3$ and $Fe_2(SO_4)_3$, are highly toxic after parenteral injection in animals. For example, the intraperitoneal LD50 of anhydrous $FeCl_3$ for the mouse is 68 mg/kg. In mice the intraperitoneal LD50 of the hexahydrate $FeCl_3$-$6H_2O$, was reported as 260 mg/kg. For this reason it may be concluded that iron phosphate also has an acute percutaneous toxicity but it is expected that ferric phosphate would have less toxicity than the other compounds because of its very low solubility.

The acute dermal toxicity and dermal irritation of ferric phosphate should be low. It is unlikely that it would be absorbed through the skin because of its particularly low water and lipid solubility.

From eye irritation studies with soluble iron compounds like iron sulfate, it is known that iron compounds may be corrosive. The corrosive effects are due to the formation of an acidic pH if the compounds are dissolved in a liquid. For this reason it may be concluded that ferric phosphate would have a moderate eye irritation. Because of its very low solubility ferric phosphate would be less corrosive than the other iron compounds.

For inhalation exposure, no chronic data was found relating to iron phosphate specifically. Predicting the chronic inhalation toxicity of this compound from that observed for the other forms of iron is problematic. However, prudence would require the inference that this insoluble form of iron also may cause siderosis if high levels are inhaled over prolonged periods. This syndrome is considered benign since, in the lungs, no progressive fibrosis occurs and, as a rule, pulmonary function is not significantly impaired. A single study was located that assessed ferric phosphate's ability to cause fibrosis of the lung after intratracheal instillation in rats up to one year after injection (Stacy, 1959). While materials such as alumina and various forms of silica caused fibrosis, ferric phosphate did not. The more severe lung diseases might also occur with heavy exposure but only if iron phosphate were contaminated with silicates or radon similar to mining/refining exposures. Excess cancers connected with iron exposure, have been attributed mostly to co-exposure to contaminants such as crystalline silica and radon (Beliles, 1992). Otherwise, only siderosis might reasonably be predicted.

Chronic iron overload is usually predisposed by pathological conditions. "In certain pathological conditions iron overload may result from an increased absorption of dietary iron, by parenteral administration of iron or both. The magnitude, rate and distribution of iron accumulation will influence the onset and severity of complications and differ for the various pathological

conditions, a number of which have an inherited genetic basis. .... Extensive tissue damage often occurs in iron loaded tissues." (British Nutrition Foundation, 1995) Some of the pathological conditions leading to chronic iron overload are: genetic haemochromatosis, neonatal haemochromatosis, secondary haemochromatosis, thalassaemia, excess absorption of orally ingested iron (rare), alcohol misuse. Chronic iron overload does not involve the ingestion of massive doses of iron but rather moderate overdoses over a prolonged period of time. At low to moderate oral doses, the water solubility of the various iron salts determines their bioavailability (i.e., propensity to be absorbed from the gastrointestinal tract into the body) this, in turn, governs toxicity. Ferric phosphate has a low bioavailability. Also this type of iron overload is usually predisposed by pathological conditions and normal, healthy people would not be at risk. Consequently, it is unlikely that ferric phosphate would be a causal factor in chronic iron overload.

The United States Environmental Protection Agency has issued a re-registration eligibility document in which they evaluated the health risk of ferric phosphate. The US EPA concluded that ferric phosphate could be approved with a "reasonable certainty of no harm". In short BPPD has not identified any subchronic, chronic, immune, endocrine, or nondietary cumulative exposure issues as they may affect infants and children and the general population." (US EPA, 1997)

In conclusion, ferric phosphate is a tightly bound mineral that is practically insoluble, highly stable and not readily available to be metabolized by animals. It is poorly bioavailable upon ingestion, and, thus, is of low toxicological risk by this route of exposure for single, second dose or repeated dose exposure. Its insolubility prevents it from exhibiting toxic effects via dermal exposure. Ferric phosphate is also of low risk from the inhalation route of exposure. In particular, as the end-use product will be a non-volatile, solid granule, inhalation exposure will most likely not occur. It can be concluded that ferric phosphate does not represent a toxicological risk. Adverse health effects would be unlikely to occur from exposure to ferric phosphate.

e) Effects on Soil Organisms, Crops and Livestock

Ferric phosphate is not expected to cause adverse effects on soil organisms, crops and livestock. This conclusion is based on: a) the natural occurrence of ferric phosphate in the soil, b) the known effect of ferric phosphate on living organisms, c) the lack of toxicity of the end-use product NEU 1165 M, d) the use of ferric phosphate as a nutrient and dietary supplement in foods, e) ferric phosphate may already be present in the food sources of the living organisms in the environment, f) the inherent function of ferric phosphate in the

metabolic pathways of living organisms, both iron and phosphorous are essential nutrients for plants and animals, g) the practical insolubility of ferric phosphate and fact that it adsorbs to the soil, and is thus rendered immobile and h) the use pattern of the product does not include aquatic uses.

"Iron is one of the earth's most abundant elements, and it is immobilized at the pH range of 5-9." (US EPA, 1993) Because ferric phosphate occurs naturally much is known about its effect on living organisms. Ferric phosphate is an iron salt. "No adverse effects to avian, mammalian or aquatic populations are anticipated from the use of iron salts. Iron is one of the most abundant elements and will be immobilized at the environmentally important pH range of 5-9. There is very little likelihood for runoff to aquatic systems since the parent compounds convert very rapidly to less soluble forms in the environment. Furthermore these oxidized iron compounds bind tightly to soil under turf." (US EPA, 1993)

In approving the US EPA registration of the end-use product the EPA concluded: "A number of ecological effects toxicology data requirements are waived based on the known lack of toxicity of iron phosphate to birds, fish and non-target insects, its low solubility in water, conversion to less soluble form in the environment (soil), and its use pattern (soil application). Based on these factors, the data requirements for the toxicity studies in Mallard duck, rainbow trout, freshwater invertebrates, and nontarget insect/honeybees are waived." (US EPA, 1997)

Ferric phosphate is included in the Food Chem Codex where it is recognized as a food additive: nutrient and dietary supplement. The Food and Agriculture Organization of the United Nations has set the ADI (Acceptable Daily Intake) for humans, of iron phosphate at 70. This "includes the free acid, PMTDI (Provisional Maximum Tolerable Daily Intake) of 0.8 mg/kg of body weight for iron from all sources except for iron oxides used as colouring agents and supplemental iron" (Food and Agriculture Organization of the United Nations. 1991). In addition, "the average human diet contains 10-15 mg of iron a day." (US EPA, 1997)

It should be noted that "grains and fruits are low in iron usually ranging from 1 to 20 mg Fe/kg. The daily recommended iron requirement for humans is 10 mg for children, adult males and non-menstruating females. A daily amount of 15 to 18 mg of iron is recommended for rapidly growing children and menstruating females." (US EPA, 1997) "Further, the iron salts are generally recognized as safe (GRAS) by the Food and Drug Administration for use as flavoring agent and nutrient

supplement in foods (please see 40 CFR 180.2(1))." (US EPA, 1993) As a matter of fact both the iron and the phosphate ions occur in foods naturally because they are an inherent part of plant and animal metabolism.

Iron is a plant micronutrient and phosphorus is a macronutrient, both of which are essential to plant growth and development. Iron is required for chloroplast development and is a component of cytochromes. Phosphorous is required for "formation of "high-energy" phosphate compounds (ATP and ADP) and is a component of nucleic acids and of several essential coenzymes. (Curtis, 1979) As a matter of fact, plants experience problems obtaining adequate phosphorous due to "an exceptionally small amount present (in soil) and a low availability to higher plants." (Brady, 1974)

In plants and animals iron is important for a) oxygen transport, b) electron transfer, c) DNA synthesis and d) many other cellular functions. Phosphorous is a component of ATP and ADP, which are the cell's primary energy sources, nucleic acids and several essential coenzymes. Both the ferric and phosphate ions of ferric phosphate are, therefore, essential in plant and animal metabolism.

Due to the composition of the end-use product (pasta noodle-like consistency and appearance) and its use pattern, there should be no significant honeybee exposure. There will likely be exposure to ground-feeding nontarget insects and earthworms. However, the toxicity tests performed on the end-use product, NEU1165M, showed it to be fairly benign, see summary below.

STUDY	**RESULTS**
Avian Acute Oral - Bobwhite quail	LD_{50} and NOEL>2000 mg/kg
Nontarget - Earthworms Acute Toxicity	LC_{50} > 1.000 mg/kg
Nontarget - Earthworms Reproduction Toxicity	significant effects on 5-times concentration
Nontarget Insect - ground beetle *Poecilus cupreus*	3.3 % mortality 16.25 % reduction in beneficial cap.
Nontarget Insect- rove beetle *Aleochara bilineata*	5.5 % reduction in beneficial capacity
Nontarget Insect - Predatory mite *Typhlodromus pyri*	6.6 % mortality 3.8 % reduction in beneficial capacity
Nontarget Insect - Aphid parasitoid *Aphidius rhopalosiphi*	0.0 % mortality 52.2 % reduction in beneficial cap.

In addition, the insolubility of ferric phosphate ensures that breakdown is a slow process. Although the solubility of ferric phosphate increases with

water temperature, 0.67 g/100 cc of 100°C water, at normal soil temperatures it is practically insoluble. The product is not intended for use in an aquatic environment but it should be noted that ferric phosphate's insolubility in water combined with its ready adsorption to the soil render it immobile. As a consequence it is unlikely that the ferric phosphate would migrate from the area of application into aquatic systems. Even if the bait existed in aquatic systems, the insolubility of ferric phosphate would minimize its risk to aquatic life. When tested on aquatic organisms, ferric phosphate elicited no toxic responses. The results of these tests are summarized below.

STUDY	**RESULTS**
Acute Toxicity - Rainbow Trout	EC_{50} > 100 mg/L with a probability of 99.9 %, NOEC > 100 mg/L
Acute Toxicity - *Daphnia magna*	EC_{50} > 100 mg/L with a probability of 99.9 %, NOEC > 100 mg/L
Toxic Effects - Single Cell Green Alga	EC_{50} > 100 mg/L with a probability of 95 %, NOEC > 100 mg/L

9.2 REFERENCES (See attached copies of references "a" to "o")

a) US EPA. 1993. The Reregistration Eligibility Document (RED) on Iron Salts, US EPA 738-2-93-001.
b) Brady, Nyle C. 1974. The Nature and Properties of Soils. 8th Edition. Macmillan Publishing Co., Inc., New York.
c) US EPA Publication. Decision Memorandum and Reregistration Eligibility Document on Iron Phosphate. US EPA. 1997.
d) Curtis, Helena. 1979. Biology, 3rd Edition, Worth Publishers, Inc. New York, NY. pp. 69-70, 164-165, 541, 696-697.
e) Sillanpää, Mikko. 1982. Micronutrients and the nutrient status of soils - a global study., Food and Agriculture Organization of the United Nations, Rome
f) Klingman, Glenn C. 1975. Weed Science: Principles and Practices, John Wiley & Sons, New York
g) Food and Agriculture Organization of the United Nations. Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives (JEFCA). p. 17; AND 29th Report - p. 11-15; AND 27th Report - p. 28-31; AND 26th Report - p. 24-27. ILSI Press.
h) Hurrell, R.F. 1997. Preventing Iron Deficiency Through Food Fortification. Nutrition Reviews. Vol. 55. No. 6.
i) Ellenhorn, M.J. & D.G. Barceloux. 1988. Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Elsevier Science Publishing. New York.

j) Stokinger, H.E. 1981. The Metals. Chapter 29 of Patty's (3rd ed). Clayton, G.D., F.E. Clayton, and M.C. Battigelli (Eds.) John Wiley & Sons, New York.
k) Stacy, B.D., E.J. King, C.V. Harrison, G. Nagelschmidt and S. Nelson. 1959. Tissue Changes in Rats' Lungs Caused by Hydroxides, Oxides and Phosphates of Aluminum and Iron. J Pathol Bactriol 77:417-426
l) Beliles, R.P. 1992. The Metals. Chapter 27 of Patty's (4th ed). Clayton, G.D., F.E. Clayton, and M.C. Battigelli (Eds.) John Wiley & Sons, New York.
m) British Nutrition Foundation. 1995. Iron Nutritional and physiological significance. Chapman & Hall.
n) Friberg, L., Nordberg, G.F., Kessler, E. and V.B. Vouk (Eds.). 1986. Handbook of the Toxicology of Metals. 2nd ed. Vols I, II. Amsterdam: Elsevier Science Publishers B.V. 276-293.
o) Budavari, S. 1996. The Merck Index. 12th Edition. Merck & Co., Inc.

10.1 MATERIAL SAFETY DATA SHEET

The material safety data sheet for ferric phosphate is found in Appendix D.

10.2 NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH STUDIES

Ferric phosphate is not listed with the National Institute of Environmental Health Studies.

11. RESEARCH INFORMATION

A search was conducted to find any toxicology information on ferric phosphate. This is the attached paper by Steven Cragg (Appendix E). Most of the available toxicology information related to iron rather than ferric phosphate.

In literature and web searches for ferric phosphate, information was not available. References to it were obtained from soil science books. The information therefrom is included in Section 9 with the actual references attached.

PART IV-JUSTIFICATION

12. PETITION JUSTIFICATION STATEMENT

Ferric phosphate is a mineral used to control pest slugs and snails. It occurs naturally in the soil, however, it is not mined in a form that could be utilized. It does not leave an unacceptable residue in foods, kill other organisms or contaminate the environment. Alternate slug and snail control methods are either unreliable, inefficient, cultural methods or synthetic chemicals that would not be acceptable in organic farming. Organic farmers desperately need an effective slug and snail control method as they currently suffer economic losses due to these pests. (See attached letters from California organic farmers in Appendix F) Controlling slugs and snails would improve their ability to compete in the market place with conventional producers. If approved, ferric phosphate would provide organic growers with an essential tool in their struggle to grow quality organic produce.

Ferric phosphate occurs in the environment as the minerals Strengite, Metastrengite, Vivianite, Dufrenite and other compounds. These minerals are relatively rare and often form crystals, which are prized as gemstones. These compounds may contain other elements or trace amounts of impurities. The ferric phosphate that is used in W. Neudorff GmbH KG's end-use product NEU1165M Slug and Snail Bait, is a highly refined, food grade material. It was specifically chosen because of its low toxicity and acceptance as a food substance.

The ferric phosphate source is very important to a slug and snail bait because the efficacy of ferric phosphate is dependent on ingestion and

absorption of the end-use bait product by slugs and snails. These pests can easily be deterred from eating bait pellets when the pellets contain substances that the slugs and snails do not like. They are also extremely sensitive to the grade of ferric phosphate used. In early trials it was found that the efficacy of the bait differed when an alternate source of food grade ferric phosphate was used. The efficacy of the alternate source was not adequate. The level of iron in both sources was identical. The only difference between the two ferric phosphate products, was the production method. This difference was enough to cause one product to be ineffective as an active ingredient in the end-use slug and snail bait. According to the Ferric Orthophosphate Technical Bulletin of Madison Chemicals Inc., the bioavailability of iron is affected by both the particle size and shape of the iron supplement. Therefore, to obtain an effective slug bait, the source of ferric phosphate used is extremely important.

In humans, different iron compounds are not metabolized in the same way. To ensure adequate nutritional levels of iron in the diet iron fortification of foods occurs. As a consequence, iron compounds have been studied to determine the best compound to use for food fortification. Not all ingested iron is absorbed by the body. The relative bioavailability refers to the amount of iron from the iron compound that the body will absorb and utilize, compared to the amount of iron the body absorbs from ferrous sulphate. Ferrous sulphate is the standard because the iron in most other iron compounds is not as readily absorbed as that in ferrous sulphate.

Ferric phosphate has a low level of toxicity to other animal species. Both ferric phosphate and its break down products occur naturally in the environment. The iron and phosphate constituents are, in fact, important nutrients in the metabolism of both plants and animals. These components occur naturally in food and residues from the ferric phosphate in the bait would not be a concern. The US EPA has granted this slug and snail bait an exemption from the requirement of a tolerance.

Cultural methods used to control slugs and snails are tedious, inefficient processes. Supply can also be a problem with some of the control methods. For an organic farmer with a large farm, it is virtually impossible to adequately control slugs using the methods currently acceptable to organic gardening.

Slugs can be captured in traps and killed manually by the farmer. These traps can consist of: a) holes in the ground with a covering; b) boards; and c) various manufactured traps that use bait, e.g. beer, yeast. There are also biological controls for slugs. Various birds will eat slugs and snails. The problem with using animals as control methods is that they also tend to damage the crop. There are fly and beetle species that might provide

control, however the supply is not consistent. Predatory snails can destroy pest snails. However, due to the fact that these snails are not native, their use is restricted to areas where they are naturalized. A predatory nematode is available in Europe and Britain but is not currently sold in the US. Botanicals, attractants and repellents that have proven effective against mollusks, have not been developed into commercial products. (Quarles, 1997)

The remaining control methods for slugs are the synthetic chemicals: the carbamates and metaldehyde. Both of these chemicals are far more toxic to mammals than ferric phosphate. Neither occurs naturally in the environment.

Without an adequate control method for slugs and snails, organic farmers suffer significant annual crop loss to these pests. Approval of ferric phosphate as an active ingredient to control pest slugs and snails, would improve the viability of these organic farms and ensure a continuous supply of quality organic products to the market.

13. COMMERCIAL CONFIDENTIAL INFORMATION STATEMENT

The manufacturing and production process of Ferric phosphate, found in Section 5 of this petition, is considered to be highly Confidential Business Information (CBI) and a trade secret of Dr. Paul Lohmann GmbH KG. This information is commercially valuable, utilized in the business of Dr. Paul Lohmann GmbH KG and is also maintained in secrecy. This manufacturing process was released to W. Neudorff GmbH KG on the condition that it is treated as protected confidential information.

Also, since the manufacturing process of ferric phosphate is confidential, we are unable to disclose the starting ingredients of this process. Therefore, the contents of the Material Safety Data Sheets (MSDS) for these beginning materials used to produce ferric phosphate also cannot be revealed. These MSDS sheets are found in Appendix A and are deleted in the CBI-deleted copy of this report.

United States Environmental Protection Agency
Office of Prevention, Pesticides And Toxic Substances (H-7508W)
EPA-738-F-93-002
February 1993

EPA R.E.D. FACTS

Iron Salts

Pesticide Reregistration

All pesticides sold or used in the United States must be registered by EPA, based on scientific studies showing that they can be used without posing unreasonable risks to people or the environment. Because of advances in scientific knowledge, the law requires that pesticides which were first registered years ago be reregistered to ensure that they meet today's more stringent standards.

In evaluating pesticides for reregistration, EPA obtains and reviews a complete set of studies from pesticide producers, describing the human health and environmental effects of each pesticide. The Agency imposes any regulatory controls that are needed to effectively manage each pesticide's risks. EPA then reregisters pesticides that can be used without posing undue hazards to human health or the environment.

When a pesticide is eligible for reregistration, EPA announces this and explains why in a Reregistration Eligibility Document, or RED. This fact sheet summarizes the information in the RED for iron salts.

Use Profile

The iron salts consist of three pesticide active ingredients that are eligible for reregistration: Iron (III) sulfate, Iron (II) sulfate monohydrate, and Iron (II) sulfate heptahydrate.

Iron salts are registered for use as herbicides to control moss on lawns, turf, ornamental herbaceous plants, woody shrubs and vines. Registered products are formulated as soluble concentrates and granulars. They are applied by sprinkler can, hose-end sprayer, spreader, or by hand.

The major use of iron salts in the United States is non-pesticidal, as a fertilizer micronutrient. Iron salts also are used as an electrolyte in dry cell batteries, as an animal feed additive, as a galvanizer and as an emulsion-breaker. They have further uses in water purification and sewage treatment, and in textile dying and calico printing.

Regulatory History

Iron salts first were registered as pesticides in 1962. In addition to the current outdoor moss control uses, iron salts were registered previously for use inside households, and in and around commercial, institutional and industrial premises.

At present, a total of 13 products are registered containing iron salts as sole or one of several active ingredients; one product contains Iron (III)

sulfate, nine contain Iron (II) sulfate monohydrate, and three contain Iron (II) sulfate heptahydrate.

A fourth active ingredient, Iron II ammonium sulfate, is not being supported for reregistration and so is not covered in this RED.

Human Health Assessment

Toxicity

Iron salts are present normally in the environment. Iron is the fourth most abundant element and the second most abundant metal in the earth's crystal rocks. Iron occurs in a wide variety of minerals, and is present in foods naturally and through added ingredients.

The iron salts are of low acute toxicity through oral, dermal and inhalation routes of exposure. They have been placed in Toxicity Category III for these effects. Although a mutagenicity study using microorganisms showed positive results, it is unlikely that such effects would result in humans or other mammals at the levels of exposure expected from the use of iron salts as pesticides. Other toxicity studies normally required for reregistration were not necessary to evaluate the risks of the iron salts.

Dietary Exposure

Dietary exposure is not expected to result from use of the iron salts as pesticides. No food or feed-related uses are registered, and no tolerances (maximum residue limits) or exemptions from the requirement of a tolerance are established. Further, the iron salts are generally recognized as safe (GRAS) by the Food and Drug Administration for use as a flavoring agent and nutrient supplement in foods (please see 40 CFR 180.2(a)).

Occupational and Residential Exposure

The potential for mixer, loader and applicator exposure exists when liquid or granular iron salts products are applied to lawns, turf and other outdoor sites using spreaders, sprinkler cans or by hand. However, these inorganic salts are of little concern from a toxicity perspective. Any exposure of mixers, loaders or applicators is considered inconsequential.

Human Risk Assessment

The risks to people from dietary, occupational and residential exposure to iron salts pesticides are considered negligible. It is general knowledge that these compounds are of low toxicity. They are intentionally added to foods as flavoring agents and nutrient supplements, and they have an inherent function in the metabolic systems of humans and domestic animals.

Environmental Assessment

Environmental Fate

The environmental fate and transport of iron salts is dominated by three processes: the conversion of Iron (II) to Iron (III), the formation of

insoluble oxides and hydroxides that also are well known components of soils, and the distinct surface chemistry of the iron salts that causes their adsorption with other soil components, forming larger soil particles.

Use of the iron salts produces iron oxides and hydroxides that are no different from those normally found in soils, and which give them their brown and red colors. Although certain bacteria can reduce Iron (III) to the more mobile Iron (II), this is rapidly immobilized.

Therefore, the use of iron salts as herbicides to control moss is not expected to contribute significantly to the chemistry and fate of the compounds existing naturally in the environment. No unreasonable effects are expected from the use of these pesticide products as directed.

Ecological Effects

In dietary acute toxicity studies, iron salts are practically nontoxic to bird species and are nontoxic or slightly toxic to rats. Iron (II) sulfate heptahydrate, the most toxic form of the iron salts compounds, is moderately toxic to aquatic invertebrates and slightly toxic to fish.

No adverse effects to avian, mammalian or aquatic populations are anticipated from the use of iron salts. Iron is one of the earth's most abundant elements, and it is immobilized at the pH range of 5-9. Runoff to aquatic systems is unlikely since the parent compounds convert very rapidly to less soluble forms in the environment. Furthermore, the oxidized iron compounds bind tightly to soil under turf.

No adverse effects to endangered species are anticipated from the use of iron salts.

Additional Data Required

EPA is requiring additional physical chemistry studies as confirmatory data and to complete the generic data base for iron salts. Product-specific product chemistry studies and revised labeling also are required for reregistration. These additional studies are being required through Data Call-Ins issued in conjunction with the iron salts RED.

Product Labeling Changes Required

The labels of all registered iron salts products must comply with EPA's current pesticide labeling requirements. In addition, to protect surface waters, end-use product labels must bear the following Environmental Hazards statement:

> "Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when disposing of equipment washwater or rinsate."

Regulatory Conclusion

- The three pesticide active ingredients discussed in the iron salts RED will not result in unreasonable adverse effects to human health or the environment, and all registered products containing these active ingredients

are eligible for reregistration. These products will be reregistered once the required generic and product-specific data and revised labeling are received and accepted by EPA.

- Registered products containing iron salts as well as other active ingredients will be reregistered once the other active ingredients also are determined to be eligible for reregistration.

For More Information

EPA is requesting public comments on the Reregistration Eligibility Document (RED) for iron salts during a 60-day time period, as announced in a Notice of Availability published in the Federal Register. To obtain a copy of the RED or to submit written comments, please contact the Pesticide Docket, Public Response and Program Resources Branch, Field Operations Division (H-7506C), Office of Pesticide Programs (OPP), US EPA, Washington, DC 20460, telephone 703-305-5805.

Following the comment period, the iron salts RED will be available from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161, telephone 703-487-4650.

For more information about iron salts or about EPA's pesticide reregistration program, please contact the Special Review and Reregistration Division (H-7508W), OPP, US EPA, Washington, DC 20460, telephone 703-308-8000. For information about reregistration of individual iron salts products, please contact Joanne Miller, Product Manager, Registration Division (H-7505C), OPP, US EPA, Washington, DC 20460, telephone 703-305-7830.

For information about the health effects of pesticides, or for assistance in recognizing and managing pesticide poisoning symptoms, please contact the National Pesticides Telecommunications Network (NPTN). Call toll-free 1-800-858-7378, between 8:00 am and 6:00 pm Central Time, Monday through Friday.

REREGISTRATION ELIGIBILITY DOCUMENT

IRON SALTS

LIST D

CASE 4058

ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDE PROGRAMS
SPECIAL REVIEW AND REREGISTRATION DIVISION
WASHINGTON, D.C.

IRON SALTS REREGISTRATION ELIGIBILITY TEAM

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VIII. APPENDICES

APPENDIX A - Use Patterns Subject to Reregistration

APPENDIX B - Table of the Generic Data Requirements and Studies Used to Make the Reregistration Decision

APPENDIX C - Citations Considered to be Part of the Data Base Supporting the Reregistration of Iron Salts

APPENDIX D - List of Available Related Documents

APPENDIX E - Pesticide Reregistration Handbook

APPENDIX F - Generic Data Call-In

Attachment A - Chemical Status Sheet
Attachment B - Generic DCI Response Forms (Form A) plus Instructions
Attachment C - Requirements Status and Registrants' Response Forms (Form B) plus Instructions
Attachment D - List of all Registrant(s) sent this DCI
Attachment E - Cost Share/Data Compensation Forms

APPENDIX G - Product Specific Data Call-In

Attachment A - Chemical Status Sheet
Attachment B - Product Specific DCI Response Forms (Form A) plus Instructions
Attachment C - Requirements Status and Registrants' Response Forms (Form B) plus Instructions
Attachment D - EPA Grouping of End Use Products for meeting Acute Toxicology Data Requirements.
Attachment E - EPA Acceptance Criteria
Attachment F - List of all Registrant(s) sent this DCI
Attachment G - Cost Share/Data Compensation Forms

GLOSSARY OF TERMS AND ABBREVIATIONS

a.i.	Active Ingredient
CAS	Chemical Abstracts Service
CSF	Confidential Statement of Formula
EEC	Estimated Environmental Concentration. The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EP	End-Use Product
EPA	U.S. Environmental Protection Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
HDT	Highest Dose Tested
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water or feed, e.g., mg/l or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
Ld_{lo}	Lethal Dose-low. Lowest Dose at which lethality occurs
LEL	Lowest Effect Level
MP	Manufacturing-Use Product
MRID	Master Record Identification (number). EPA's system of recording and tracking studies submitted.
N/A	Not Applicable
NPDES	National Pollutant Discharge Elimination System

GLOSSARY OF TERMS AND ABBREVIATIONS (cont.)

NOEL	No Observed Effect Level
OPP	Office of Pesticide Programs
ppm	Parts Per Million
TD	Toxic Dose. The dose at which a substance produces a toxic effect.
TC	Toxic Concentration. The dose at which a substance produces a toxic effect.

I. EXECUTIVE SUMMARY

The active ingredients covered in this document include iron (III) sulfate, iron (II) sulfate monohydrate and iron (II) sulfate heptahydrate in the chemical case iron salts. Products containing these active ingredients are used as herbicides for the control of moss on ornamental herbaceous plants, lawns, turf, wood shrubs and vines. This Reregistration Eligibility Document (RED) addresses the eligibility for reregistration of products containing these active ingredients for the above mentioned use sites only.

The U.S. EPA (hereafter referred to as "the Agency") has determined that the uses of these three active ingredients, as they are currently registered, will not cause unreasonable risk to humans or the environment. Therefore, products containing the iron salts are eligible for reregistration. The Agency is requiring additional studies on physical chemistry as confirmatory data and for purposes of labeling to complete the generic data base.

Before reregistering the products containing these iron salts, the Agency is requiring that product specific data and revised labeling be submitted within eight months of the issuance of this document. These data include product chemistry and acute toxicity testing. After reviewing these data and any revised labels and finding them acceptable, the Agency will reregister a product based on whether or not that product meets the requirements in Section 3(c)(5) of FIFRA.

II. INTRODUCTION

In 1988, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was amended to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984. The amended Act provides a schedule for the reregistration process to be completed in nine years. There are five phases to the reregistration process. The first four phases of the process focus on identification of data requirements to support the reregistration of an active ingredient and the generation and submission of data to fulfill the requirements. The fifth phase is a review by the U.S. Environmental Protection Agency (referred to as "the Agency") of all data submitted to support reregistration.

FIFRA Section 4(g)(2)(A) states that in Phase 5 "the Administrator shall determine whether pesticides containing such active ingredient are eligible for registration" before calling in data on products and either reregistering products or taking "other appropriate regulatory action." Thus, reregistration involves a thorough review of the scientific data base underlying a pesticide's registration. The purpose of the Agency's review is to reassess the potential hazards arising from the currently registered uses of the pesticide; to determine the need for additional data on health and environmental effects; and to determine whether the pesticide meets the "no unreasonable adverse effects" criterion of FIFRA.

This document presents the Agency's decision regarding the reregistration eligibility of the registered uses of iron (III) sulfate, iron (II) sulfate monohydrate, and iron (II) sulfate heptahydrate. The document consists of six sections. Section I is the introduction. Section II describes these iron salts, their uses, data requirements and regulatory history. Section III discusses the human health and environmental assessment based on the data available to the Agency. Section IV presents the reregistration decision for iron salts. Section V discusses the reregistration requirements for iron salts. Finally, Section VI is the Appendices which support this Reregistration Eligibility Document. Additional details concerning the Agency's review of applicable data are available on request.[1]

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[1] EPA's reviews of data on the set of registered uses considered for EPA's analysis may be requested from the Public Response and Program Resources Branch, Field Operations Division (H7506C), Office of Pesticide Programs, EPA, Washington, DC 20460.

III. CASE OVERVIEW

A. Chemical Overview

The following active ingredients are covered by this Reregistration Eligibility Document:

1. Chemical Name: Iron (III) sulfate
   - o CAS Registry Number: 10028-22-5
   - o Office of Pesticide Programs Chemical Code: 34902
   - o Empirical Formula: $Fe_2(SO_4)_3$

2. Chemical Name: Iron (II) sulfate monohydrate
   - o CAS Registry Number: 17375-41-6
   - o Office of Pesticide Programs Chemical Code: 50507
   - o Empirical Formula: $FeSO_4H_2O$

3. Chemical Name: Iron (II) sulfate heptahydrate
   - o CAS Registry Number: 7782-63-0
   - o Office of Pesticide Programs Chemical Code: 50502
   - o Empirical Formula: $FeSO_47H_2O$

B. Use Profile

The following is information on the current registered uses with an overview of use sites and application methods. A detailed table of these uses of iron (III) sulfate, iron (II) sulfate monohydrate and iron (II) sulfate heptahydrate is in Appendix A.

1. For Iron (III) sulfate:

Type of Pesticide: Herbicide

Use Sites: Ornamental lawns and turf--terrestrial non-food, outdoor residential

Target Pest: Mosses

Formulation Types Registered:
Soluble concentrate/liquid

Method and Rates of Application:

Equipment - Sprinkler can and hose-end sprayer.

Method and Rate - Soluble concentrate/liquid (1 qt./500 sq.ft.)

Timing - When needed.

2. For Iron (II) sulfate monohydrate:

Type of Pesticide: Herbicide

Use Sites: Ornamental herbaceous plants, ornamental lawns and turf, ornamental woody shrubs and vines--terrestrial non-food, outdoor residential.

Target Pests: Mosses

Formulation Types Registered:
Granular

Method and Rates of Application:

Equipment - By hand and spreader

Method and Rate - Ground; broadcast; sprinkle; spot treatment

Ornamental Hervaceous Plants
35 lb iron/A.
Ornamental Lawns
35 lb iron/A.
Ornamental Woody Srubs and Vines
35 lb iron/A.

Timing - When needed; Fall; Winter; Spring; Early Spring.

3. For Iron (II) sulfate heptahydrate:

Type of Pesticide: Herbicide

Use Sites: Ornamental lawns and turf--terrestrial non-food, Outdoor Residential

Target Pests: Mosses

Formulation Types Registered:
Soluble concentrate/liquid, Soluble concentrate/solid, Granular

Method and Rates of Application:

Equipment
Spreader; sprinkler can; by hand; sprayer

Method and Rate Spray
Ornamental lawns and turf
57 lb iron/A.

Timing
When needed.

C. Regulatory History

Pesticidal products containing iron salts were first registered in the United States in 1962. In addition to active products which are currently approved for use on ornamental herbaceous plants, ornamental perennial, ornamental lawns, ornamental woody shrubs and ornamental turfs, iron salts were previously registered for household or domestic dwellings (indoor) and commercial institutional and industrial areas/premises. The current uses include moss control in areas where moss growth is profuse due to high precipitation rates, primarily in the Northwest. Currently there are 14 registered products with these ingredients; 1 with iron (III) sulfate, 9 with iron (II) sulfate monohydrate, and 3 with iron (II) sulfate heptahydrate.

The major use of iron salts in the United States is non-pesticidal, as a fertilizer micronutrient. Other uses include as an electrolyte in dry cell batteries, as an animal feed additive, as a galvanizer, as an emulsion-breaker, as a coagulant, in water purification and sewage treatment, and as mordant in textile dyeing and calico printing.

Iron II ammonium sulfate is currently not being supported and is not covered in this Reregistration Eligibility Document.

IV. SCIENCE ASSESSMENT OF IRON SALTS

The Agency has conducted a thorough review of the scientific data base for iron salts for the purposes of determining the reregistration eligibility of these pesticides. These findings are summarized below. The complete references cited in the text are in the Bibliography (Appendix C).

A. Physical Chemistry Assessment

Iron (III) sulfate is a grayish-white powder, or rhombic or rhombohedral crystals. The commercial product usually contains about 20% water and is yellowish in color. It is slowly soluble in water, rapidly soluble in the presence of a trace of iron (III) sulfate, sparingly soluble in alcohol, practically insoluble in acetone and ethyl acetate.

Iron (II) sulfate monohydrate is white to a yellow crystal powder. It is soluble in water and forms a monohydrate at 65°C.

Iron (II) sulfate heptahydrate may appear as blue green crystals or granules and is usually odorless. It is efflorescent in dry air and oxidizes in moist air forming a brown coating of basic iron (III) sulfate. The tetrahydrate is formed at 56.6°C. iron (II) sulfate heptahydrate is soluble in water and practically insoluble in alcohol.

B. Human Health Assessment

1. Toxicology Assessment

The toxicological data base on iron (III) sulfate, iron (II) sulfate monohydrate, and iron (II) sulfate heptahydrate is adequate and will support reregistration eligibility.

a. Acute and Subchronic Toxicity

ACUTE TOXICITY VALUES

TEST Iron III Sulfate	RESULT	TOXICITY CATEGORY
Oral LD_{50}--rat	1487 - 2102 mg/kg	III
Inhalation LC_{50}--rat	>1.10 mg/L	III
Dermal LD_{50}--rabbit	>2000 mg/kg	III
Eye Irritation	corrosive	I
Dermal Irritation	corrosive	IV
Dermal Sensitization	negative	-

Iron (III) sulfate, in an acute oral study in rats, had an LD_{50} of 1487 mg/kg in females and 2102 mg/kg in males. An acute dermal toxicity test in rabbits with Iron (III) sulfate found an LD_{50} greater than 2000 mg/kg. An acute inhalation toxicity study in rats using iron (III) sulfate determined the LC_{50} to be greater than 1.10 mg/L.

Iron (II) sulfate heptahydrate, in an acute oral study in rats, showed an LD_{lo} of 1389 mg/kg and an acute oral study in rabbits showed an LD_{lo} of 2778 mg/kg(4). The LD_{50} determined for this compound in mice was 1520 mg/kg(4). A sensitization study using guinea pigs with iron (II) sulfate monohydrate and iron (III) sulfate found no indication of contact sensitization by this compound.

b. Mutagenicity

A mutation study in E. coli reported positive results at 30 umol/L(4). With due regard for the continuing exposure that human beings have had to the iron and sulfate components of these chemicals over many generations, it is considered unlikely that this reported result in microorganisms has any bearing on probable effects in humans or other mammals at the levels expected from use of these compounds as pesticides.

c. Metabolism

Iron sulfates are normal constituents of the diet and are metabolized and utilized by the body.

d. Other Toxicological Consideration

The toxicological data on iron sulfates within the Agency and in the literature are adequate for assessing risk to humans. Not all of the toxicity data usually required for pesticide registration or reregistration are necessary for the present uses of iron sulfates. There are some unusual factors in this case which indicate that specific studies to fulfill the usual data requirements are not necessary to regulate these substances as pesticides. Iron sulfates are normally present in the environment. They may be present in foods naturally and as added ingredients. There is no reason to expect that pesticide usage in accordance with the product label or labeling accompanying the product will constitute any hazard beyond that from ordinary exposure.

2. Exposure Assessment

a. Dietary

Dietary exposure to iron (III) sulfate, iron (II) sulfate heptahydrate, and iron (II) sulfate monohydrate is not expected to occur from pesticidal use. There are no active products involving pesticidal uses on food or animal feed. Therefore, there are no tolerances or exemptions from the requirements of tolerances established for iron salts. Since there are no toxicological endpoints of concern and no food uses, no risk assessment was performed for dietary exposure. Iron (II) sulfate is generally recognized as safe as noted in 40 CFR 180.2(a). The Food and Drug Administration has affirmed that iron (III) sulfate and iron (II) sulfate (hepta and monohydrate) are generally recognized as safe (GRAS) for use in food as flavoring agents and nutrient supplements, respectively, with no limitations other than

current good manufacturing practice.

b. Occupational and Residential

As stated in Appendix A, iron (III) sulfate and iron (II) sulfate hepta- and monohydrate are applied to turf and ornamental lawns using drop and broadcast spreaders, sprinkler cans, and by hand. These inorganic salts are formulated as a granular and soluble concentrate (liquid and solid). They are used as a herbicide to control moss on residential lawns and ornamental turf. The potential for mixer/loader/applicator exposure exists; however, these inorganic salts are of little concern from a toxicity perspective. Any mixer/loader/applicator exposure to these inorganic salts is considered inconsequential and no additional exposure data are required for reregistration eligibility.

3. Risk Assessment

The human risks from both dietary and occupational exposures are considered to be negligible. The general knowledge of iron (III) sulfate and iron (II) sulfate hepta- and monohydrate indicate low toxicities associated with these compounds. They are used by humans as food flavoring agents and food nutrient supplements, and have inherent function in the metabolic pathways of humans and domestic animals. No additional hazard or exposure data are required for reregistration eligibility.

C. Environmental Assessment

1. Environmental Fate

The Agency is relying on data available in the scientific literature to assess the environmental fate and transport of iron salts as used in pesticidal compounds. No environmental fate data were submitted by registrants.

a. Environmental Chemistry and Fate

Iron is the fourth most abundant element and the second most abundant metal in the Earth's crystal rocks. Iron occurs in a wide variety of minerals among them the oxides hematite (α-Fe_2O_3) and magnetite (Fe_3O_4), the "hydrated oxide oxide limonite" ($\sim$"$2Fe_2O_3 \cdot 3H_2O$"), the oxyhydroxide geothite and its polymorph lepidocrocite (α-FeOOH and γ-FeOOH, respectively), ferrihydrite ("$5Fe_2O_3 \cdot 9H_2O$"), in carbonates such as siderite ($FeCO_3$), in sulfides

(pyrite and marcasite, FeS_2; chalcopyrite, $CuFeS_2$, etc.), phosphates (for example vivianite) and incomplex silicates.(1,2) Weathering (that is, "the group of processes such as the chemical action of air, rainwater, plants and bacterial, and the mechanical action of changes of temperature whereby rocks on exposure to weather change in character, decay and finally crumble into soil")(3) has considerably influenced the distribution of iron in the earth. The oxides and hydroxide minerals of iron are strong pigments and are responsible, for the most part, for the brown and red colors of soils. The presence of hematite and goethite in soils (usually associated with gibsite and kaolinite) is indicative of an advanced stage of weathering.(4)

The oxidation of ferrous iron to ferric iron (from here on referred to as Fe(II) and Fe(III), respectively) is a very important aspect of the chemistry of iron salts in the environment. The oxidation is dependent on the pH and the redox potential of the medium (water; soil) and the nature of the ligands that may be complexed to Fe(II). But in general, Fe(II) is more prevalent only in very acid media of very low oxygen content, rather than in more basic media of normal-to-high oxygen content, the latter being the most commonly encountered condition. The speciation and subsequent fate and transport of Fe(II) and Fe(III) in the environment is, therefore, determined by the pH and redox potential of the media and by the nature of the ligands to which they complex. (1,2,5,6)

Under normal environmental conditions (pH 5 to 9; aerobic environments), the highly soluble Fe(II) salts will be rapidly oxidized to Fe(III), but this oxidation is accompanied by the formation of less soluble oxide and hydroxide.(7) The precipitation of Fe(III) oxides/oxyhydroxides from oxidation of Fe(II) salts or from Fe(III) salts occurs in a stepwise manner, which involves (a) formation of low-molecular weight species of poor crystalline ordering; (b) formation of red cationic polymers; (c) aging of the polymers, with eventual conversion to better defined oxide phases; (d) precipitation of oxide/oxyhydroxide phases of well defined crystallographic characteristics.(5) The rate of formation and the onset of the polymeric species are known to be strongly influenced by the nature of the counter anion of the salts.(5) In the case of salts of the divalent sulfate counter anion, precipitation occurs at lower pHs than with salts of monovalent counter anions (for example, nitrate, chloride). Like in laboratory experiments, the use of Fe(II) and Fe(II) sulfates in a terrestrial environment leads to the formation of insoluble oxide/oxyhydroxide species.(7)

The oxide/oxyhydroxide species that form from the use of Fe

(II) or Fe(III) sulfates are the same oxide/oxyhydroxide species (principally ferrihydrite, goethite, lepidocrocite, and hematite) that are present in soils as a result of weathering.(4,7) Thermodynamic and kinetic factors influence the predominance of certain species over other.(7) Soil temperature, soil moisture and soil pH are significant environmental factors that control the distribution of these species.(8) For example, it has been observed that goethite is commonly the sole iron oxide in cool and temperate zones, but in the majority of tropical or subtropical regions hematite is the predominant oxide, although it is rarely free of goethite.(8) The lepidocrocite-goethite association in soils is less understood. The predominance of lepidocrocite in a soil has been attributed to the prevalence of conditions favoring reduction of Fe(III) to Fe(II) followed by movement of Fe(II) to better aerated sites, where oxidation to Fe(III) and precipitation of lepidocrocite occurs.(9) Ferrihydrite may be considered as a young iron oxide of low order of crystallinity. Subsequent transformation of ferrihydrite into other oxides of iron is dominated by the environmental conditions.(10)

One of the most important properties of iron oxides/ oxydroxides (naturally occurring or formed by precipitation from iron salts) is their very active surface chemistry.(11) The surfaces of iron oxides and hydroxides acquire a pH-dependent charge, which controls the adsorption of a wide range of chemical species. Anions (such as molybdate, sulfate, arsenate, silicate, phosphate, and organic anions) as well as metal cations are known to chemisorb onto iron oxides and oxyhydroxide surfaces.(6,11,12,13) In the environment, iron oxides/oxyhydroxides are known to serve as a sink for metals such as copper, lead, zinc, cadmium, cobalt, nickel and manganese.(11) Adsorption of phosphate by iron oxides/ oxyhydroxides is an important process in soils; together with aluminum, calcium, magnesium, potassium, and manganese (II), they control the solubility of phosphates in soils.(14) Soils rich in iron oxide/oxyhydroxides (for example, oxisols) are known to fix large amounts of phosphate fertilizers.(15) Humic substances and other organic materials are known to adsorb onto oxide/ oxyhydroxide particulates. The surface properties of oxides/ oxyhydroxides determine the degree of aggregation/cementation of soil and mineral particulates, where the iron oxides/hydroxides are believed to behave as binding agents for the particulates.(16,17)

Some microorganisms (mainly anaerobic bacteria) are known to reduce Fe(III) oxide/oxyhydroxides to Fe(II),(18) with the subsequent re-mobilization of iron as more soluble Fe(II) species. This occurs predominantly in oxygen deficient soils, such as poorly drained soils. However, Fe(II) can be immobilized again by precipitation (for example, as siderite, vivianite or a sulfide) or by re-oxidation.

Although acid mine drainage could potentially stabilize Fe(II) species, the effect of bacterially mediated oxidation by organisms such as Thiobacillus ferrooxidans results in formation of insoluble Fe(III) oxides/oxyhydroxides.(19) Free, mobile Fe(II) or Fe(III) cations are not expected to persist under normal environmental conditions when the Fe(II) and (III) sulfates are used as herbicides to control moss in outdoor residential sites or as foliar spray fertilizers to correct iron chlorosis. The chemical species that are produced from the reactions of Fe(II) and Fe(III) sulfates under environmental conditions are not expected to differ from those iron minerals commonly encountered in soils. No unreasonable environmental effects are expected from the use of these salts as directed.

b. Environmental Fate Assessment

In summary, the fate and transport of Fe(II) and Fe(III) salts in the environment is dominated by three major processes: (1) the pH-redox potential dependent oxidation of Fe(II) to Fe(III); (2) the formation of insoluble oxides and hydroxides that are also well known components of soils; and (3) the distinct surface chemistry of the oxides and hydroxides of iron that control the adsorption of anions, cations and organic material or the adsorption of iron species onto the surfaces of mineral and organic components of soils, contributing to the aggregation of soil particles into larger units.

In terrestrial environments, the use of Fe(II) and Fe(III) sulfates is expected to produce iron oxides and hydroxides that are no different from the iron oxides and hydroxides found in soils and which are responsible for their brown and red colors. Although certain bacteria can reduce Fe(III) to the more mobile Fe(II), reoxidation and re-precipitation to Fe(III) oxides and hydroxides will rapidly immobilize any free Fe(II) that may form.

Therefore, the use of iron salts as herbicides to control moss in residential outdoor ornamentals (herbaceous and woody plants; lawns and turf) or as fertilizers to correct chlorosis in plants is not expected to contribute significantly to the chemistry and fate of the compounds existing naturally in the environment.

2. Ecological Effects

Ecological effects data presented here are derived from the six basic tests typically required by the Agency for assessing ecological hazard.

a. Ecological Effects Data

(1) Non-Target Terrestrial

Iron (II) sulfate heptahydrate and iron (II) sulfate monohydrate are classified as practically non-toxic to the bobwhite quail on an acute oral basis. The LD_{50} was 2250 mg/kg for iron (II) sulfate heptahydrate and for sulfate monohydrate the LD_{50} is >2150 mg/kg. On a dietary basis, both active ingredients are classified as practically non-toxic for the bobwhite quail and the mallard duck. The LC_{50} for iron (II) sulfate heptahydrate was >5620 ppm for both the bobwhite quail and the mallard duck. For iron (II) sulfate monohydrate, the LC_{50} was >5000 ppm for both the bobwhite quail and the mallard duck.

Iron (II) sulfate heptahydrate was classified as practically non-toxic to rats on an acute oral basis. The LD_{50} was >5 g/kg. Iron (III) sulfate was classified as non-toxic to male rats on an acute oral basis. The LD_{50} was 2,102 mg/kg. The LD_{50} for female rats was 1,487 mg/kg which classifies iron (III) sulfate as slightly toxic on an acute oral basis.

(2) Non-Target Aquatic

Iron (II) sulfate heptahydrate is the most toxic form of the iron salts compounds. The EC_{50} of 7.1 ppm for Daphnia pulex and LC_{50} of 20.8 ppm for rainbow trout classify iron salts as moderately toxic to aquatic invertebrates and slightly toxic to fish.

b. Ecological Effects Risk Assessment

(1) Non-Endangered Species

No adverse effects to avian, mammalian or aquatic populations are anticipated from the use of iron salts. Iron is one of the most abundant elements and will be immobilized at the environmentally important pH range of 5-9. There is very little likelihood for runoff to aquatic systems since the parent compounds convert very rapidly to less soluble forms in the environment. Furthermore these oxidized iron compounds bind tightly to soil under turf.

Endangered Species

No adverse effects to terrestrial or aquatic endangered species are anticipated from the use of iron salts.

V. RISK MANAGEMENT AND REREGISTRATION DECISION FOR IRON SALTS

A. Determination of Eligibility

Section 4(g)(2)(A) of FIFRA calls for the Agency to determine, after submission of relevant data concerning an active ingredient, whether products containing the active ingredient are eligible for reregistration. The Agency has completed its review of data from the open literature and generic data submitted by registrants, and has determined that the data are sufficient to support reregistration of products containing iron salts. Appendix B identifies the generic data that the Agency reviewed as part of its determination of reregistration eligibility of iron salts, and lists the submitted studies that the Agency found acceptable.

The data identified in Appendix B were sufficient to allow the Agency to assess registered uses of iron salts and to determine that these uses can be used without resulting in unreasonable adverse effects to humans and the environment. The Agency therefore finds that products containing iron salts as an active ingredient are eligible for reregistration. The reregistration of particular products is addressed in Section VI of this document.

The Agency made its reregistration eligibility determination based upon the target data base required for reregistration, the current guidelines for conducting acceptable studies to generate such data and the data identified in Appendix B. Although the Agency has found that current products containing iron salts are eligible for reregistration, it should be understood that the Agency may take appropriate regulatory action, and/or require the submission of additional data to support the registration of products containing iron salts, if new information comes to the Agency's attention or if the data requirements for reregistration (or the guidelines for generating such data) change.

The following is a summary of the regulatory positions and rationales for iron salts. Where labeling revisions are imposed, specific language is set forth in Section V of this document.

VI. ELIGIBILITY DECISION

The Agency has sufficient information on the human health effects of iron salts and on its potential for causing effects in fish and wildlife and the environment when used to control moss growth in outdoor residential areas. The Agency concludes that products

containing iron salts for these uses are eligible for reregistration. Only certain generic physical chemistry data studies on iron salts are needed as confirmatory information. The Agency has determined that iron salt containing products, labeled and used as specified in this Reregistration Eligibility Document, will not pose unreasonable risks or adverse effects to humans or the environment.

A. Eligible and Ineligible Uses

The Agency has determined that all currently registered uses are eligible for reregistration at this time.

VII. ACTIONS REQUIRED BY REGISTRANTS

A. Additional Generic Data Requirements

The generic data base supporting the reregistration of iron salt-containing products has been reviewed and determined to be substantially complete. Although some of the generic product chemistry data requirements are acceptable, additional data are required as confirmatory. The required confirmatory data is based on the fact that not all companies complied with all product chemistry guideline requirements. These are part of the generic Data Call-In requirements in Appendix F.

B. Product specific data requirements

1. Additional Product-Specific Data Requirements

Based on the reviews of the generic data for iron salts, the products containing iron salts are eligible for reregistration. Section 4(g)(2)(B) of FIFRA calls for the Agency to obtain any needed product-specific data regarding the pesticide after a determination of eligibility has been made. The product specific data requirements are listed in Appendix G, the Product Specific Data Call-In Notice.

Registrants must review previous data submissions to ensure that they meet current EPA acceptance criteria (Appendix G; Attachment E) and if not, commit to conduct new studies. If the registrant believes that previously submitted data meet current testing standards, then study MRID numbers should be cited according to the instructions in the Requirement Status and Registrants Response Form provided for each product.

C. Labeling Requirements for Manufacturing-Use and End-Use Products

All labels or labeling of end-use products and Manufacturing-Use Products must contain the following label statements:

1. Manufacturing-Use Products

In addition to the above requirements under 40 CFR §156.10 and the Pesticide Reregistration Handbook, for end-use products, labels and labeling of all manufacturing-use products must contain the following Environmental Hazards statement:

"Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or public waters unless this product is specifically identified and addressed in an NPDES permit. Do not discharge this product into sewer systems without previously notifying the sewage treatment plant authority. For guidance, contact your State Water Board or Regional Office of U.S. EPA."

2. End-Use Products

The labels and labeling of all products must comply with EPA's current regulations and requirements as specified in 40 CFR §156.10. Labels must consistently reflect any potential eye and skin hazard. Please follow the instructions in the Pesticide Reregistration Handbook with respect to labels and labeling.

IV. APPENDICES

APPENDIX A - Case 4058, [Iron Salts] Chemical 034902 [Ferric sulfate]

SITE Application Type, Application Timing, Application Equipment	Form	Minimum Application Rate	Maximum Application Rate	Max. # Apps.	Max. # Apps. @ Max. Rate	Min. Interval Between Apps. @ Max. Rate (Days)	Restricted Entry Interval (Days)	Geographic Limitations		Use Limitations
								Allowed	Disallowed	
USES ELIGIBLE FOR REREGISTRATION										
NONFOOD/NONFEED USES										
Ornamental Lawns and Turf Use Groups: Terrestrial Non-Food Crop and Outdoor Residential										
Spray, When needed, Hose-end Sprayer	SC/L	na	Dose cannot be calculated	not spec	not spec	As needed	not spec			
Spray, When needed, Sprinkler can	SC/L	na	Dose cannot be calculated	not spec	not spec	As needed	not spec			

Abbreviations used

Header:max = maximum; min = minimum; apps = applications; not spec = not specified; na = not applicable

Form : SC/L = soluble concentrate/liquid

APPENDIX A - Case 4058, [Iron Salts] Chemical 050507 [Ferrous sulfate monohydrate]

SITE Application Type, Application Timing, Application Equipment	Form	Minimum Application Rate	Maximum Application Rate	Max. # Appls.	Max. # Appls. @ Max. Rate	Min. Interval Between Appls. @ Max. Rate (Days)	Restricted Entry Interval (Days)	Geographic Limitations		Use Limitations
								Allowed	Disallowed	
USES ELIGIBLE FOR REREGISTRATION										
NONFOOD/NONFEED USES										
Ornamental Herbaceous Plants Use Groups: Terrestrial Non-Food Crop and Outdoor Residential										
Broadcast, Fall, Spreader	G	na	34.848 lb Iron per acre	not spec	not spec	not spec	not spec			
Broadcast, Fall, By hand	G	na	34.848 lb Iron per acre	not spec	not spec	not spec	not spec			
Sprinkle, When needed, Not on Label	G	na	Dose cannot be calculated	not spec	not spec	not spec	not spec			
Ornamental Lawns and Turf Use Groups: Terrestrial Non-Food Crop and Outdoor Residential										
Broadcast, Early Spring, Not on Label	G	na	Dose cannot be calculated	not spec	not spec	not spec	not spec			
Broadcast, Early Spring, Spreader	G	na	27.8784 lb Iron per acre	not spec	not spec	not spec	not spec			
Spot treatment, Fall, Not on Label	G	na	Dose cannot be calculated	not spec	not spec	not spec	not spec			
Broadcast, Spring, Spreader	G	na	19.1936 lb Iron per acre	not spec	not spec	not spec	not spec			
Broadcast, When needed, Spreader	G	na	36.3 lb Iron per acre	not spec	not spec	not spec	not spec			
Broadcast, Winter, Spreader	G	na	10.0052 lb Iron per acre	not spec	not spec	not spec	not spec			
Spot treatment, Early Spring, Not on Label	G	na	Dose cannot be calculated	not spec	not spec	not spec	not spec			
Broadcast, Fall, By hand	G	na	34.848 lb Iron per acre	not spec	not spec	not spec	not spec			
Broadcast, Fall, Not on Label	G	na	Dose cannot be calculated	not spec	not spec	not spec	not spec			

APPENDIX A - Case 4058, [Iron Salts] Chemical 050507 [Ferrous sulfate monohydrate]

SITE Application Type, Application Timing, Application Equipment	Form	Minimum Application Rate	Maximum Application Rate	Max. # Apps.	Max. # Apps. @ Max. Rate	Min. Interval Between Apps. @ Max. Rate (Days)	Restricted Entry Interval (Days)	Geographic Limitations		Use Limitations
								Allowed	Disallowed	
Broadcast, Fall, Spreader	G	na	34.848 lb Iron per acre	not spec	not spec	not spec	not spec			
Ornamental Woody Shrubs and Vines Use Groups: Terrestrial Non-Food Crop and Outdoor Residential										
Broadcast, Fall, Spreader	G	na	34.848 lb Iron per acre	not spec	not spec	not spec	not spec			
Broadcast, Fall, By hand	G	na	34.848 lb Iron per acre	not spec	not spec	not spec	not spec			
Sprinkle, When needed, Not on Label	G	na	Dose cannot be calculated	not spec	not spec	not spec	not spec			

Abbreviations used

Header: max = maximum; min = minimum; apps = applications; not spec = not specified; na = not applicable

Form : G = granular

APPENDIX B

Table of The Generic Data Requirements and Studies Used to Make the Reregistration Decision

GUIDE TO APPENDIX B

Appendix B contains listings of data requirements which support the reregistration for the iron salts covered by this Reregistration Eligibility document. It contains generic data requirements that apply to iron salts in all products, including data requirements for which a "typical formulation" is the test substance.

The data table is organized in the following format:

1. Data Requirement (Column 1). The data requirements are listed in the order in which they appear in 40 CFR Part 158. the reference numbers accompanying each test refer to the test protocols set in the Pesticide assessment Guidelines, which are available from the National Technical Information Service, 5285 Port Royal Road, Springfield, VA 22161 (703) 487-4650.

2. Use Pattern (Column 2). This column indicates the use patterns for which the data requirements apply. The following letter designations are used for the given use patterns:

A Terrestrial food
B Terrestrial feed
C Terrestrial non-food
D Aquatic food
E Aquatic non-food outdoor
F Aquatic non-food industrial
G Aquatic non-food residential
H Greenhouse food
I Greenhouse non-food
J Forestry
K Residential
L Indoor food
M Indoor non-food
N Indoor medical.
O Indoor residential

3. Bibliographic citation (Column 3). If the Agency has acceptable data in its files, this column lists the identifying number of each study. This normally is the Master Record Identification (MRID) number, but may be a "GS" number if no MRID number has been assigned. Refer to the Bibliography appendix for a complete citation of the study.

IRON III SULFATE

GUIDELINE	GUIDELINE NAME	USE SITES	BIBLIOGRAPHIC CITATION
§158.120 Product Chemistry			
61-1	Chemical Identity	All	41764501, 41764502
61-2(a)	Beginning Materials and Manufacturing Process	All	41764501, 41764502
61-2(b)	Formulation of Impurities	All	41764501, 41764502
62-1	Preliminary Analysis	All	41764501, 41764502
62-2	Certification of Limits	All	41764501, 41764502
62-3	Analytical Methods	All	41764501, 41764502
63-2	Color	All	DATA GAP
63-3	Physical State	All	DATA GAP
63-4	Odor	All	DATA GAP
63-5	Melting Point	All	DATA GAP
63-6	Boiling Point	All	DATA GAP
63-7	Density	All	DATA GAP
63-8	Solubility	All	DATA GAP
63-10	Dissociation Constant	All	DATA GAP
63-12	pH	All	DATA GAP
63-13	Storage Stability	All	DATA GAP

IRON III SULFATE

GUIDELINE	GUIDELINE NAME	USE SITES	BIBLIOGRAPHIC CITATION
§158.130 Environmental Fate			
All environmental fate data requirements have been waived.			
§158.135 Toxicology			
81-1	Acute oral tox. rat	All	42170701
81-2	Acute dermal tox. rabbit	All	42171702
81-3	Acute inhal. tox rat	All	42171703
81-4	Primary eye irritation-rabbit	All	41758701
81-5	Primary dermal irritation	All	41758702
81-6	Dermal sensitization/guinea pig	All	41758703
§158.145 Ecological Effects			
71-1(a)	Acute Avian Oral Toxicity -Quail/Duck	All	WAIVED
71-2(a)	Avian Dietary Toxicity -Quail/Duck	All	WAIVED
71-2(b)	Acute avian diet. duck	All	WAIVED
72-1(a)	Freshwater Fish Toxicity -Bluegill	All	WAIVED
72-1(c)	Fish toxicity rainbow trout	All	WAIVED
72-2(a)	Freshwater Invertebrate Toxicity	All	WAIVED

IRON II SULFATE MONOHYDRATE

GUIDELINE	GUIDELINE NAME	USE SITES	BIBLIOGRAPHIC CITATION
§158.120	Product Chemistry		
61-1	Chemical Identity	All	142309
61-2(a)	Beginning Materials and Manufacturing Process	All	142309
61-2(b)	Formulation of Impurities	All	142309
62-1	Preliminary Analysis	All	142309
62-2	Certification of Limits	All	142309
62-3	Analytical Methods	All	142309
63-2	Color	All	142309
63-3	Physical State	All	142309
63-4	Odor	All	142309
63-5	Melting Point	All	142309
63-6	Boiling Point	All	142309
63-7	Density	All	142309
63-8	Solubility	All	142309
63-10	Dissociation Constant	All	142309
63-12	pH	All	142309
63-13	Storage Stability	All	142309

IRON II SULFATE MONOHYDRATE

GUIDELINE	GUIDELINE NAME	USE SITES	BIBLIOGRAPHIC CITATION
§158.130 Environmental Fate			
All environmental fate data requirements have been waived.			
§158.135 Toxicology			
81-1	Acute oral tox. rat	All	WAIVED
81-2	Acute dermal tox. rabbit	All	WAIVED
81-3	Acute inhal. tox rat	All	WAIVED
81-4	Primary eye irration-rabbit	All	WAIVED
81-5	Primary dermal irritation	All	WAIVED
81-6	Dermal sensitization/Guinea pigs	All	41763701
§158.145 Ecological Effects			
71-1(a)	Acute Avian Oral Toxicity -Quail/Duck	All	40091902
71-2(a)	Avian Dietary Toxicity -Quail/Duck	All	40091903
71-2(b)	Acute avian diet. duck	All	40091904
72-1(a)	Freshwater Fish Toxicity -Bluegill	All	40091905
72-1(c)	Fish toxicity rainbow trout	All	40091906
72-2(a)	Freshwater Invertebrate Toxicity	All	40091907

IRON II HEPTAHYDRATE

GUIDELINE	GUIDELINE NAME	USE SITES	BIBLIOGRAPHIC CITATION
§158.120 Product Chemistry			
61-1	Chemical Identity	All	1
61-2(a)	Beginning Materials and Manufacturing Process	All	1
61-2(b)	Formulation of Impurities	All	1
62-1	Preliminary Analysis	All	1
62-2	Certification of Limits	All	1
62-3	Analytical Methods	All	1
63-2	Color	All	1
63-3	Physical State	All	1
63-4	Odor	All	1
63-5	Melting Point	All	1
63-6	Boiling Point	All	1
63-7	Density	All	1
63-8	Solubility	All	1
63-10	Dissociation Constant	All	1
63-12	pH	All	1
63-13	Storage Stability	All	1

[1] Public literature and information was provided to the Agency as part of the reregistration process. The public literature is identified the bibliography.

IRON II HEPTAHYDRATE

GUIDELINE	GUIDELINE NAME	USE SITES	BIBLIOGRAPHIC CITATION
§158.130 Environmental Fate			
All environmental fate data requirements have been waived.			
§158.135 Toxicology			
81-1	Acute oral tox. rat	All	WAIVED
81-2	Acute dermal tox. rabbit	All	WAIVED
81-3	Acute Inhalation-Rat	All	137725
81-4	Primary eye irration-rabbit	All	137726
81-5	Primary dermal irritation	All	137726
81-6	Dermal sensitization/Guinea pigs	All	WAIVED
§158.145 Ecological Effects			
71-1(a)	Acute avian oral quail/duck	All	40142201
71-2(a)	Acute avian diet. quail	All	40142202
71-2(b)	Acute avian diet. duck	All	40142203
72-1(a)	Fish toxicity bluegill	All	40142204
72-1(c)	Fish toxicity rainbow trout	All	40142205
72-2(a)	Invertebrate toxicity	All	40142206

APPENDIX C
IRON SALTS BIBLIOGRAPHY

Citations Considered to be Part of the Data Base Supporting the Reregistration of Iron Salts

GUIDE TO APPENDIX C

1. CONTENTS OF BIBLIOGRAPHY. This bibliography contains citations of all studies considered relevant by EPA in arriving at the positions and conclusions stated elsewhere in the Reregistration Eligibility Document. Primary sources for studies in this bibliography have been the body of data submitted to EPA and its predecessor agencies in support of past regulatory decisions. Selections from other sources including the published literature, in those instances where they have been considered, are included.

2. UNITS OF ENTRY. The unit of entry in this bibliography is called a "study". In the case of published materials, this corresponds closely to an article. In the case of unpublished materials submitted to the Agency, the Agency has sought to identify documents at a level parallel to the published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes of review and can be described with a conventional bibliographic citation. The Agency has also attempted to unite basic documents and commentaries upon them, treating them as a single study.

3. IDENTIFICATION OF ENTRIES. The entries in this bibliography are sorted numerically by Master Record Identifier, or "MRID number". This number is unique to the citation, and should be used whenever a specific reference is required. It is not related to the six-digit "Accession Number" which has been used to identify volumes of submitted studies (see paragraph 4(d)(4) below for further explanation). In a few cases, entries added to the bibliography late in the review may be preceded by a nine character temporary identifier. These entries are listed after all MRID entries. This temporary identifying number is also to be used whenever specific reference is needed.

4. FORM OF ENTRY. In addition to the Master Record Identifier (MRID), each entry consists of a citation containing standard elements followed, in the case of material submitted to EPA, by a description of the earliest known submission. Bibliographic conventions used reflect the standard of the American National Standards Institute (ANSI), expanded to provide for certain special needs.

a. Author. Whenever the author could confidently be identified, the Agency has chosen to show a personal author. When no individual was identified, the Agency has shown an identifiable laboratory or testing facility as the author. When no author or laboratory could be identified, the Agency has shown the first submitter as the author.

b. Document date. The date of the study is taken directly from the document. When the date is followed by a question mark, the bibliographer has deduced the date from the evidence contained in the document. When the date appears as (19??), the Agency was unable to determine or estimate the date of the document.

c. Title. In some cases, it has been necessary for the Agency bibliographers to create or enhance a document title. Any such editorial insertions are contained between square brackets.

d. Trailing parentheses. For studies submitted to the Agency in the past, the trailing parentheses include (in addition to any self-explanatory text) the following elements describing the earliest known submission:

(1) Submission date. The date of the earliest known submission appears immediately following the word "received."

(2) Administrative number. The next element immediately following the word "under" is the registration number, experimental use permit number, petition number, or other administrative number associated with the earliest known submission.

(3) Submitter. The third element is the submitter. When authorship is defaulted to the submitter, this element is omitted.

(4) Volume Identification (Accession Numbers). The final element in the trailing parentheses identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol "CDL," which stands for "Company Data Library." This accession number is in turn followed by an alphabetic suffix which shows the relative position of the study within the volume.

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4. Schulze, D.G. "An Introduction to Soil Mineralogy" in Minerals in Soil Environments, Second Edition edited by J.B. Dixon and S.B. Weed. Soil Science Society of America, Madison, WI, 1989, p.5.

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9. Reference 7, p. 403.

10. Reference 7, p. 405.

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15. Reference 7. p. 415.

16. Reference 7. p. 416-418.

17. Healey, T.W. "Principles of Dispersion and Aggregation of Mineral Fines", in Beneficiation of Mineral Fines, edited by P. Scnmasnndaran and N. Arbiter, Society of Mining Engineering, AIME, 1979, pp 12-161 to 12-178.

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19. Karasthannasis, A.D., Evangelou, V.P. and Thompson, Y.L. "Aluminum and Iron Equilibria in Soil Solutions and Surface Waters of Acid Mine Watersheds", J. Environ. Qual., Vol. 17, 1988, pp. 534-543.

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MRID	CITATION
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40091904	Fletcher, D. (1986) 8-Day Dietary LC_{50} Study with Ferrous Sulfate Monohydrate in Bobwhite Quail: Laboratory Project ID: BLAL No. 85 QC 61. Unpublished study prepared by Bio-Life Associates, Ltd. 28 p.
40091905	Surprenant, D. (1986) Acute Toxicity of Ferrous Sulfate Monohydrate to Rainbow Trout: Laboratory Project ID: BW-86-11-2227: Study #11501.0886.6100.103. Unpublished study prepared by Springborn Bionomics, Inc. 19 p.
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40142202	Grimes, J.; Jaber, M. (1986) Ferrous Sulfate Heptahydrate: A Dietary LC50 Study with the Bobwhite: Laboratory Project ID: 223101. Unpublished study prepared by Wildlife International Ltd. 17 p.
40142203	Grimes, J.; Jaber, M. (1986) Ferrous Sulfate Heptahydrate: A Dietary LC50 Study with the Mallard: Laboratory Project ID: 223102. Unpublished study prepared by Wildlife International Ltd.
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40142205	Surprenant, D. (1986) Acute Toxicity of Ferrous Sulfate Heptahydrate...to Rainbow Trout (Salmo gairdneri): Bionomics Report #BW-87-3-2317: Bionomics Study #1297.0786.6101.103. Unpublished study prepared by Springborn Bionomics, Inc. 7 p.

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40142206	Surprenant, D. (1986) Acute Toxicity of Ferrous Sulfate Heptahydrate...to Daphnids (Daphnia pulex): Bionomics Report #BW-87-32318: Bionomics Study #1297.0786.6101.110. Unpublished study prepared by Springborn Bionomics, Inc. 6 p.
41758701	Robbins, G., Pimary Eye Irritatancy Study in Rabbits, Ferric Sulfate, Ferri Floc: Lab Project No. D3082. Unpublished Study prepared by Cosmopolitan Safety Evaluation, 1990.
41758702	Robbins, G., Pimary Eye Irritatancy Study in Rabbits, Ferric Sulfate, Ferri Floc: Lab Project No. E3082. Unpublished Study prepared by Cosmopolitan Safety Evaluation, 1990.
41758703	Robbins, G., Guinea Pig Sensitization, Ferric Sulfate, Ferri Floc: Lab Project No. F3082. Unpublished Study prepared by Cosmopolitan Safety Evaluation, 1991.
41763701	Robbins, G. (1990) Guinea Pig Sensitization (Buhler): WGM-30 Brand: Lab Project Number: F3081. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 19 p.
41764501	Gohlke, A., Product Identity and Disclosure of Ingredients, Tennessee Chemical Company's Ferri-Floc, Ferric Sulfate Lab Project No 1991-1. Unpublished Study prepared by Tennessee Chemical Co., 1991.
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42171701	Robbins, G. (1992) Acute Oral Toxicity in Rats: Ferric Sulfate, Ferri Floc: Lab Project Number: A3251. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 28 p.
42171702	Robbins, G. (1991) Acute Dermal Absorption in Rabbits: Ferric Sulfate, Ferri Floc: Lab Project Number: B3251. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 24 p.
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APPENDIX D
List of Available Related Documents

The following is a list of available documents related to iron salts. Its purpose is to provide a path to more detailed information if it is needed. These accompanying documents are part of the Administrative Record for iron salts and are included in the EPA's Office of Pesticide Programs Public Docket.

1. Health and Environmental Effects Science Chapters
2. Detailed Label Usage Information System (LUIS) Report
3. Iron salts RED Fact Sheet
4. PR Notice 91-2 (included in this appendix) pertains to the Label Ingredient Statement

Appendix E, F, & G are separate docucments

APPENDIX E

Pesticide Reregistration Handbook and PR Notice 91-2

PR Notice 91-2

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

PR NOTICE 91-2

NOTICE TO MANUFACTURERS, PRODUCERS, FORMULATORS, AND REGISTRANTS OF PESTICIDES

ATTENTION: Persons Responsible for Federal Registration of Pesticide Products.

SUBJECT: Accuracy of Stated Percentages for Ingredients Statement

I. PURPOSE:

The purpose of this notice is to clarify the Office of Pesticide Program's policy with respect to the statement of percentages in a pesticide's label's ingredient statement. Specifically, the amount (percent by weight) of ingredient(s) specified in the ingredient statement on the label must be stated as the nominal concentration of such ingredient(s), as that term is defined in 40 CFR 158.153(i). Accordingly, the Agency has established the nominal concentration as the only acceptable label claim for the amount of active ingredient in the product.

II. BACKGROUND

For some time the Agency has accepted two different methods of identifying on the label what percentage is claimed for the ingredient(s) contained in a pesticide. Some applicants claimed a percentage which represented a level between the upper and the lower certified limits. This was referred to as the nominal concentration. Other applicants claimed the lower limit as the percentage of the ingredient(s) that would be expected to be present in their product at the end of the product's shelf-life. Unfortunately, this led to a great deal of confusion among the regulated industry, the regulators, and the consumers as to exactly how much of a given ingredient was in a given product. The Agency has established the nominal concentration as the only acceptable label claim for the amount of active ingredient in the product.

Current regulations require that the percentage listed in the active ingredient statement be as precise as possible reflecting good manufacturing practices 40 CFR 156.10(g)(5). The certified limits required for each active ingredient are intended to encompass any such "good manufacturing practice" variations 40 CFR 158.175(c)(3).

The upper and lower certified limits, which must be proposed in connection with a product's registration, represent the

amounts of an ingredient that may legally be present 40 CFR 158.175. The lower certified limit is used as the enforceable lower limit for the product composition according to FIFRA section 12(a)(1)(C), while the nominal concentration appearing on the label would be the routinely achieved concentration used for calculation of dosages and dilutions.

The nominal concentration would in fact state the greatest degree of accuracy that is warranted with respect to actual product composition because the nominal concentration would be the amount of active ingredient typically found in the product.

It is important for registrants to note that certified limits for active ingredients are not considered to be trade secret information under FIFRA section 10(b). In this respect the certified limits will be routinely provided by EPA to States for enforcement purposes, since the nominal concentration appearing on the label may not represent the enforceable composition for purposes of section 12(a)(1)(C).

III. REQUIREMENTS

As described below under Unit V. " **COMPLIANCE SCHEDULE,**" all currently registered products as well as all applications for new registration must comply with this Notice by specifying the nominal concentration expressed as a percentage by weight as the label claim in the ingredient(s) statement and equivalence statements if applicable (e.g., elemental arsenic, metallic zinc, salt of an acid). In addition, the requirement for performing sample analyses of five or more representative samples must be fulfilled. Copies of the raw analytical data must be submitted with the nominal ingredient label claim. Further information about the analysis requirement may be found in the 40 CFR 158.170. All products are required to provide certified limits for each active, inert ingredient, impurities of toxicological significance(i.e., upper limit(s) only) and on a case by case basis as specified by EPA. These limits are to be **set based on representative sampling** and chemical analysis(i.e., quality control) of the product.

The format of the ingredient statement must conform to 40 CFR 156-Labeling Requirements For Pesticides and Devices.

After July 1, 1997, all pesticide ingredient Statements must be changed to nominal concentration.

IV. PRODUCTS THAT REQUIRE EFFICACY DATA

All pesticides are required to be efficacious. Therefore, the certified lower limits may not be lower then the minimum level to achieve efficacy. This is extremely important for products which are intended to control pests which threaten the public health, e.g., certain antimicrobial and rodenticide products. Refer to 40 CFR 153.640.

In those cases where efficacy limits have been established, the Agency will not accept certified lower limits which are below that level for the shelf life of the product.

V. COMPLIANCE SCHEDULE

As described earlier, the purpose of this Notice is to make the registration process more uniform and more manageable for both the agency and the regulated community. It is the Agency's intention to implement the requirements of this notice as smoothly as possible so as not to disrupt or delay the Agency's high priority programs, i.e., reregistration, new chemical, or fast track (FIFRA section 3(c)(3)(B). Therefore, applicants/registrants are expected to comply with the requirements of this Notice as follows:

(1) Beginning July 1, 1991, all new product registrations submitted to the Agency are to comply with the requirements of this Notice.

(2) Registrants having products subject to reregistration under FIFRA section 4(a) are to comply with the requirements of this Notice when specific products are called in by the Agency under Phase V of the Reregistration Program.

(3) All other products/applications that are not subject to (1) and (2) above will have until July 1, 1997, to comply with this Notice. Such applications should note "Conversion to Nominal Concentrations on the application form. These types Or amendments will not be handled as "Fast Track" applications but will be handled as routine requests.

VI. FOR FURTHER INFORMATION

Contact Tyrone Aiken for information or questions concerning this notice on (703) 557-5024

Anne E. Lindsay

Anne E. Lindsay, Director
Registration Division (H-7505

APPENDIX F

Generic Data Call-In

Attachment A

Chemical Status Sheet

IRON SALTS: DATA CALL-IN CHEMICAL STATUS SHEET

INTRODUCTION

You have been sent this Generic Data Call-In Notice because you have product(s) containing Iron Salts.

This Generic Data Call-In Chemical Status Sheet, contains an overview of data required by this notice, and point of contact for inquiries pertaining to the reregistration of ieon salts. This attachment is to be used in conjunction with (1) the Generic Data Call-In Notice, (2) the Generic Data Call-In Response Form (Attachment B), (3) the Requirements Status and Registrant's Form (Attachment C), (4) a list of registrants receiving this DCI (Attachment D), (5) the EPA Acceptance Criteria (Attachment E), and (6) the Cost Share and Data Compensation Forms in replying to this Iron Salts Generic Data Call-In (Attachment F). Instructions and guidance accompany each form.

DATA REQUIRED BY THIS NOTICE

The additional data requirements needed to complete the generic database for iron salts are contained in the Requirements Status and Registrant's Response, Attachment C. The Agency has concluded that additional product chemistry data on iron salts are needed. These data are needed to fully complete the reregistration of all eligible zinc salts products.

INQUIRIES AND RESPONSES TO THIS NOTICE

If you have any questions regarding the generic data requirements and procedures established by this Notice, please contact Yvonne Brown at (703) 308-8073.

All responses to this Notice for the generic data requirements should be submitted to:

Yvonne Brown, Chemical Review Manager
Accelerated Reregistration Branch
Special Review and Registration Division (H7508W)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, D.C. 20460

RE: IRON SALTS

Attachment B

Generic DCI Response Forms (Form A) plus Instructions

SPECIFIC INSTRUCTIONS FOR THE GENERIC DATA CALL-IN RESPONSE FORM

This Form is designed to be used to respond to call-ins for generic and product specific data for th purpose of reregistering pesticides under the Federal Insecticide Fungicide and Rodenticide Act. F out this form each time you are responding to a data call-in for which EPA has sent you the form entitled "Requirements Status and Registrant's Response."

Items 1-4 will have been preprinted on the form Items 5 through 7 must be completed by the registrant as appropriate Items 8 through 11 must be completed by the registrant before submitting a response to the Agency.

Public reporting burden for this collection of information is estimated to average 15 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggesting for reducing this burden, to Chief, Information Policy Branch, PM-223, U S Environmental Protection Agency, 401 M St , S W , Washington, D C 20460; and to the Office o Management and Budget, Paperwork Reduction Project 2070-0107, Washington, D C 20503

INSTRUCTIONS

Item 1 — This item identifies your company name, number and address.

Item 2 — This item identifies the ease number, ease name, EPA chemical number and chemic name.

Item 3 — This item identifies the date and type of data call-in.

Item 4 — This item identifies the EPA product registrations relevant to the data call-in. Pleas note that you are also responsible for informing the Agency of your response regarding any product that you believe may be covered by this data call-in but that not listed by the Agency in Item 4. You must bring any such apparent omission to the Agency's attention within the period required for submission of this response form.

Item 5 — Cheek this item for each product registration you wish to cancel voluntarily. If a registration number is listed for a product for which you previously requested voluntary cancellation, indicate in Item 5 the date of that request. You do not need to complete any item on the Requirements Status and Registrant's Response Form for any product that is voluntarily cancelled.

Item 6a — Check this item if this data call-in is for generic data as indicated in Item 3 and if y are eligible for a Generic Data Exemption for the chemical listed in Item 2 and used in the subject product. By electing this exemption, you agree to the terms and conditions of a Generic Data Exemption as explained in the Data Call-In Notice.

If you are eligible for or claim a Generic Data Exemption, enter the EPA registratio Number of each registered source of that active ingredient that you use in your product.

Typically, if you purchase an EPA-registered product from one or more other producers (who, with respect to the incorporated product, are in compliance with th and-any other outstanding Data Call-In Notice), and incorporate that product into al your products, you may complete this item for all products listed on this form If, however, you produce the active ingredient yourself, or use any unregistered produc (regardless of the fact that some of your sources are registered), you may not claim a Generic Data Exemption and you may not select this item.

Item 6b — Check this Item if the data call-in is a generic data call-in as indicated in Item 3 and if you are agreeing to satisfy the generic data requirements of this data call-in. Attac the Requirements Status and Registrant's Response Form that Indicates how you wil satisfy those requirements.

Item 7a — Check this item if this call-in if a data call-in as indicated in Item 3 for a manufacturing use product (MUP), and if your product is a manufacturing use product for which you agree to supply product-specific data. Attach the Requireme Status and Registrants' Response Form that indicates how you will satisfy those requirements.

Item 7b — Check this item if this call-in is a data call-in for an end use product (EUP) as indicated in Item 3 and if your product is an end use product for which you agree to supply product-specific data. Attach the Requirements Status and Registrant's Response Form that indicates how you will satisfy those requirements.

Item 8 — This certification statement must be signed by an authorized representative of your company and the person signing must include his/her title. Additional pages used in your response must be initialled and dated in the space provided for the certification

Item 9 — Enter the date of signature.

Item 10 — Enter the name of the person EPA should contact with questions regarding your response.

Item 11 — Enter the phone number of your company contact.

Attachment C

Requirements Status and Registrants' Response Forms (Form B) plus Instructions

SPECIFIC INSTRUCTION[illegible] FOR COMPLETING THE REQUIREMENTS STATUS AND REGISTRANTS RESPON8[illegible] FORM

Generle Data

This form is designed to be used for registrants to respond to eall-in- for generie and produet-speeifie data as part of EPA's reregistration program under the Federal Insectieide Fungieide and Rodenticide Act. Although the form is the same for both produet speeifie and generie data, instructions for eompleting the forms differ slightly. Specifieally, options for satisfying produet specific data reguirements do not inelude (1) deletion of uses or (2) request for a low volume/minor use waivcr. These instructions are for completion of generic data reguirements

EPA has developed this form individually for each data call-in addressed to each registrant, and ha preprinted this form with a number of items. DO NOT use this form for any other active ingredient.

Items 1 through 8 (inclusive) will have been preprinted on the form. You must complete all other items on this form by typing or printing legibly.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggesting for reducing this burden, to Chief, Information Policy 8ranch, PM-223, U.S. Environmental Protection Agency, 401 M St., S.W., Washington, D.C. 20460; and to the Office of Nanagement and Budget, Paperwork Reduction Project 2070-0107, Washington, D.C. 20503.

INSTRICIONS

Item 1. This item identifies your company name, number, and address.

Item 2. This Item identifies the case number, case name, EPA chemical number and chemic name.

Item 3. This item identifies the date and type of data call-in.

Item 4. This item identifies the guideline reference numbers of studies reguired to support t product(s) being reregistered. These guidelines, in addition to requirements specified in the Data Call-In Notice, govern the conduct of the required studies.

Item 5. This item identifies the study title associated with the guideline reference number an whether protocols and 1, 2, or 3-year progress reports are reguired to be submitted in connection with the study. As noted in Section III of the Data Call-In Notice, 90-d progress reports are required for all studies.

If an asterisk appears in Item 5, EPA has attached information relevant to this guideline reference number to the Reguirements Status and Registrant's Response Form.

Item 6. This item identifies the code [illegible] with the use pattern of the pesticide. A bri[illegible] description of each code fol[illegible]

A.	Terrestrial food
B.	Terrestrial feed
C.	Terrestrial non-food
D.	Aquatic food
E.	Aquatic non-food outdoor
F.	Aguatic non-food industrial
G.	Aquatic non-food residential
H.	Greenhouse food
I.	Greenhouse non-food crop
J.	Forestry
K.	Residential
L.	Indoor food
M.	Indoor non-food
N.	Indoor medical
O.	Indoor residential

Item 7. This item identifies the code assigned to the substance that must be used for testing. A brief description of each code follows.

EP	End-Use Product
MP	Manufacturing-Use Product
MP/TGAI	Hanufacturing-Use Product and Technical Grade Active Ingredient
PAI	Pure Active Ingredient
PAI/M	Pure Active Ingredient and Metabolites
PAI/PAIRA	Pure Active Ingredient or Pure Active Ingredient Radiolabelled
PAIRA	Pure Active Ingredient Radiolabelled
PAIRA/M	Pure Active Ingredient Radiolabelled and Metabolites
PAIRA/PM	Pure Active Ingredient Radiolabelled and Plant Metabolites
TEP	Typical End-Use Product
TEP *	Typical End-Use Product, Percent Active Ingredient Specified
TEP/MET	Typical End-Use Product and Metabolites
TEP/PAI/M	Typical End-Use Product or Pure Active Ingredient and Metabolites
TGAI/PAIRA	Technical Grade Active Ingredient or Pure Active Ingredient Radiolabelled
TGAI	Technical Grade Active Ingredient
TCAI/TEP	Technical Grade Active Ingredient or Typical End-Use Produc
TGAI/PAI	Technical Grade Active Ingredient or Pure Active Ingredient
MET	Metabolites
IMP	Impurities
DEGR	Degradates

*See: guideline comment

Item 8. This item identifies the time frame allowed for submission of the study or protocol identified in item 2. The time frame runs from the date of **your** receipt of the Data Call-In Notice.

Item 9. Enter the appropriate Response Code or Codes to show how you intend to comply with each data reguirement. Brief dcscriptions of each code follow. The Data Call-I Notice contains a fuller description of oach of these options.

1. (Developing Data) I will conduct a new study and submit it within the time frames specifled in item 8 above. By indicating that I have chosen this option I certify that I will comply with all the reguirements pertaining to the conditions for submittal of this study as outlined in the Data Call-In Notice a that I will provide the protocol and progress reports reguired in item 5 above

2. (Agreement to Cost Share) I have entered into an agreement with one or mo registrants to develop data jointly. By indicating that I have chosen this optio I certify that I will comply with all the requirements pertaining to sharing in the cost of developing data as outlined in the Data Call-In Notice.

3. (Offer to Cost Share) I have made an offer to enter into an agreement with o or more registrants to develop data jointly. I am submitting a copy of the for "Certification of Offer to Cost Share in the Development of Data" that describes this offer/agreement. By indicating that I have chosen this option, I certify that I will comply with all the requirements pertaining to making an offer to share in the cost of developing data as outlined in the Data Call-In Notice.

4. (Submitting Existing Data) I am submitting an existing study that has never before been submitted to EPA. By indicating that I have chosen this option, I certify that this study meets all the requirements pertaining to the conditions for submittal of existing data outlined in the Data Call-In Notice and I have attached the needed supporting information along with this response.

5. (Upgrading a Study) I am submitting or citing data to upgrade a study that EPA has classified as partially acceptable and potentially upgradeable. By indicating that I have chosen this option, I certify that I have met all the requirements pertaining to the conditions for submitting or citing existing dat to upgrade a study described in the Data Call-In Notice. I am indicating on attached correspondence the Master Record Identification Number (MRID) th EPA has assigned to the data that I am citing as well as the MRID of the stu I am attempting to upgrade.

6. (Citing a Study) I am citing an existing study that has been previously classified by EPA as acceptable, core, core minimum, or a study that has no yet been revicwed by the Agency. I am providing the Agency's classfication of the study.

7. (Deleting Uses) I am attaching an application for amendment to my

Attachment D
List of Registrant(s) sent this DCI

APPENDIX G

Product Specific Data Call-In

ATTACHMENT A
Chemical Status Sheet

IRON SALTS: DATA CALL-IN CHEMICAL STATUS SHEET

INTRODUCTION

You have been sent this Product Specific Data Call-In Notice because you have product(s) containing iron salts.

This Product Specific Data Call-In Chemical Status Sheet, contains an overview of data required by this notice, and point of contact for inquiries pertaining to the reregistration of iron salts. This attachment is to be used in conjunction with (1) the Product Specific Data Call-In Notice, (2) the Product Specific Data Call-In Response Form (Attachment B), (3) the Requirement Status and Registrant's Form (Attachment C), (4) EPA's Grouping of End-Use Products for Meeti Acute Toxicology Data Requirement (Attachment D), (5) the EPA Acceptance Criteria (Attachmen E), (6) a list of registrants receiving this DCI (Attachment F) and (7) the Cost Share and Data Compensation Forms in replying to this iron salts Product Specific Data Call-In (Attachment G). Instructions and guidance accompany each form.

DATA REQUIRED BY THIS NOTICE

The additional data requirements needed to complete the database for iron salts are containe in the Requirements Status and Registrant's Response, Attachment C. The Agency has concluded that additional data on iron salts are needed for specific products. These data are required to be submitted to the Agency within the timeframe listed. These data are needed to fully complete the reregistration of all eligible iron salts products.

INQUIRIES AND RESPONSES TO THIS NOTICE

If you have any questions regarding the generic database of iron salts, please contact Yvon Brown at (703) 308-8073.

If you have any questions regarding the product specific data requirements and procedures established by this Notice, please contact Joanne Miller (703) 305-7830.

United States Environmental Protection Agency
Washington, DC 20460

EPA Formulator's Exemption Statement

(40 CFR 152.85)

Form Approved
OMB No. 2070-0060
Approval expires 9-30-90

Applicant's Name and Address	EPA File Symbol/Registration Number
	Product Name
	Date of Confidential Statement of Formula *(EPA Form 8570-4)*

As an authorized representative of the applicant for registration of the product identified above, I hereby certify that:

(1) This product contains the following active ingredient(s):

(2) Of these, each active ingredient listed in paragraph (4) is present solely as the result of the incorporation into the product *(during formulation or packaging)* of another product which contains that active ingredient, which is registered under FIFRA Section 3, and which is purchased by us from another producer.

(3) Indicate by checking (A) or (B) below which paragraph applies:

☐ (A) An accurate Confidential Statement of Formula *(EPA Form 8570-4)* for the above identified product is attached to this statement. That formula statement indicates, by company name, registration number, and product name, the source of the active ingredient(s) listed in paragraph (1).

OR

☐ (B) The Confidential Statement of Formula *(CSF) (EPA Form 8570-4)* referenced above and on file with the EPA is complete, current, and accurate and contains the information required on the current CSF.

(4) The following active ingredients in this product qualify for the formulator's exemption.

Active Ingredient	Source	
	Product Name	Registration Number

Signature	Name and Title	Date

EPA Form 8570-27 (10-86)

All responses to this Notice for the Product Specific data requirements should be submitted to:

Joanne Miller, Product Manager Team 23
Herbicide/Fungicide Branch
Registration Division (H7505C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, D.C. 20460

RE: IRON SALTS

ATTACHMENT B

PRODUCT SPECIFIC DATA CALL-IN RESPONSE FORMS (Form A) PLUS INSTRUCTIONS

INSTRUCTIONS FOR COMPLETING THE "DATA CALL-IN RESPONSE" FORM FOR PRODUCT SPECIFIC DATA

Item 1-4. Already completed by EPA.

Item 5. If you wish to **voluntarily cancel** your product, answer "yes." If you choose this option, you will not have to provide the data required by the Data Call-In Notice an you will not have to complete any other forms. Further sale and distribution of your product after the effective date of cancellation must be in accordance with the Existi Stocks provision of the Data Call-In Notice (Section IV-C).

Item 6. Not applicable since this form calls in product specific data only. However, if your product is **identical** to another product and you qualify for a **data exemption,** you must respond with "yes" to Item 7a (MUP) or 7B (EUP) on this form, provide the **EPA registration numbers of your source(s);** you would **not** complete the "Requirements Status and Registrant's Response" form. Examples of such products include **repackaged** products and **Special Local Needs (Section 24c)** products whic are identical to federally registered products.

Item 7a. For each **manufacturing use product** (MUP) for which you wish to maintain registration, you must agree to satisfy the data requirements by responding "yes."

Item 7b. For each **end use product** (EUP) for which you wish to maintain registration, you must agree to satisfy the data requirements by responding "yes." If you are requesti a **data waiver,** answer **"yes"** here; in addition, on the "Requirements Status and Registrant's Response" form under Item 9, you must respond with Option 7 (Waive Request) for each study for which you are requesting a waiver. See Item 6 with regard to identical products and data exemptions.

Items 8-11. Self-explanatory.

NOTE: You may provide **additional information** that does not fit on this form in a signed letter that accompanies this form. For example, you may wish to repo that your product has already been transferred to another company or that yo have already voluntarily cancelled this product. For these cases, please suppl all relevant details so that EPA can ensure that its records are correct.

ATTACHMENT C

PRODUCT SPECIFIC REQUIREMENT STATUS AND REGISTRANT'S RESPONSE FORMS (Form B) PLUS INSTRUCTIONS

INSTRUCTIONS FOR COMPLETING THE "REQUIREMENTS STATUS AND REGISTRANT'S RESPONSE" FORM FOR PRODUCT SPECIFIC DATA

Item 1-3 Completed by EPA. Note the **unique identifier number** assigned by EPA in Item 3 This number **must be used in the transmittal document for any data submissions** in response to this Data Call-In Notice.

Item 4. The guideline reference numbers of studies required to support the product's continued registration are identified. These guidelines, in addition to the requiremen specified in the Notice, govern the conduct of the required studies. Note that series 61 and 62 in product chemistry are now listed under 40 CFR 158.155 through 158.180 Subpart C.

Item 5. The study title associated with the guideline reference number is identified.

Item 6. The use pattern(s) of the pesticide associated with the product specific requirements is (are) identified. For most product specific data requirements, all use patterns are covered by the data requirements. In the case of efficacy data, the required studies only pertain to products which have the use sites and/or pests indicated.

Item 7. The substance to be tested is identified by EPA. For product specific data, the product as formulated for sale and distribution is the test substance, except in rare cases.

Item 8. The due date for submission of each study is identified. It is normally based on 8 **months after issuance of the** Reregistration Eligibility Document unless EPA determines that a longer time period is necessary.

Item 9. **Enter <u>only one</u> of the following response Codes <u>for each</u> <u>data requirement</u> to show how you intend to comply with the data requirements listed in this table.** Fuller descriptions of each option are contained in the Data Call-In Notice.

1. I will generate and submit data by the specified due date (Developing Data). By indicating that I have chosen this option, I certify that I will comply with all the requirements pertaining to the conditions for submittal of this study as outlined in th Data Call-In Notice.

2. I have entered into an agreement with one or more registrants to develop data jointl **(Cost Sharing). I am submitting a Copy of this agreement.** I understand that this option is available **only** for acute toxicity or certain efficacy data and only if EPA indicates in an attachment to this Notice that my product is similar enough to anothe product to qualify for this option. I certify that another party in the agreement is committing to submit or provide the required data: if the required study is not submitted on time, my product may be subject to suspension.

3. I have made offers to share in the cost to develop data **(Offers to Cost Share).** I understand that this option is available **only** for acute toxicity or certain efficacy dat and **only** if EPA indicates in an attachment to this Data Call-In Notice that my

product is similar enough to another product to qualify for this option. I am **submitting evidence that I have made an offer to another** registrant (who has an obligation to submit data) to share in the cost of that data. I am also submitting a completed **"Certification of Offer to Cost Share in the Development Data" form** I am including a copy of my offer and proof of the other registrant's receipt of that offer. I am identifying the party which is committing to submit or provide the required data: if the required study is not submitted on time, my product may be subject to suspension. I understand that other terms under Option 3 in the Data Call-In Notice (Section III-C.1.) apply as well.

4. By the specified due date, I will submit an existing study that has not been submitte previously to the Agency by anyone **(Submitting an Existing Study).** I certify that this study will meet all the requirements for submittal of existing data outlined in Option 4 in the Data Call-In Notice (Section III-C.1.) and will meet the attached acceptance criteria (for acute toxicity and product chemistry data). I will attach the needed supporting information along with this response. I also certify that I have determined that this study will fill the data requirement for which I have indicated t choice.

5. By the specified due date, I will submit or cite data to upgrade a study classified by the Agency as partially acceptable and **upgradable (upgrading a Study).** I will submit **evidence of the Agency's review** indicating that the study may be upgraded and what information is required to do so. I will provide the MRID or Accession number of the study at the due date. I understand that the conditions for this option outlined Option 5 in the Data Call-In Notice (Section III-C.1.) apply.

6. By the specified due date, I will cite an existing study that the Agency has classified as acceptable or an existing study that has been submitted but not reviewed by the Agency **(Citing an Existing Study).** If I am citing another registrant's study, I understand that this option is available only for acute toxicity or certain efficacy

dat... **nly** if the cited study was conducted on my product, an identical product or a pro... which EPA has "grouped" with one or more other products for purposes of depend...g on the same data. I may also choose this option if I am citing my own data. In either case, I will provide the **MRID or Accession Number(s)** for the cited data on a "Product Specific Data Report" form or in a similar format. If I cite anoth registrant's data, I will submit a completed **"Certification with Respect To Data Compensation Requirements" form.**

7. I request a waiver for this study because it is inappropriate for my product (waiver Request). I am attaching a complete justification for this request, including technical reasons, data and references to relevant EPA regulations, guidelines or policies. [Note: any supplemental data must be submitted in the format required by P.R. Notice 86-5]. I understand that this is my **only** opportunity to state the reasons or provide information in support of my request. If the Agency approves my waiver request, I will not be required to supply the data pursuant to Section 3(c)(2)(B) of FIFRA. If the Agency denies my waiver request, I **must choose** a method of meetin the data requirements of this Notice by the due date stated by this Notice. In this case, I must, within 30 days of my receipt of the Agency's written decision, submit a revised "Requirements Status and Registrant's Response" Form indicating the option chosen. I also understand that the deadline for submission of data as specified by th original data call-in notice will not change.

Items 10-13 Self-explanatory.

NOTE: You may provide **additional information** that does not fit on this form in a signed letter that accompanies this form. For example, you may wish to report that your product has already been transferred to another company or that you have already voluntarily cancelled this product. For these cases, please supply all relevant details so that EPA can ensure that its records are correct.

ATTACHMENT D

EPA GROUPING OF END-USE PRODUCTS FOR MEETING DATA REQUREMENTS FOR REREGISTRATION

EPA'S DECISION NOT TO BATCH END-USE PRODUCTS CONTAINING IRON SALTS FOR PURPOSES OF MEETING ACUTE TOXICITY DATA REQUIREMENTS FOR REREGISTRATION

In an effort to reduce the time, resources and number of animals needed to fulfill the acute toxicity data requirements for reregistration of end-use products containing the active ingredient iron salts, the Agency considered batching end-use products. This process involves grouping simi products for purposes of acute toxicity. Factors considered in the sorting process include each product's active and inert ingredients (identity, percent composition and biological activity), type o formulation (e.g., emulsifiable concentrate, aerosol, wettable powder, granular, etc.), and labeling (e.g., signal word, use classification, precautionary labeling, etc.).

Batching has been attempted using the readily available information described above, and frequently acute toxicity data on individual end-use products has been found to be incomplete. Notwithstanding the batching process, the Agency reserves the right to require, at any time, acute toxicity data for an individual end-use product should the need arise.

After consideration of the available information described above, batching of end-use products containing iron salts was not possible. The accompanying table lists all the end-use products containing iron salts. These products were either considered not to be similar for purpos of acute toxicity or the Agency lacked sufficient information for decision making purposes. Registrants of these products are responsible for meeting the acute toxicity data requirements for each product. Registrants must generate all the required acute toxicological studies for each of their products. If a registrant chooses to rely upon previously submitted acute toxicity data, he/sh may do so provided that the data base is complete and valid by today's standards (see acceptance criteria attached), the formulation tested is considered by the Agency to be similar for acute toxici and the formulation has not been significantly altered since submission and acceptance of the acute toxicity data. Regardless of whether new data is generated or existing data is referenced, registran must clearly identify the test material by it's EPA Registration Number.

In deciding how to meet the product specific data requirements, registrants must follow the directions given in the Data Call-In Notice and its attachments appended to the RED. The DCI Notice contains two response forms which are to be completed and submitted to the Agency within 90 days of receipt. The first form, "Data Call-In Response," asks whether the registrant will mee the data requirements for each product. The second form, "Requirements Status and Registrant's Response," lists the product specific data required for each product, including the standard six acu toxicity tests. A registrant must select one of the following options: Developing Data (Option 1), Submitting an Existing Study (Option 4), Upgrading an Existing Study (Option 5) or Citing an Existing Study (Option 6). Since the end-use products containing iron salts could not be batched, registrants cannot choose from the remaining options: Cost sharing (Option 2) or Offers to Cost Share (Option 3).

End-Use Products Containing Irons Salts (none were batched).

EPA Reg. No.	% Active Ingredient	Formulation Type
538-223	15.2% ferrous sulfate monohydrate	granular
557-1838	40.0% ferrous sulfate heptahydrate	granular
802-504	4.78% ferrous sulfate heptahydrate 8.80% ferrous sulfate monohydrate	granular
802-509	35.0% ferric sulfate	soluble conc.
802-543	32.0% ferric sulfate monohydrate	granular
802-558	95.4% ferrous sulfate monohydrate	granular
3234-44	32.5% ferrous sulfate monohydrate	granular
7001-290	15.0% ferrous sulfate monohydrate	granular
7404-03	25.38% ferrous sulfate monohydrate	granular
7404-04	17.05% ferrous sulfate monohydrate	granular
7404-10	39.85% ferrous sulfate monohydrate	granular
34704-713	65.0% ferrous sulfate heptahydrate	soluble conc.
64864-13	17.0% ferrous sulfate monohydrate	granular
64864-14	6.6% ferrous sulfate heptahydrate	soluble conc.

ATTACHMENT E

EPA ACCEPTANCE CRITERIA

SUBDIVISION D

Guideline	Study Title
Series 61	Product Identity and Composition
Series 62	Analysis and Certification of Product Ingredients
Series 63	Physical and Chemical Characteristics

61 Product Identity and Composition

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.____ Name of technical material tested (include product name and trade name, if appropriate).

2.____ Name, nominal concentration, and certified limits (upper and lower) for each active ingredient and e intentionally-added inert ingredient.

3.____ Name and upper certified limit for each impurity or each group of impurities present at $\geq$ 0.1% by weight and for certain toxicologically significant impurities (e.g., dioxins, nitrosamines) present at <0.1%.

4.____ Purpose of each active ingredient and each intentionally-added inert.

5.____ Chemical name from Chemical Abstracts index of Nomenclature and Chemical Abstracts Service (CAS) Regi Number for each active ingredient and, if available, for each intentionally-added inert.

6.____ Molecular, structural, and empirical formulas, molecular weight or weight range, and any company assig experimental or internal code numbers for each active ingredient.

7.____ Description of each beginning material in the manufacturing process.
- ____ EPA Registration Number if registered; for other beginning materials, the following:
- ____ Name and address of manufacturer or supplier.
- ____ Brand name, trade name or commercial designation.
- ____ Technical specifications or data sheets by which manufacturer or supplier describes composition, proper or toxicity.

8.____Description of manufacturing process.
- ____ Statement of whether batch or continuous process.
- ____ Relative amounts of beginning materials and order in which they are added.
- ____ Description of equipment.
- ____ Description of physical conditions (temperature, pressure, humidity) controlled in each step and the parameters that are maintained.
- ____ Statement of whether process involves intended chemical reactions.
- ____ Flow chart with chemical equations for each intended chemical reaction.
- ____ Duration of each step of process.
- ____ Description of purification procedures.
- ____ Description of measures taken to assure quality of final product.

9.____ Discussion of formation of impurities based on established chemical theory addressing (1) each impurity wh may be present at $\geq$ 0.1% or was found at $\geq$ 0.1% by product analyses and (2) certain toxicologically signific impurities (see #3).

62 Analysis and Certification of Product Ingredients

ACCEPTANCE CRITERIA

The following criteria apply to the technical grade of the active ingredient being reregistered. Use a table to present the information in items 6, 7, and 8.

Does your study meet the following acceptance criteria?

1.____ Five or more representative samples (batches in case of batch process) analyzed for each active ingredient and all impurities present at $\geq$ 0.1%.
2.____ Degree of accountability or closure $\geq$ ca 98%.
3.____ Analyses conducted for certain trace toxic impurities at lower than 0.1% (examples, nitrosamines in the case of products containing dinitroanilines or containing secondary or tertiary amines/alkanolamines plus nitri polyhalogenated dibenzodioxins and dibenzofurans). [Note that in the case of nitrosamines both fresh and sto samples must be analyzed.].
4.____ Complete and detailed description of each step in analytical method used to analyze above samples.
5.____ Statement of precision and accuracy of analytical method used to analyze above samples.
6.____ Identities and quantities (including mean and standard deviation) provided for each analyzed ingredient.
7.____ Upper and lower certified limits proposed for each active ingredient and intentionally added inert along w explanation of how the limits were determined.
8.____ Upper certified limit proposed for each impurity present at $\geq$ 0.1% and for certain toxicologically signific impurities at <0.1% along with explanation of how limit determined.
9.____ Analytical methods to verify certified limits of each active ingredient and impurities (latter not required if exe from requirement of tolerance or if generally recognized as safe by FDA) are fully described.
10.____ Analytical methods (as discussed in #9) to verify certified limits validated as to their precision and accuracy.

63 Physical and Chemical Characteristics

ACCEPTANCE CRITERIA

The following criteria apply to the technical grade of the active ingredient being reregistered.

Does your study meet the following acceptance criteria?

63-2 Color

____ Verbal description of coloration (or lack of it)
____ Any intentional coloration also reported in terms of Munsell color system

63-3 Physical State

____ Verbal description of physical state provided using terms such as "solid, granular, volatile liquid"
____ Based on visual inspection at about 20-25° C

63-4 Odor

____ Verbal description of odor (or lack of it) using terms such as "garlic-like, characteristic of aromatic compoun

____ Observed at room temperature

63-5 Melting Point

____ Reported in °C
____ Any observed decomposition reported

63-6 Boiling Point

____ Reported in °C
____ Pressure under which B.P. measured reported
____ Any observed decomposition reported

63-7 Density, Bulk Density, Specific Gravity

____ Measured at about 20-25° C
____ Density of technical grade active ingredient reported in g/ml or the specific gravity of liquids reported w reference to water at 20° C. [Note: Bulk density of registered products may be reported in lbs/ft^3 or lbs/gallo

63-8 Solubility

____ Determined in distilled water and representative polar and non-polar solvents, including those used in formulat and analytical methods for the pesticide
____ Measured at about 20-25° C
____ Reported in g/100 ml (other units like ppm acceptable if sparingly soluble)

63-9 Vapor Pressure

____ Measured at 25° C (or calculated by extrapolation from measurements made at higher temperature if press too low to measure at 25° C)
____ Experimental procedure described
____ Reported in mm Hg (torr) or other conventional units

63-10 Dissociation Constant

____ Experimental method described
____ Temperature of measurement specified (preferably about 20-25°C)

63-11 Octanol/water Partition Coefficient

____ Measured at about 20-25° C
____ Experimentally determined and description of procedure provided (preferred method-45 Fed. Register 7735

____ Data supporting reported value provided

63-12 pH

____ Measured at about 20-25° C
____ Measured following dilution or dispersion in distilled water

63-13 Stability

____ Sensitivity to metal ions and metal determined
____ Stability at normal and elevated temperatures
____ Sensitivity to sunlight determined

SUBDIVISION F

Guideline	Study Title
81-1	Acute Oral Toxicity in the Rat
81-2	Acute Dermal Toxicity in the Rat, Rabbit or Guinea Pig
81-3	Acute Inhalation Toxicity in the Rat
81-4	Primary Eye Irritation in the Rabbit
81-5	Primary Dermal Irritation Study
81-6	Dermal Sensitization in the Guinea Pig

81-1 Acute Oral Toxicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.____ Identify material tested (technical, end-use product, etc).
2.____ At least 5 young adult rats/sex/group.
3.____ Dosing, single oral may be administered over 24 hrs.
4.____ Vehicle control if other than water.
5.____ Doses tested, sufficient to determine a toxicity category or a limit dose (5000 mg/kg).
6.____ Individual observations at least once a day.
7.____ Observation period to last at least 14 days, or until all test animals appear normal whichever is longer.
8.____ Individual daily observations.
9.____ Individual body weights.
10.____ Gross necropsy on all animals.

81-2 Acute Dermal toxicity in the Rat, Rabbit or Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1._____ Identify material tested (technical, end-use product, etc).
2._____ At least 5 animals/sex/group.
3.*____ Rats 200-300 gm, rabbits 2.0-3.0 kg or guinea pigs 350-450 gm.
4._____ Dosing, single dermal.
5._____ Dosing duration at least 24 hours.
6.*____ Vehicle control, only if toxicity of vehicle is unknown.
7._____ Doses tested, sufficient to determine a toxicity category or a limit dose (2000 mg/kg).
8._____ Application site clipped or shaved at least 24 hours before dosing.
9._____ Application site at least 10% of body surface area.
10._____ Application site covered with a porous nonirritating cover to retain test material and to prev ingestion.
11._____ Individual observations at least once a day.
12._____ Observation period to last at least 14 days.
13._____ Individual body weights.
14._____ Gross necropsy on all animals.

Criteria marked with an * are supplemental and may not be required for every study.

81-3 Acute Inhalation Toxicity in the Rat

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.____ Identify material tested (technical, end-use product, etc).
2.____ Product is a gas, a solid which may produce a significant vapor hazard based on toxicity and expected use or contains particles of inhalable size for man (aerodynamic diameter 15 μm or less).
3.____ At least 5 young adult rats/sex/group.
4.____ Dosing, at least 4 hours by inhalation.
5.____ Chamber air flow dynamic, at least 10 air changes/hour, at least 19% oxygen content.
6.____ Chamber temperature, 22° C ($\pm$2°), relative humidity 40-60%.
7.____ Monitor rate of air flow.
8.____ Monitor actual concentrations of test material in breathing zone.
9.____ Monitor aerodynamic particle size for aerosols.
10.___ Doses tested, sufficient to determine a toxicity category or a limit dose (5 mg/L actual concentration of respira substance).
11.___ Individual observations at least once a day.
12.___ Observation period to last at least 14 days.
13.___ Individual body weights.
14.___ Gross necropsy on all animals.

81-4 Primary Eye Irritation in the Rabbit

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.____ Identify material tested (technical, end-use product, etc).
2.____ Study not required if material is corrosive, causes severe dermal irritation or has a pH of ≤ 2 or ≥ 11.5.
3.____ 6 adult rabbits.
4.____ Dosing, instillation into the conjunctival sac of one eye per animal.
5.____ Dose, 0.1 ml if a liquid; 0.1 ml or not more than 100 mg if a solid, paste or particulate substance.
6.____ Solid or granular test material ground to a fine dust.
7.____ Eyes not washed for at least 24 hours.
8.____ Eyes examined and graded for irritation before dosing and at 1, 24, 48 and 72 hr, then daily until eyes are normal or 21 days (whichever is shorter).
9.*___ Individual daily observations.

Criteria marked with an * are supplemental and may not be required for every study.

81-5 Primary Dermal Irritation Study

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.____ Identify material tested (technical, end-use product, etc).
2.____ Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3.____ 6 adult animals.
4.____ Dosing, single dermal.
5.____ Dosing duration 4 hours.
6.____ Application site shaved or clipped at least 24 hours prior to dosing.
7.____ Application site approximately 6 cm^2.
8.____ Application site covered with a gauze patch held in place with nonirritating tape.
9.____ Material removed, washed with water, without trauma to application site.
10.___ Application site examined and graded for irritation at 1, 24, 48 and 72 hr, then daily until normal or 14 d (whichever is shorter).
11.*__ Individual daily observations.

Criteria marked with an * are supplemental and may not be required for every study.

81-6 Dermal Sensitization in the Guinea Pig

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1.___ Identify material tested (technical, end-use product, etc).
2.___ Study not required if material is corrosive or has a pH of ≤ 2 or ≥ 11.5.
3.___ One of the following methods is utilized:
   _____ Freund's complete adjuvant test
   _____ Guinea pig maximization test
   _____ Split adjuvant technique
   _____ Buehler test
   _____ Open epicutaneous test
   _____ Mauer optimization test
   _____ Footpad technique in guinea pig.
4.___ Complete description of test.
5.*___ Reference for test.
6.___ Test followed essentially as described in reference document.
7.___ Positive control included (may provide historical data conducted within the last 6 months).

Criteria marked with an * are supplemental and may not be required for every study.

ATTACHMENT F

LIST OF ALL REGISTRANTS SENT THIS DATA CALL-IN NOTICE

ATTACHMENT G

COST SHARE AND DATA COMPENSATION FORMS

EPA

United States Environmental Protection Agency
Washington, DC 20460

CERTIFICATION OF OFFER TO COST SHARE IN THE DEVELOPMENT OF DATA

Form Approved
OMB No. 2070-0106
Approval Expires 12-31-92

Public reporting burden for this collection of information is estimated to average 15 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M St., S.W., Washington, DC 20460; and to the Office of Management and Budget, Paperwork Reduction Project (2070-0106), Washington, DC 20503.

Please fill in blanks below.

Company Name	Company Number

Chemical Name	EPA Chemical Number

Certify that:

My company is willing to develop and submit the data required by EPA under the authority of the Federal nsecticide, Fungicide and Rodenticide Act (FIFRA), if necessary. However, my company would prefer to nter into an agreement with one or more registrants to develop jointly or share in the cost of developing lata. —

My firm has offered in writing to enter into such an agreement. That offer was irrevocable and included an ffer to be bound by arbitration decision under section 3(c)(2)(B)(iii) of FIFRA if final agreement on all erms could not be reached otherwise. This offer was made to the following firm(s) on the following ate(s):

Name of Firm(s)	Date of Offer

rtification:

ertify that I am duly authorized to represent the company named above, and that the statements that I have made on s form and all attachments therein are true, accurate, and complete. I acknowledge that any knowingly false or sleading statement may be punishable by fine or imprisonment or both under applicable law.

gnature of Company's Authorized Representative	Date

Title (Please Type or Print)

Form 8570-32

EPA

United States Environmental Protection Agency
Washington, DC 20460

CERTIFICATION WITH RESPECT TO DATA COMPENSATION REQUIREMENTS

Form Approved
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Approval Expires 12-31-92

Public reporting burden for this collection of information is estimated to average 15 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M St., S.W., Washington, DC 20460; and to the Office of Management and Budget, Paperwork Reduction Project (2070-0106), Washington, DC 20503.

Please fill in blanks below.

Company Name	Company Number
Chemical Name	EPA Chemical Number

I Certify that:

1. For each study cited in support of registration or reregistration under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) that is an exclusive use study, I am the original data submitter, or I have obtained the written permission of the original data submitter to cite that study.

2. That for each study cited in support of registration or reregistration under FIFRA that is NOT an exclusive use study, I am the original data submitter, or I have obtained the written permission of the original data submitter, or I have notified in writing the company(ies) that submitted data I have cited and have offered to: (a) Pay compensation for those data in accordance with sections 3(c)(1)(D) and 3(c)(2)(D) of FIFRA; and (b) Commence negotiation to determine which data are subject to the compensation requirement of FIFRA and the amount of compensation due, if any. The companies I have notified are: (check one)

   [ ] All companies on the data submitters' list for the active ingredient listed on this form (Cite-All Method or Cite-All Option under the Selective Method). (Also sign the General Offer to Pay below.)

   [ ] The companies who have submitted the studies listed on the back of this form or attached sheets, or indicated on the attached "Requirements Status and Registrants' Response Form,"

3. That I have previously complied with section 3(c)(1)(D) of FIFRA for the studies I have cited in support of registration or reregistration under FIFRA.

Signature	Date
Name and Title (Please Type or Print)	

GENERAL OFFER TO PAY: I hereby offer and agree to pay compensation to other persons, with regard to the registration or reregistration of my products, to the extent required by FIFRA sections 3(c)(1)(D) and 3(c)(2)(D).

Signature	Date
Name and Title (Please Type or Print)	

THE NATURE AND PROPERTIES OF SOILS *8th Edition*

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Chapter 17

SUPPLY AND AVAILABILITY OF PHOSPHORUS AND POTASSIUM

CONSIDERABLE nitrogen can be added to soils through biochemical fixation brought about by microorganisms. If the proper legume is chosen, for example, the organisms will often fix this element from the air in quantities sufficient to temporarily increase the nitrogen already present. With other nutrient elements, such as phosphorus and potassium, however, there is no such microbial aid. Consequently, other sources must be depended upon to meet the demands of plants.

There are at least four main sources of phosphorus and potassium from which these demands can be met: (a) commercial fertilizer; (b) animal manures; (c) plant residues, including green manures; and (d) native compounds of these elements, both organic and inorganic, already present in the soil. Since the first three sources are to be considered in later chapters, attention now will be focused on the ways and means of utilizing the body of the soil as source of these mineral elements.

17:1. IMPORTANCE OF PHOSPHORUS

With the possible exception of nitrogen, no other element has been as critical in the growth of plants in the field as has phosphorus. A lack of this element is doubly serious since it may prevent other nutrients from being acquired by plants. For example, prior to the extensive usage of commercial fertilizers, most soil nitrogen was indirectly dependent upon the supply of phosphorus. This was due to the vital influence of phosphorus on legume growth. Today the demand for phosphorus by nitrogen-yielding legumes is universally recognized.

The need of plants for phosphorus has been especially considered in the formulation of commercial fertilizers. This element, in the form of superphosphate, was the first to be supplied as a manufactured product. Until fairly recently the amount of "phosphoric acid" in mixed fertilizers almost invariably exceeded that of nitrogen or potash. Even today the total tonnage of phosphorus, expressed as P_2O_5, is exceeded only by that of nitrogen.

17:2. INFLUENCE OF PHOSPHORUS ON PLANTS

It is difficult to state in detail the functions of phosphorus in the economy of even the simplest plants. Only the more important functions will be considered here. Phosphorus makes its contribution through its favorable effect on the following:

1. Cell division and fat and albumin formation.
2. Flowering and fruiting, including seed formation.
3. Crop maturation, thus counteracting the effects of excess nitrogen applications.
4. Root development, particularly of the lateral and fibrous rootlets.
5. Strength of straw in cereal crops, thus helping to prevent lodging.
6. Crop quality, especially of forages and of vegetables.
7. Resistance to certain diseases.

17:3. THE PHOSPHORUS PROBLEM

Although the amount of total phosphorus in an average mineral soil compares favorably with that of nitrogen, it is much lower than potassium, calcium, or magnesium (see Table 2:3). Of even greater importance, however, is the fact that most of the phosphorus present in soils is currently unavailable to plants. Also, when soluble sources of this element are supplied to soils in the form of fertilizers, their phosphorus is often "fixed" or rendered insoluble or unavailable to higher plants, even under the most ideal field conditions (see p. 465).

Fertilizer practices in many areas exemplify the problem of phosphorus availability. As already emphasized, the tonnage of phosphorus-supplying materials used as fertilizers definitely exceeds all except the nitrogen carriers. The removal of phosphorus from soils by crops, however, is low compared to that of nitrogen and potassium, often being only one third or one fourth that of the latter elements. The necessity for high fertilizer dosage when relatively small quantities of phosphorus are being removed from soils indicates that much of the added phosphates becomes unavailable to growing plants.

The influence of this situation on fertilizer practice is clearly shown when considering the additions of fertilizer phosphorus in comparison with crop removal.

In the United States, phosphorus added in fertilizers exceeds that removed by crops by more than 24 percent (see Table 17:1). In some areas, notably the eastern seaboard states, additions of phosphorus more than triple the removal of this element by crops. Since phosphorus is lost only sparingly by leaching, the inefficiency of utilization of phosphate fertilizers is obvious.

Briefly, then, the overall phosphorus problem is threefold: (a) a small total amount present in soils, (b) the unavailability of such native phosphorus, and (c) a marked "fixation" of added soluble phosphates. Since crop removal

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of phosphorus is relatively low and world phosphate supplies are huge, problem (a), that of supplying sufficient total phosphorus, is not serious. Increasing the availability of native soil phosphorus and the retardation of fixation or reversion of added phosphates are, therefore, the problems of greatest importance. These two phases will be discussed following a brief review of the phosphorus compounds present in soils.

TABLE 17:1. *Nutrients Removed by Crops in the United States Compared to That Added in Fertilizers* (1965)[a]

	N	P	K
Removed in crops (thousands of tons)	8,838	1,207	4,152
Added in fertilizers (thousands of tons)	4,580	1,499	2,313
Addition as percent of removal	52	124	56

[a] Nutrient removal figures calculated from White (25). Fertilizer additions from Tennessee Valley Authority (23).

17:4. PHOSPHORUS COMPOUNDS IN SOILS[1]

Both inorganic and organic forms of phosphorus occur in soils and both are important to plants as sources of this element. There is a serious lack of information, however, on the relative amounts of these two forms in different soils. Data available from Oregon, Iowa, and Arizona (Table 17:2) give some idea of their relative proportions. Despite the variation which occurs, it is evident that a consideration of soil phosphorus would not be complete unless some attention were given to both forms (see Fig. 17:1).

INORGANIC COMPOUNDS. Most inorganic phosphorus compounds in soils fall into one of two groups: (a) those containing *calcium*, and (b) those containing *iron* and *aluminum*. The calcium compounds of most importance are listed in Table 17:3. Fluorapatite, the most insoluble and unavailable of the group, usually is an original mineral. It is found in even the more weathered soils, especially in their lower horizons. This fact is an indication of the extreme insolubility and consequent unavailability of the phosphorus contained therein. The simpler compounds of calcium, such as mono and dicalcium phosphate, are readily available for plant growth. Except on recently fertilized soils, however, these compounds are present in extremely small quantities only since they easily revert to the more insoluble forms.

Much less is known of the exact constitution of the iron and aluminum phosphates contained in soils. The compounds involved are probably hydroxy phosphates such as dufrenite, wavellite, strengite, and variscite (10). These compounds are most stable in acid soils and are extremely insoluble.

[1] For a review of soil phosphorus, see Larsen (17).

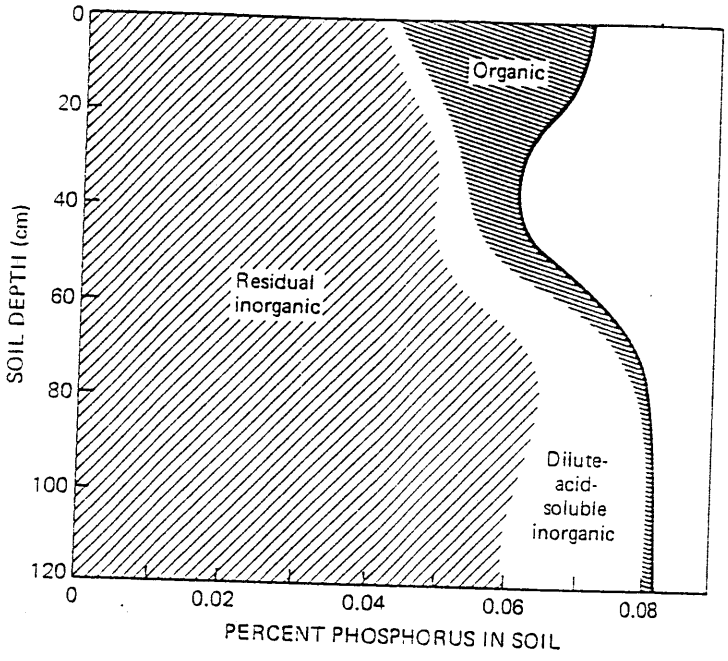

FIGURE 17:1. Distribution of phosphorus in organic and inorganic forms in an Iowa soil. The dilute-acid-soluble inorganic phosphorus is more readily available than the residual inorganic forms. In heavily fertilized soils the upper horizons would likely be much higher in inorganic phosphorus. [*From Black* (6).]

TABLE 17:2. *Total Phosphorus Content of Soils from Three States and the Percentage of Total Phosphorus in the Organic Form*

Soils	Number of Samples	Total P (ppm)	Organic Fraction (%)
Western Oregon soils			
Hill soils	4	357	65.9
Old valley-filling soils	4	1,479	29.4
Recent valley soils	3	848	25.6
Iowa soils			
Prairie soils	2	613	41.6
Gray-brown podzolic soils	2	574	37.3
Planosols	2	495	52.7
Arizona soils			
Surface soils	19	703	36.0
Subsoils	5	125	34.0

[a] Figures for Oregon from Bertramson and Stephenson (5), for Iowa from Pearson and Simonson (19), and for Arizona from Fuller and McGeorge (13).

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TABLE 17:3. *Inorganic Calcium Compounds of Phosphorus Often Found in Soils*

Compound	Formula	
Fluor apatite	$3\ Ca_3(PO_4)_2 \cdot CaF_2$	Solubility increases
Carbonate apatite	$3\ Ca_3(PO_4)_2 \cdot CaCO_3$	
Hydroxy apatite	$3\ Ca_3(PO_4)_2 \cdot Ca(OH)_2$	
Oxy apatite	$3\ Ca_3(PO_4)_2 \cdot CaO$	
Tricalcium phosphate	$Ca_3(PO_4)_2$	
Dicalcium phosphate	$CaHPO_4$	
Monocalcium phosphate	$Ca(H_2PO_4)_2$	

Many investigators have shown that phosphates react with certain iron or aluminum silicate minerals such as kaolinite. There is some uncertainty, however, as to the exact form in which this phosphorus is held in the soil. Most evidence indicates that it, too, is probably fixed as iron or aluminum phosphates, such as those described in the preceding paragraph.

ORGANIC PHOSPHORUS COMPOUNDS. There has been relatively less work done on the organic phosphorus compounds in soils, even though this fraction in some cases comprises more than one half of the total soil phosphorus. One of the reasons for lack of information on these compounds is because they apparently are exceedingly complex. The meager data available, however, indicate that the three main groups of organic phosphorus compounds[2] found in plants are also present in soils (7). These are (a) phytin and phytin derivatives, (b) nucleic acids, and (c) phospholipids. There are likely other organic phosphorus compounds present in soils; some investigators doubt that those listed account for all the organic phosphorus.

17:5. FACTORS THAT CONTROL THE AVAILABILITY OF INORGANIC SOIL PHOSPHORUS

The availability of inorganic phosphorus is largely determined by the following factors: (a) soil pH; (b) soluble iron, aluminum, and manganese; (c) presence of iron-, aluminum-, and manganese-containing minerals; (d) available calcium and calcium minerals; (e) amount and decomposition of organic matter; and (f) activities of microorganisms. The first four factors are interrelated because their effects are largely dependent upon soil pH.

17:6. pH AND PHOSPHATE IONS

As indicated in Chapter 14 (pp. 389–90), the availability of phosphorus to plants is determined to no small degree by the ionic form of this element

[2] Phytin is a calcium–magnesium salt of inositol phosphoric acid and is rather widely distributed in plants, especially in the seeds. Nucleic acids are found in both plants and animals and are even more complex than is phytin. They are apparently polymeric combinations of phosphoric acid, carbohydrates, and bases such as pyrimidine and purine.

(see Fig. 17:2). The ionic form in turn is determined by the pH of the solution in which the ion is found. Thus, in highly acid solutions only the $H_2PO_4^-$ ions are present. If the pH is increased, first the HPO_4^{--} ions and finally PO_4^{3-} ions dominate. This situation is shown by the following equations:

$$\underset{\text{(Very acid solutions)}}{H_2PO_4^-} \overset{OH}{\rightleftharpoons} H_2O + HPO_4^{--} \overset{OH}{\rightleftharpoons} H_2O + \underset{\text{(Very alkaline solutions)}}{PO_4^{3-}}$$

At intermediate pH levels two of the phosphate ions may be present simultaneously. Thus, in solutions at pH 6.0, both $H_2PO_4^-$ and HPO_4^{--} ions are found.

In general, the $H_2PO_4^-$ ion is considered somewhat more available to plants than is the HPO_4^{--} ion. In soils, however, this relationship is complicated by the presence or absence of other compounds or ions. For example, the presence of soluble iron and aluminum under very acid conditions, or calcium at high pH values, will markedly affect the availability of the phosphorus. Clearly, therefore, the effect of soil pH on phosphorus availability is determined in no small degree by the various cations present. The effect of these ions in acid soils will be discussed first.

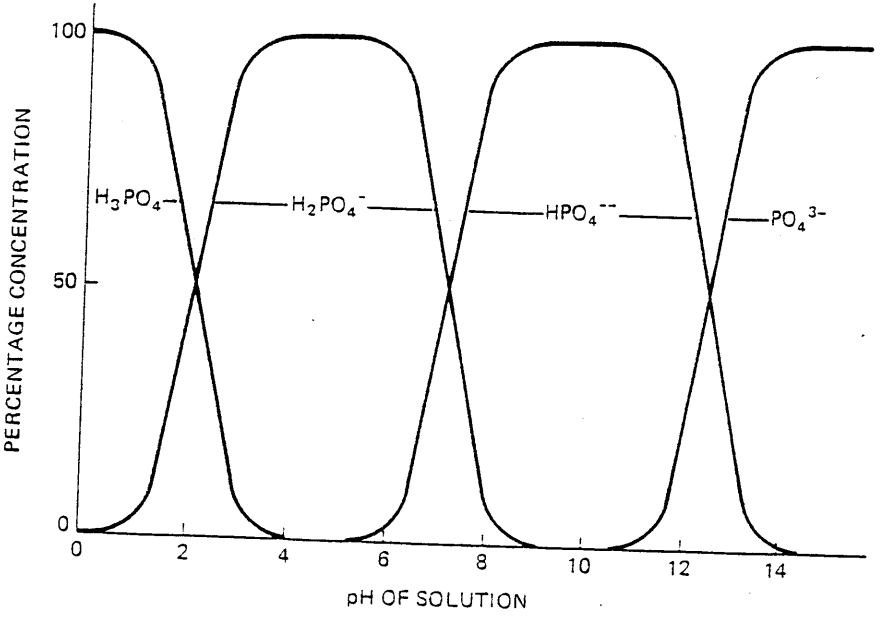

FIGURE 17:2. Relationship between solution pH and the relative concentrations of three soluble forms of phosphate. In the pH range common for soils, the $H_2PO_4^-$ ions predominate.

17:7. Inorganic Phosphorus Availability in Acid Soils

Assume that there is either a nutrient solution or an organic soil very low in inorganic matter (see Fig. 17:3). Assume also that these media are acid in reaction but that they are low in iron, aluminum, and manganese. The $H_2PO_4^-$ ions, which would dominate under these conditions, would be readily available for plant growth. Normal phosphate absorption by plants would be expected so long as the pH was not too low.

PRECIPITATION BY IRON, ALUMINUM, AND MANGANESE IONS. If the same degree of acidity should exist in a normal mineral soil, however, quite different results would be expected. Some soluble iron, aluminum, and manganese are usually found in strongly acid mineral soils. Reaction with the $H_2PO_4^-$ ions would immediately occur, rendering the phosphorus insoluble and also unavailable for plant growth.

The chemical reactions occurring between the soluble iron and aluminum and the $H_2PO_4^-$ ions probably result in the formation of hydroxy phosphates (15). This may be represented as follows, using the aluminum cation as an example:

$$Al^{3+} + \underset{\text{(Soluble)}}{H_2PO_4^-} + 2H_2O \rightleftharpoons 2H^+ + \underset{\text{(Insoluble)}}{Al(OH)_2H_2PO_4}$$

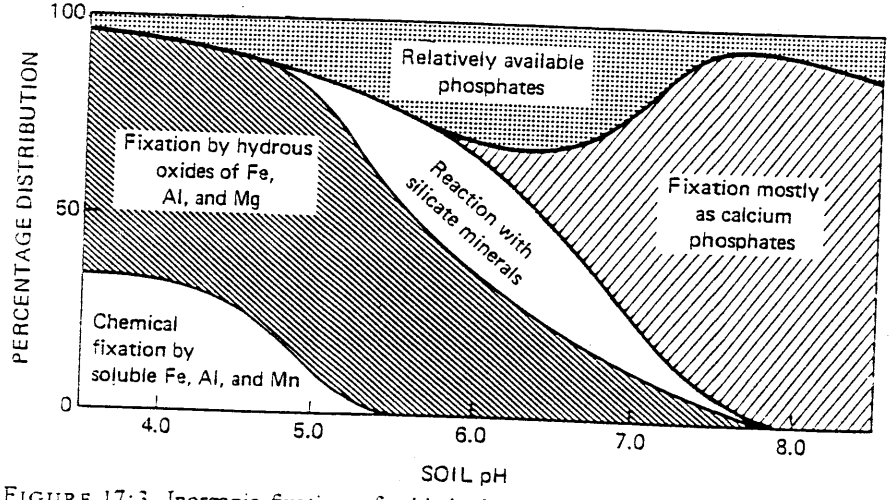

FIGURE 17:3. Inorganic fixation of added phosphates at various soil pH values. Average conditions are postulated and it is not to be inferred that any particular soil would have exactly the same distribution. The actual proportion remaining in an available form will depend upon contact with the soil, time for reaction, and other factors. It should be kept in mind that some of the added phosphorus may be changed to an organic form in which it would be temporarily unavailable.

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In most strongly acid soils the concentration of the iron and aluminum ions greatly exceeds that of the $H_2PO_4^-$ ions. Consequently, the above reaction moves to the right, forming the insoluble phosphate. This leaves only minute quantities of the $H_2PO_4^-$ ion immediately available for plants under these conditions.

An interesting series of reactions occur when fertilizers containing $Ca(H_2PO_4)_2$ are added to soils, even those relatively high in pH (18) (see Fig. 17:4). The $Ca(H_2PO_4)_2$ in the fertilizer granules attracts water from the soil and the following reaction occurs:

$$Ca(H_2PO_4)_2 \cdot H_2O + H_2O \longrightarrow CaHPO_4 \cdot 2H_2O + H_3PO_4$$

As more water is attracted, a H_3PO_4-laden solution with a pH of about 1.4 moves outward from the granule. This solution is sufficiently acid to dissolve and displace large quantities of iron, aluminum, and manganese. These ions react with the phosphate to form complex compounds, which later probably revert to the hydroxy phosphates of iron, aluminum, and manganese in acid soils and of calcium in neutral to alkaline soils. In any case, the immediate products of the addition to soils of a water-soluble compound $[Ca(H_2PO_4)_2 \cdot H_2O]$ are a group of insoluble iron, aluminum, manganese, and calcium compounds. Even so, the phosphorus in these compounds is released quite readily for plant growth. It is only after these freshly precipitated compounds are allowed to "age" or to revert to more insoluble forms that availability to plants is greatly reduced.

FIXATION BY HYDROUS OXIDES. It should be emphasized that the $H_2PO_4^-$ ion reacts not only with the soluble iron, aluminum, and manganese but also with insoluble hydrous oxides of these elements, such as limonite and goethite. The actual quantity of phosphorus fixed by these minerals in acid soils quite likely exceeds that due to chemical precipitation by the soluble iron, aluminum, and manganese cations (see Fig. 17:3).

The compounds formed as a result of fixation by iron and aluminum oxides are likely to be hydroxy phosphates, just as in the case of chemical precipitation described above (15). Their formation can be illustrated by means of the following equation if the hydrous oxide of aluminum is represented as aluminum hydroxide:

$$\underset{\text{(Soluble)}}{\begin{matrix} OH \\ Al{-}OH \\ OH \end{matrix}} + H_2PO_4^- \rightleftharpoons \underset{\text{(Insoluble)}}{\begin{matrix} OH \\ Al{-}OH \\ H_2PO_4 \end{matrix}} + OH^-$$

By means of this and similar reactions the formation of several basic phosphate minerals containing either iron or aluminum or both is thought to occur. Since several such compounds are possible, fixation of phosphorus by this mechanism probably takes place over a relatively wide pH range.

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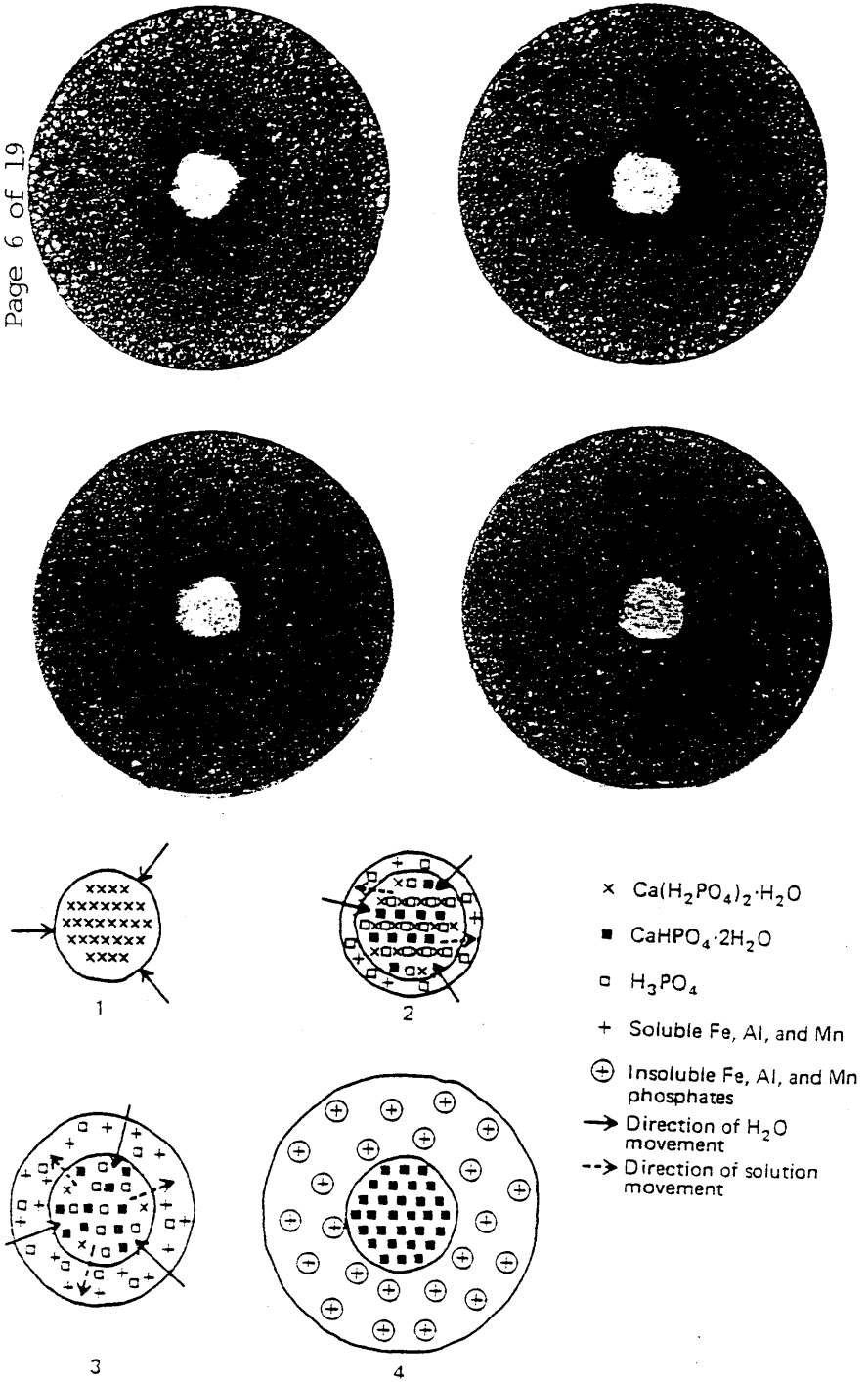

Also the large quantities of hydrous iron and aluminum oxides present in most soils make possible the fixation of tremendous total amounts of phosphorus by this means.

Thus, as both of the equations above show, the acid condition which would make possible the presence of the readily available $H_2PO_4^-$ ion in mineral soils at the same time results in conditions conducive to the vigorous *fixation* or precipitation of the phosphorus by iron, aluminum, and manganese compounds (see Fig. 17:4).

FIXATION BY SILICATE CLAYS. A third means of fixation of phosphorus under moderately acid conditions involves silicate minerals such as kaolinite, montmorillonite, and illite. Although there is some doubt about the actual mechanisms involved, the overall effect is essentially the same as when phosphorus is fixed by simpler iron and aluminum compounds. Some scientists visualize the fixation of phosphates by silicate minerals as a surface reaction between exposed —OH groups on the mineral crystal and the $H_2PO_4^-$ ions. Other investigators have evidence that aluminum and iron ions are removed from the edges of the silicate crystals forming hydroxy phosphates of the same general formula as those already discussed. This type of reaction might be expressed as follows:

$$\underset{\text{(In silicate crystal)}}{[Al]} + H_2PO_4^- - 2H_2O \rightleftharpoons 2H^+ + \underset{\text{(Insoluble)}}{Al(OH)_2H_2PO_4}$$

Thus, even though phosphates react with different ions and compounds in acid soils, apparently the same insoluble iron and aluminum compounds are formed in each case. Major differences from soil to soil are probably due to differences in rate of phosphate precipitation and in the surface area of the phosphates once the reaction has occurred. This will be discussed again later.

ANION EXCHANGE. Part of the phosphate which has reacted with iron and aluminum compounds and with silicate clays is subject to replacement by other anions, such as the hydroxyl ion. Such replacement is called *anion exchange*. It may be illustrated by a reverse of the reaction on page 463.

FIGURE 17:4 [OPPOSITE]. Reaction of $Ca(H_2PO_4)_2 \cdot H_2O$ granules with moist soil. (1) The granule has just been added to the soil and is beginning to absorb water from it. (2) In the moistened granule H_3PO_4 and $CaHPO_4 \cdot 2H_2O$ are being formed and more soil water is being absorbed. (3) The H_3PO_4-laden solution moves into the soil, dissolving and displacing Fe, Al, and Mn and leaving insoluble $CaHPO_4 \cdot 2H_2O$ in the granule. (4) The Fe, Al, and Mn ions have reacted with the phosphate to form insoluble compounds, which, along with the residue of $CaHPO_4 \cdot 2H_2O$, are the primary reaction products. [*Photos courtesy G. I. Terman and National Plant Food Institute, Washington, D.C.*]

Thus,

$$Al(OH)_2H_2PO_4 + OH^- \rightleftharpoons Al(OH)_3 + H_2PO_4^-$$

One anion (OH) has been exchanged for another (H_2PO_4). This reaction shows how anion exchange can take place and illustrates the importance of liming in helping to maintain a higher level of available phosphates.

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17:8. Inorganic Phosphorus Availability at High pH Values

In alkaline soils, phosphate precipitation is caused mostly by calcium compounds (see Fig. 17:3). Such soils are plentifully supplied with exchangeable calcium and in most cases with calcium carbonate. Available phosphates will react with both the calcium ion and its carbonate. As an illustration, assume that concentrated superphosphate is added to a calcareous soil. The reactions would be as follows:

$$\underset{\text{(Soluble)}}{Ca(H_2PO_4)_2} + \underset{\text{(Adsorbed)}}{2Ca^{++}} \rightleftharpoons \underset{\text{(Insoluble)}}{Ca_3(PO_4)_2} + 4H^+$$

$$\underset{\text{(Soluble)}}{Ca(H_2PO_4)_2} + 2CaCO_3 \rightleftharpoons \underset{\text{(Insoluble)}}{Ca_3(PO_4)_2} + 2CO_2\uparrow + 2H_2O$$

Although the $Ca_3(PO_4)_2$ thus formed is quite insoluble, it may be converted in the soil to even more insoluble compounds. Hydroxy, oxy, carbonate, and even fluor apatite compounds may be formed if conditions are favorable and if sufficient time is allowed (see Table 17:3).

This type of reversion may occur in soils of the eastern United States which have been heavily limed. It is much more serious, however, in Western soils, owing to the widespread presence of excess $CaCO_3$. The problem of utilizing phosphates in alkaline soils of the arid West is thus fully as serious as it is on highly acid soils in the East.

17:9. pH for Maximum Inorganic Phosphorus Availability

With insolubility of phosphorus occurring at both extremes of the soil pH range (see Fig. 17:3), the question arises as to the range in soil reaction in which minimum fixation occurs. The basic iron and aluminum phosphates have a minimum solubility around pH 3 to 4. At higher pH values some of the phosphorus is released and the fixing capacity somewhat reduced. Even at pH 6.5, however, much of the phosphorus is still probably chemically combined with iron and aluminum. As the pH approaches 6, precipitation as calcium compounds begins; at pH 6.5 the formation of insoluble calcium salts is a factor in rendering the phosphorus unavailable. Above pH 7.0, even more insoluble compounds, such as apatites, are formed.

These facts seem to indicate that maximum phosphate availability to

plants is obtained when the soil pH is maintained in the range from 6.0 to 7.0 (see Fig. 17:3). Even in this range, however, the fact should be emphasized that phosphate availability may still be very low and that added soluble phosphates are readily fixed by soils. The low recovery (perhaps 10 to 30 percent) by plants of added phosphates in a given season is partially due to this fixation.

17:10. Availability and Surface Area of Phosphates

When soluble phosphates are added to soils two kinds of compounds form immediately: (a) fresh precipitates of calcium, or iron and aluminum phosphates; and (b) similar compounds formed on the surfaces of either calcium carbonate or iron and aluminum oxide particles. In each case, the total surface area of the phosphate is high, and consequently the availability of the phosphorus contained therein is reasonably rapid. Thus, even though the water-soluble phosphorus in superphosphate may be precipitated in the soil in a matter of a few days, the freshly precipitated compounds will release much of their phosphorus to growing plants.

EFFECTS OF AGING. With time, changes take place in the reaction products of soluble phosphates and soils. These changes generally result in a reduction in surface area of the phosphates and a similar reduction in their availability. An increase in the crystal size of precipitated phosphates occurs in time. This decreases their surface area. Also, there is a penetration of the phosphorus held by calcium carbonate and iron or aluminum oxide particles into the particle itself (see Fig. 17:5). This leaves less of the phosphorus near the surface where it can be made available to growing plants. By these

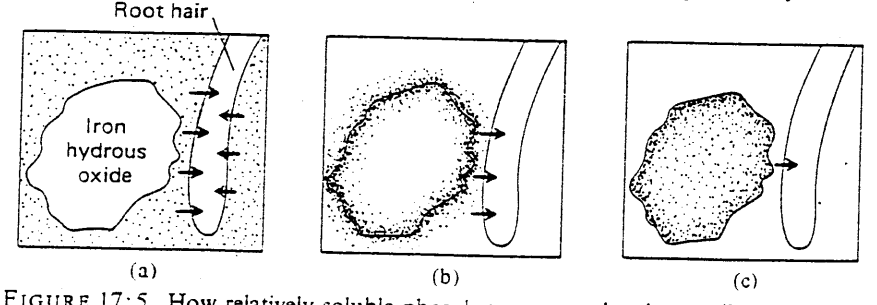

FIGURE 17:5. How relatively soluble phosphates are rendered unavailable by compounds such as hydrous oxide. (a) The situation just after application of a soluble phosphate. The root hair and the hydrous iron oxide particle are surrounded by soluble phosphates. Within a very short time (b) most of the soluble phosphate has reacted with the surface of the iron oxide crystal. The phosphorus is still fairly readily available to the plant roots since most of it is located at the surface of the particle where exudates from the plant can encourage exchange. In time (c) the phosphorus penetrates the crystal and only a small portion is found near the surface. Under these conditions its availability is low.

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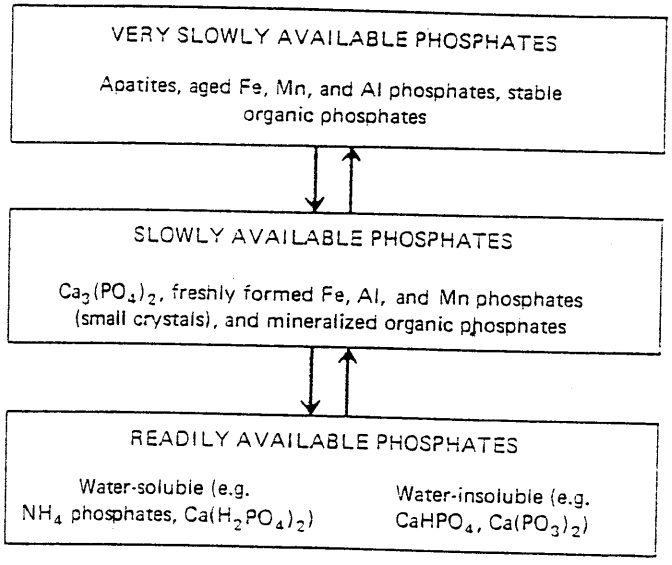

FIGURE 17:6. Classification of phosphate compounds in three major groups. Fertilizer phosphates are generally in the "readily available phosphate" group but are quickly converted to the slowly available forms. These can be utilized by plants at first but upon aging are rendered less available and are then classed as very slowly available. At any one time perhaps 80–90 percent of the soil phosphorus is in "very slowly available" forms. Most of the remainder is in the slowly available form since perhaps less than 1 percent would be expected to be readily available.

processes of aging, phosphate availability is reduced. Thus, the supply of available phosphorus to plants is determined not only by the kinds of compounds which form but also by their surface areas (see Fig. 17:6).

17:11. Phosphorus-Fixing Power of Soils

In light of the above discussion it is interesting to note the actual quantity of phosphorus which soils are capable of fixing. Data from three New Jersey soils presented in Table 17:4 emphasize the tremendous power of certain soils in this respect. For example, to satisfy the phosphorus-fixing power of the unlimed Collington soil, nearly 47 tons of superphosphate containing 20 percent P_2O_5 would be required. Although liming definitely reduced the fixing capacity, the quantity of phosphorus fixed even on the limed soils is enormous. Thus, over 25 tons of superphosphate would be required to completely satisfy the phosphorus-fixing power of the limed Collington soil.

One Coastal Plain soil was reported (4) to have a phosphate-fixing capacity of 125 tons of 20 percent superphosphate per acre-furrow slice. Although such values are somewhat higher than usual because of the nature and amounts of the iron and aluminum compounds in the soils, they do not overemphasize the problem of phosphate fixation.

TABLE 17:4. *Phosphorus-Adsorbing Power of Three New Jersey Soils Limed and Unlimed*[a]

Expressed as pounds of 20 percent superphosphate per acre-furrow slice.

Soil	Treatment	pH	Phosphorus Fixing Power (lb 20% super/A.F.S.)
Sassafras	No lime	3.6	28,400
Sassafras	Lime	6.5	13,916
Collington	No lime	3.2	93,720
Collington	Lime	6.5	50,268
Dutchess	No lime	3.8	68,728
Dutchess	Lime	6.5	44,020

[a] From Toth and Bear (24).

17:12. Influence of Soil Organisms and Organic Matter on the Availability of Inorganic Phosphorus

In addition to pH and related factors, organic matter and microorganisms strikingly affect inorganic phosphorus availability. Just as was the case with nitrogen, the rapid decomposition of organic matter and consequent high microbial population results in the *temporary* tying up of inorganic phosphates in microbial tissue.

Products of organic decay such as organic acids and humus are thought to be effective in forming complexes with iron and aluminum compounds. This engagement of iron and aluminum reduces inorganic phosphate fixation to a remarkable degree. The exact importance of this effect has not as yet been completely ascertained. The ability of humus and lignin to reduce phosphate fixation, however, is shown in Fig. 17:7. Both materials were effective in releasing phosphorus after it had been fixed as basic iron phosphate. Thus, organic decomposition products undoubtedly play an important role in organic phosphorus availability.

17:13. Availability of Organic Phosphorus

Only meager information has been obtained on the factors affecting the availability to higher plants or organic phosphorus compounds. It has been established that both *phytin* and *nucleic acids* can be utilized as sources of phosphorus (20). Apparently the phytin is absorbed directly by the plants while the nucleic acids probably are broken down by enzymes at the root surfaces and the phosphorus is adsorbed in either the organic or inorganic form. In spite of the readiness with which these compounds may be assimilated, however, plants commonly suffer from a phosphorus deficiency even in the presence of considerable quantities of organic forms of this element. Just as with inorganic phosphates, the problem is one of availability.

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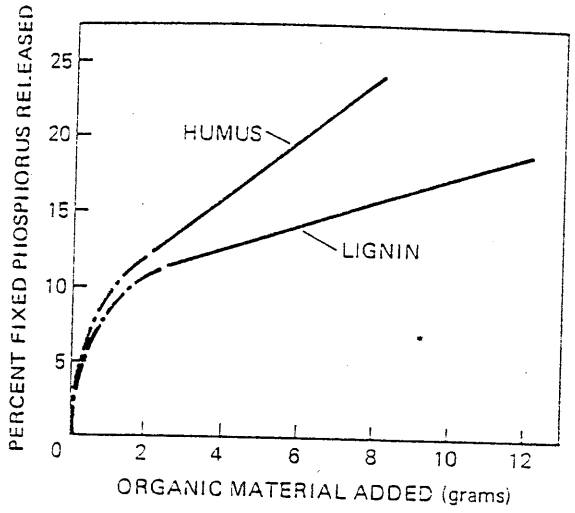

FIGURE 17:7. Effect of added organic materials on the release of phosphorus previously fixed by iron compounds. Both humus and lignin are effective, the humus to the greater degree. These results suggest that mineral fixation of phosphorus may be lower in soils comparatively high in organic matter. [*After Swenson et al.* (22).]

Phytin behaves in the soil much as do the inorganic phosphates (8), forming iron, aluminum, and calcium phytates. In acid soils the phytin is rendered insoluble and thus unavailable because of reaction with iron and aluminum. Under alkaline conditions calcium phytate is precipitated and the phosphorus carried is rendered unavailable.

The fixation of nucleic acids involves an entirely different mechanism, but the end result—low phosphorus availability—is the same. Evidently, nucleic acids are strongly adsorbed by clays, especially montmorillonite.

This adsorption is particularly pronounced under acid conditions and results in a marked decrease in the rate of decomposition of the nucleic acids. Consequently, the available phosphorus supply from this source is low, especially in acid soils which contain appreciable amounts of montmorillonite.

The judicious application of lime to acid soils is thus fully as important in organic phosphorus nutrition as it is in rendering inorganic compounds available. Whether we are dealing with inorganic soil phosphates, added fertilizers, or organic materials, the importance of lime as a controlling factor in phosphate availability is clearly evident.

17:14. Practical Control of Phosphorus Availability

From a practical standpoint, the phosphorus-utilization picture is not too encouraging. The inefficient utilization of applied phosphates by plants has long been known. The experimental use of radioactive phosphorus materials has emphasized this point even more thoroughly. By adding fertilizers containing traceable phosphorus, it has been possible to determine the proportion of the applied phosphates absorbed during the year of application.

The results of experiments on corn, soybeans, and potatoes are shown in Table 17:5. Even though on some soils marked responses were obtained from the addition of phosphate fertilizers, the efficiency of phosphorus utilization was very low. Apparently maximum yields were obtained only by supplying much more phosphorus than the plants absorbed in a given season.

TABLE 17:5. *Recovery of Applied Fertilizer Phosphates During the First Crop Year*

Soil	Crop	Fertilizer Phosphorus Recovered the First Year (%)
Bladen	Corn	11.8
Bladen	Potatoes	7.6
Bladen	Soybeans	18.2
Webster	Corn	6.5
Clarion	Corn	3.4

[a] Data for bladen soil from Krantz, et al. (16) and for other soils from Stanford and Nelson (21).

LIMING AND PLACEMENT OF FERTILIZERS. The small amount of control that can be exerted over phosphate availability seems to be associated with *liming*, *fertilizer placement*, and *organic matter maintenance*. By holding the pH of soils between 6.0 and 7.0, the phosphate fixation can be kept at a minimum (see Figs. 14:7 and 17:2). In order to prevent rapid reaction of phosphate fertilizers with the soil, these materials are commonly placed in localized bands. In addition, phosphatic fertilizers are quite often pelleted or aggregated to retard still more their contact with the soil. The effective utilization of phosphorus in combination with animal manures is evidence of the importance of organic matter in increasing the availability of this element.

In spite of these precautions, a major portion of the added phosphates still reverts to less available forms (see Fig. 17:8). It should be remembered, however, that the reverted phosphorus is not lost from the soil and through the years undoubtedly is slowly available to growing plants. This becomes an important factor, especially in soils which have been heavily phosphated for years.

In summary, maintaining sufficient available phosphorus in a soil largely narrows down to a twofold program: (a) the addition of phosphorus-containing fertilizers, and (b) the regulation in some degree of the fixation in the soil of both the added and the native phosphates.

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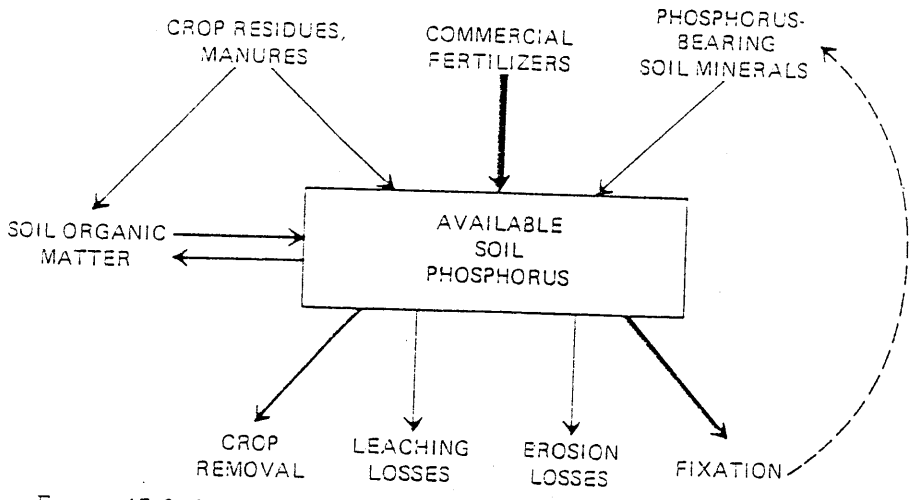

FIGURE 17:8. How the available phosphorus level in a soil is depleted and replenished. Note that the two main features are the addition of phosphate fertilizers and the fixation of this element in insoluble forms. It should be remembered that the amount of available phosphorus in the soil at any one time is relatively small, especially when compared to that of calcium, magnesium, and potassium.

17:15. POTASSIUM—THE THIRD "FERTILIZER" ELEMENT

The history of fertilizer usage in the United States shows that nitrogen and phosphorus received most of the attention when commercial fertilizers first appeared on the market. Although the role played by potassium in plant nutrition has long been known, the importance of potash fertilization has received full recognition only in comparatively recent years.

The reasons that a widespread deficiency of this element did not develop earlier are at least twofold. First, the supply of available potassium originally was so high in most soils that it took many years of cropping for a serious depletion to appear. Second, even though the potassium in certain soils may have been insufficient for optimum crop yields, production was much more drastically limited by a lack of nitrogen and phosphorus. With an increased usage of fertilizers carrying these latter elements, crop yields have been correspondingly increased. As a consequence, the drain on soil potassium has been greatly increased. This, coupled with considerable loss by leaching, has enhanced the demand for potassium in commercial fertilizers.

17:16. EFFECTS OF POTASSIUM ON PLANT GROWTH

The presence of adequate available potassium in the soil has much to do with the general tone and vigor of the plants grown. Moreover, by increasing

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TABLE 2:2. *Range in Micronutrient Content Commonly Found in Soils and a Suggested Analysis of a Representative Surface Soil*

Nutrient	Normal Range		Suggested Analysis of a Representative Surface Soil (ppm)
	Percent	ppm[a]	
Iron	0.500 –5.000	5,000–50,000	25,000
Manganese	0.020 –1.000	200–10,000	2,500
Zinc	0.001 –0.025	10– 250	100
Boron	0.0005 –0.015	5– 150	50
Copper	0.0005 –0.015	5– 150	50
Chlorine	0.001 –0.1	10– 1,000	50
Cobalt	0.0001 –0.005	1– 50	15
Molybdenum	0.00002–0.0005	0.2– 5	2

[a] ppm = parts per million. These estimates are based on published data from a number of sources, especially Mitchell (4).

The deficiencies of micronutrients discovered in many of our soils in recent years have highlighted the practical significance of these elements. Because macronutrient fertility problems are more widespread, however, they will be given our first attention. Micronutrients will be considered in more detail in Chapter 18.

FOUR NUTRIENT QUESTIONS. To arrive at a logical conclusion as to why nutrient deficiencies often occur in soils, four phases must be examined. They are (a) the macronutrient contents of mineral soils, (b) their forms of combination, (c) the processes by which these elements become available to plants, and (d) the soil solution and its pH. These phases will be considered in order.

2:5. MACRONUTRIENT CONTENTS OF MINERAL SOILS

The chemical composition for representative surface soils of humid temperate and arid temperate regions is given in Table 2:3. It should be noted that such figures do not fit any particular soil but present a very rough average of the data available for top soils of these two regions. These data suggest that soils of arid regions are in general higher in all of the important constituents except organic matter and nitrogen. An exception even to this is found in the black earth soils (Mollisols) of subhumid regions, which sometimes range as high as 16 percent of organic matter and 0.70 to 0.80 percent of nitrogen.

ORGANIC MATTER, NITROGEN, AND PHOSPHORUS. The percentage of organic matter exceeds that of any other constituent listed in Table 2:3. Yet its

TABLE 2:3. *Total Amounts of Organic Matter and Primary Nutrients Present in Temperate Region Mineral Surface Soils*[a]

Constituents	Ranges That Ordinarily May Be Expected (%)	Representative Analyses			
		Humid Region Soil		Arid Region Soil	
		Percent	lb/acre-furrow slice	Percent	lb/acre-furrow slice[b]
Organic matter	0.40–10.00	4.00	80,000	3.25	65,000
Nitrogen (N)	0.02– 0.50	0.15	3,000	0.12	2,400
Phosphorus (P)	0.01– 0.20	0.04	800	0.07	1,400
Potassium (K)	0.17– 3.30	1.70	34,000	2.00	40,000
Calcium (Ca)	0.07– 3.60	0.40	8,000	1.00	20,000
Magnesium (Mg)	0.12– 1.50	0.30	6,000	0.60	12,000
Sulfur (S)	0.01– 0.20	0.04	800	0.08	1,600

[a] As a supplement to the generalized figures of Table 2:3 the analyses of eight representative United States surface soils are presented as published by Marbut (3):

Constituents	Norfolk Fine Sand, Florida (%)	Sassafras Sandy Loam, Virginia (%)	Ontario Loam, New York (%)	Loam from Ely, Nevada (%)	Hagerstown Silt Loam, Tennessee (%)	Cascade Silt Loam, Oregon (%)	Marshall Silt Loam, Iowa (%)	Summit Clay from Kansas (%)
SiO_2	91.49	85.96	76.54	61.69	73.11	70.40	72.63	71.60
TiO_2	0.50	0.59	0.64	0.47	1.05	1.08	0.63	0.81
Fe_2O_3	1.75	1.74	3.43	3.87	6.12	3.90	3.14	3.56
Al_2O_3	4.51	6.26	9.38	13.77	8.30	13.14	12.03	11.45
MnO	0.007	0.04	0.08	0.12	0.44	0.07	0.10	0.06
CaO	0.01	0.40	0.80	5.48	0.37	1.78	0.79	0.97
MgO	0.02	0.36	0.75	2.60	0.45	0.97	0.82	0.86
K_2O	0.16	1.54	1.95	2.90	0.91	2.11	2.23	2.42
Na_2O	Trace	0.58	1.04	1.47	0.20	1.98	1.36	1.04
P_2O_5	0.05	0.02	0.10	0.18	0.16	0.16	0.12	0.09
SO_3	0.05	0.07	0.08	0.12	0.07	0.21	0.12	0.11
Nitrogen	0.02	0.02	0.16	0.10	0.27	0.08	0.17	0.09

[b] The furrow slice of a representative mineral soil is considered to contain approximately 2 million pounds of dry earth to the acre.

amount in most surface soils usually is critical. It is of prime importance in keeping the soil loose and open and is an essential source of several nutrient elements. The addition and subsequent decay of organic matter in the soil is thus highly significant both physically and chemically.

Nitrogen and phosphorus are almost always present in comparatively small amounts in mineral soils. Moreover, a large proportion of these elements at any one time is held in combinations unavailable to plants. For example, even the more simple compounds of phosphorus are relatively

insoluble in most soils. As a result, this element is doubly critical—low total amounts and very low availability to plants.

POTASSIUM, CALCIUM, AND MAGNESIUM. The total quantity of potassium, in marked contrast to phosphorus, is usually plentiful except in sandy soils. The main problem is one of availability. Calcium shows great variation but it is generally present in lesser amounts than is potassium. When it is lacking, soils tend to be acid. Calcium-containing limestones are generally added to correct this condition.

Magnesium, besides its importance as a nutrient, functions in the soil much as does calcium. Its deficiency in some soils has long been suspected. Until recently, however, it has not been considered especially critical because it is carried by most limestones, sometimes in large amounts. Where liming[1] is practiced, the lack of magnesium often is automatically rectified. In spite of this, magnesium deficiency is a major problem in many areas in the eastern United States.

SULFUR. Although it is usually no more plentiful than phosphorus, sulfur is more readily available. This is because its simple inorganic compounds are not rendered insoluble by reacting with certain other soil constituents as is the case with phosphorus. As already suggested, the addition of sulfur in farm manure, rain water, and fertilizers tends in an automatic way to relieve a possible deficiency in humid temperate regions. In certain areas of the west and south, however, specific additions of sulfur-containing compounds are required.

CRITICAL CONSTITUENTS. The above discussion seems to indicate that three constituents are likely to be critical in almost all mineral soils. Two—*organic matter* and *nitrogen*—merit particular attention because of the small amounts originally present and because of their ready loss through oxidation, leaching, or crop removal. The third, *phosphorus*, faces a double handicap as already explained—an exceptionally small amount present and a low availability to higher plants.

Under humid conditions *calcium* by all means must be included in the above list because it is sure to be much depleted by leaching. Consequently, it is needed not only as a nutrient but also as a means of controlling soil acidity. In arid regions, where the leaching of calcium usually is negligible, this nutrient is likely to be present in abundance, especially in the subsoil.

[1] Liming refers to the application to agricultural soils of basic calcium- and magnesium-containing materials with the objective of reducing soil acidity. Ground limestones are most commonly used, although burned lime (CaO) or slaked lime [$Ca(OH)_2$] are sometimes added. Collectively, these materials are referred to as *lime* and the practice of adding them as *liming* (see Chapter 15).

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17:2. Influence of Phosphorus on Plants

It is difficult to state in detail the functions of phosphorus in the economy of even the simplest plants. Only the more important functions will be considered here. Phosphorus makes its contribution through its favorable effect on the following:

1. Cell division and fat and albumin formation.
2. Flowering and fruiting, including seed formation.
3. Crop maturation, thus counteracting the effects of excess nitrogen applications.
4. Root development, particularly of the lateral and fibrous rootlets.
5. Strength of straw in cereal crops, thus helping to prevent lodging.
6. Crop quality, especially of forages and of vegetables.
7. Resistance to certain diseases.

17:3. The Phosphorus Problem

Although the amount of total phosphorus in an average mineral soil compares favorably with that of nitrogen, it is much lower than potassium, calcium, or magnesium (see Table 2:3). Of even greater importance, however, is the fact that most of the phosphorus present in soils is currently unavailable to plants. Also, when soluble sources of this element are supplied to soils in the form of fertilizers, their phosphorus is often "fixed" or rendered insoluble or unavailable to higher plants, even under the most ideal field conditions (see p. 465).

Fertilizer practices in many areas exemplify the problem of phosphorus availability. As already emphasized, the tonnage of phosphorus-supplying materials used as fertilizers definitely exceeds all except the nitrogen carriers. The removal of phosphorus from soils by crops, however, is low compared to that of nitrogen and potassium, often being only one third or one fourth that of the latter elements. The necessity for high fertilizer dosage when relatively small quantities of phosphorus are being removed from soils indicates that much of the added phosphates becomes unavailable to growing plants.

The influence of this situation on fertilizer practice is clearly shown when considering the additions of fertilizer phosphorus in comparison with crop removal.

In the United States, phosphorus added in fertilizers exceeds that removed by crops by more than 24 percent (see Table 17:1). In some areas, notably the eastern seaboard states, additions of phosphorus more than triple the removal of this element by crops. Since phosphorus is lost only sparingly by leaching, the inefficiency of utilization of phosphate fertilizers is obvious.

Briefly, then, the overall phosphorus problem is threefold: (a) a small total amount present in soils, (b) the unavailability of such native phosphorus, and (c) a marked "fixation" of added soluble phosphates. Since crop removal

of phosphorus is relatively low and world phosphate supplies are huge, problem (a), that of supplying sufficient total phosphorus, is not serious. Increasing the availability of native soil phosphorus and the retardation of fixation or reversion of added phosphates are, therefore, the problems of greatest importance. These two phases will be discussed following a brief review of the phosphorus compounds present in soils.

TABLE 17:1. *Nutrients Removed by Crops in the United States Compared to That Added in Fertilizers* (1965)[a]

	N	P	K
Removed in crops (thousands of tons)	8,838	1,207	4,152
Added in fertilizers (thousands of tons)	4,580	1,499	2,313
Addition as percent of removal	52	124	56

[a] Nutrient removal figures calculated from White (25). Fertilizer additions from Tennessee Valley Authority (23).

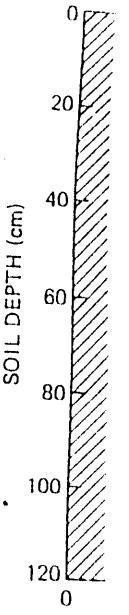
17:4. PHOSPHORUS COMPOUNDS IN SOILS[1]

Both inorganic and organic forms of phosphorus occur in soils and both are important to plants as sources of this element. There is a serious lack of information, however, on the relative amounts of these two forms in different soils. Data available from Oregon, Iowa, and Arizona (Table 17:2) give some idea of their relative proportions. Despite the variation which occurs, it is evident that a consideration of soil phosphorus would not be complete unless some attention were given to both forms (see Fig. 17:1).

INORGANIC COMPOUNDS. Most inorganic phosphorus compounds in soils fall into one of two groups: (a) those containing *calcium*, and (b) those containing *iron* and *aluminum*. The calcium compounds of most importance are listed in Table 17:3. Fluorapatite, the most insoluble and unavailable of the group, usually is an original mineral. It is found in even the more weathered soils, especially in their lower horizons. This fact is an indication of the extreme insolubility and consequent unavailability of the phosphorus contained therein. The simpler compounds of calcium, such as mono and dicalcium phosphate, are readily available for plant growth. Except on recently fertilized soils, however, these compounds are present in extremely small quantities only since they easily revert to the more insoluble forms.

Much less is known of the exact constitution of the iron and aluminum phosphates contained in soils. The compounds involved are probably hydroxy phosphates such as dufrenite, wavellite, strengite, and variscite (10). These compounds are most stable in acid soils and are extremely insoluble.

[1] For a review of soil phosphorus, see Larsen (17).



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[a] Figures for Oregon fr
for Arizona from Full

plants is obtained when the soil pH is maintained in the range from 6.0 to 7.0 (see Fig. 17:3). Even in this range, however, the fact should be emphasized that phosphate availability may still be very low and that added soluble phosphates are readily fixed by soils. The low recovery (perhaps 10 to 30 percent) by plants of added phosphates in a given season is partially due to this fixation.

17:10. Availability and Surface Area of Phosphates

When soluble phosphates are added to soils two kinds of compounds form immediately: (a) fresh precipitates of calcium, or iron and aluminum phosphates; and (b) similar compounds formed on the surfaces of either calcium carbonate or iron and aluminum oxide particles. In each case, the total surface area of the phosphate is high, and consequently the availability of the phosphorus contained therein is reasonably rapid. Thus, even though the water-soluble phosphorus in superphosphate may be precipitated in the soil in a matter of a few days, the freshly precipitated compounds will release much of their phosphorus to growing plants.

EFFECTS OF AGING. With time, changes take place in the reaction products of soluble phosphates and soils. These changes generally result in a reduction in surface area of the phosphates and a similar reduction in their availability. An increase in the crystal size of precipitated phosphates occurs in time. This decreases their surface area. Also, there is a penetration of the phosphorus held by calcium carbonate and iron or aluminum oxide particles into the particle itself (see Fig. 17:5). This leaves less of the phosphorus near the surface where it can be made available to growing plants. By these

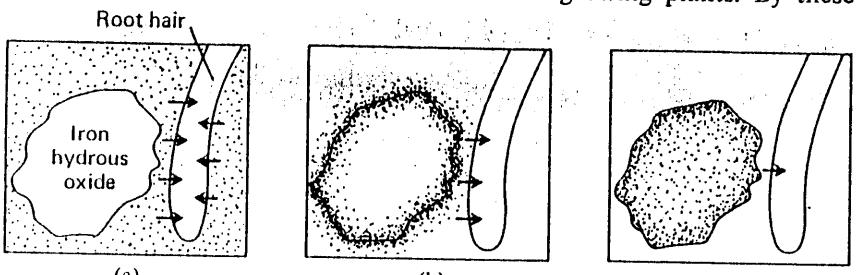

FIGURE 17:5. How relatively soluble phosphates are rendered unavailable by compounds such as hydrous oxide. (a) The situation just after application of a soluble phosphate. The root hair and the hydrous iron oxide particle are surrounded by soluble phosphates. Within a very short time (b) most of the soluble phosphate has reacted with the surface of the iron oxide crystal. The phosphorus is still fairly readily available to the plant roots since most of it is located at the surface of the particle where exudates from the plant can encourage exchange. In time (c) the phosphorus penetrates the crystal and only a small portion is found near the surface. Under these conditions its availability is low.

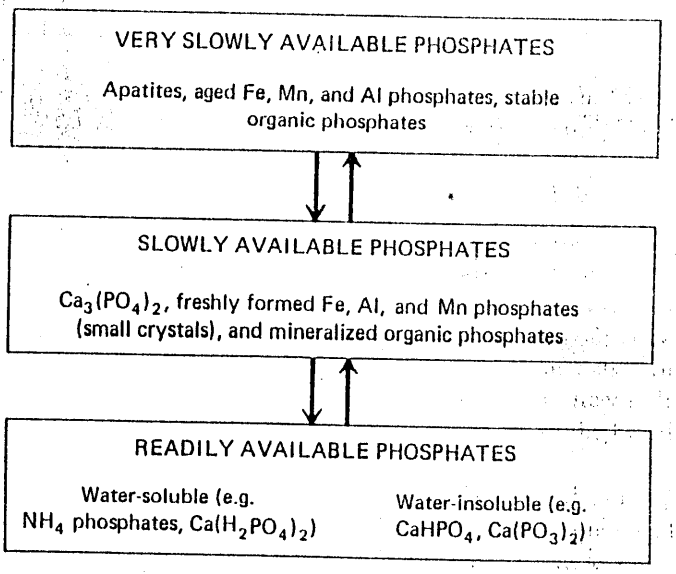

FIGURE 17:6. Classification of phosphate compounds in three major groups. Fertilizer phosphates are generally in the "readily available phosphate" group but are quickly converted to the slowly available forms. These can be utilized by plants at first but upon aging are rendered less available and are then classed as very slowly available. At any one time perhaps 80–90 percent of the soil phosphorus is in "very slowly available" forms. Most of the remainder is in the slowly available form since perhaps less than 1 percent would be expected to be readily available.

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17:11. PHOSPHORUS-FIXING POWER OF SOILS

In light of the above discussion it is interesting to note the actual quantity of phosphorus which soils are capable of fixing. Data from three New Jersey soils presented in Table 17:4 emphasize the tremendous power of certain soils in this respect. For example, to satisfy the phosphorus-fixing power of the unlimed Collington soil, nearly 47 tons of superphosphate containing 20 percent P_2O_5 would be required. Although liming definitely reduced the fixing capacity, the quantity of phosphorus fixed even on the limed soils is enormous. Thus, over 25 tons of superphosphate would be required to completely satisfy the phosphorus-fixing power of the limed Collington soil.

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Reference b
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TABLE 17:4. *Phosphorus-Adsorbing Power of Three New Jersey Soils Limed and Unlimed*[a]

Expressed as pounds of 20 percent superphosphate per acre-furrow slice

Soil	Treatment	pH	Phosphorus Fixing Power (lb 20% super/A.F.S.)
Sassafras	No lime	3.6	28,400
Sassafras	Lime	6.5	13,916
Collington	No lime	3.2	93,720
Collington	Lime	6.5	50,268
Dutchess	No lime	3.8	68,728
Dutchess	Lime	6.5	44,020

[a] From Toth and Bear (24).

17:12. INFLUENCE OF SOIL ORGANISMS AND ORGANIC MATTER ON THE AVAILABILITY OF INORGANIC PHOSPHORUS

In addition to pH and related factors, organic matter and microorganisms strikingly affect inorganic phosphorus availability. Just as was the case with nitrogen, the rapid decomposition of organic matter and consequent high microbial population results in the *temporary* tying up of inorganic phosphates in microbial tissue.

Products of organic decay such as organic acids and humus are thought to be effective in forming complexes with iron and aluminum compounds. This engagement of iron and aluminum reduces inorganic phosphate fixation to a remarkable degree. The exact importance of this effect has not as yet been completely ascertained. The ability of humus and lignin to reduce phosphate fixation, however, is shown in Fig. 17:7. Both materials were effective in releasing phosphorus after it had been fixed as basic iron phosphate. Thus, organic decomposition products undoubtedly play an important role in organic phosphorus availability.

17:13. AVAILABILITY OF ORGANIC PHOSPHORUS

Only meager information has been obtained on the factors affecting the availability to higher plants or organic phosphorus compounds. It has been established that both *phytin* and *nucleic acids* can be utilized as sources of phosphorus (20). Apparently the phytin is absorbed directly by the plants while the nucleic acids probably are broken down by enzymes at the root surfaces and the phosphorus is adsorbed in either the organic or inorganic form. In spite of the readiness with which these compounds may be assimilated, however, plants commonly suffer from a phosphorus deficiency even in the presence of considerable quantities of organic forms of this element. Just as with inorganic phosphates, the problem is one of availability.

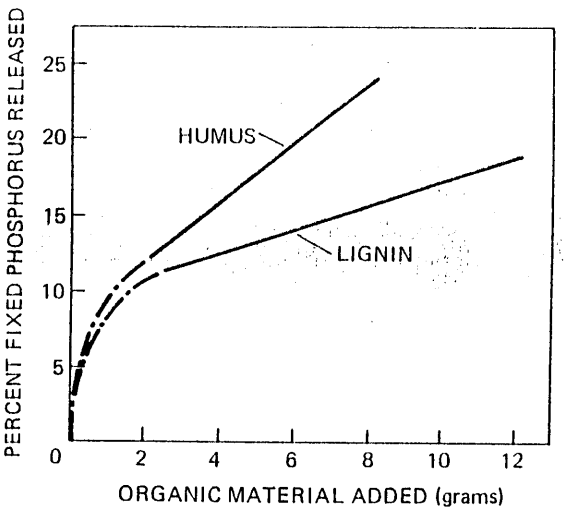

FIGURE 17:7. Effect of added organic materials on the release of phosphorus previously fixed by iron compounds. Both humus and lignin are effective, the humus to the greater degree. These results suggest that mineral fixation of phosphorus may be lower in soils comparatively high in organic matter. [*After Swenson et al.* (22).]

Phytin behaves in the soil much as do the inorganic phosphates (8), forming iron, aluminum, and calcium phytates. In acid soils the phytin is rendered insoluble and thus unavailable because of reaction with iron and aluminum. Under alkaline conditions calcium phytate is precipitated and the phosphorus carried is rendered unavailable.

The fixation of nucleic acids involves an entirely different mechanism, but the end result—low phosphorus availability—is the same. Evidently, nucleic acids are strongly adsorbed by clays, especially montmorillonite.

This adsorption is particularly pronounced under acid conditions and results in a marked decrease in the rate of decomposition of the nucleic acids. Consequently, the available phosphorus supply from this source is low, especially in acid soils which contain appreciable amounts of montmorillonite.

The judicious application of lime to acid soils is thus fully as important in organic phosphorus nutrition as it is in rendering inorganic compounds available. Whether we are dealing with inorganic soil phosphates, added fertilizers, or organic materials, the importance of lime as a controlling factor in phosphate availability is clearly evident.

17:14. PRACTICAL CONTROL OF PHOSPHORUS AVAILABILITY

From a practical standpoint, the phosphorus-utilization picture is not too encouraging. The inefficient utilization of applied phosphates by plants

Reference b
Page 19 of 19

Sec. 17:14 CONTRO. OF

has long been known th
materials has emphasized
fertilizers containing trace
the proportion of the app
application.

The results of experimen
in Table 17:5. Even though
from the addition of nos
utilization was very low A
by supplying much more p
season.

TABLE 17:5. *Recovery of App*

Soil	
Bladen	
Bladen	
Bladen	
Webster	
Clarion	

[a] Data for bladen soil from Kruz. et

LIMING AND PLACEMENT

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or aggregated to retar stil
utilization of phosphorus i
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element.

In spite of these precaut
still reverts to less available
however, that the reverted p
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an important factor, especia
for years.

In summary, maintaining
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containing fertilizers, nd (
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

AUG 13 1997

MEMORANDUM

SUBJECT: Consideration of Registration of an end-use product (NEU 1165M Slug and Snail Bait, EPA File Symbol 67702-G) containing the new active ingredient, iron phosphate - - **DECISION MEMORANDUM**

FROM: Janet L. Andersen, Ph.D., Director
Biopesticides and Pollution Prevention Division

TO: Daniel M. Barolo, Director
Office of Pesticide Programs

ISSUE

Should the Agency grant registration under FIFRA § 3(c)(5) for the end-use product, NEU 1165M Slug and Snail Bait (EPA file symbol No. 067702-G) containing the new biochemical-like pesticide active ingredient, iron phosphate (PC Code 34903) at a concentration of 1%, for use on terrestrial, noncommercial food crops (vegetables, berries, and fruit trees, including citrus), domestic outdoor ornamental, lawn and garden use, and noncommercial greenhouses for control of slugs and snails?

CONCLUSION

Data requirements for granting this registration under Section 3(c)(5) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) have been fulfilled. Available and submitted data have been reviewed and the Biopesticides and Pollution Prevention Division (BPPD) has made a determination of reasonable certainty of no harm to humans, especially infants and children, and the environment from the use of this active ingredient. BPPD recommends unconditional registration.

BASIS FOR CONCLUSION

A. DATA GAPS

There are no data gaps.

B. SUMMARY OF FINDINGS

(1) Product Identity

NEU 1165M Slug and Snail Bait (EPA File Symbol No. 067702-G) is the first product containing the active ingredient iron phosphate (PC Code 34903). The product contains the active ingredient at a concentration of 1% incorporated into a solid matrix, which is odorless and has a white-to-buff color, and noodle-like appearance.

(2) Use Sites/Usage

The proposed end-use involves spreading the bait granules on the soil around or near the plants to be protected, at a rate of approximately 1 lb. per 1,000 square feet (0.15 oz., or 1 level teaspoon per square yard). The bait should be scattered on the soil around the perimeter of garden plots, at the base of the plants, and between rows where slugs and snails are a problem. The product may be reapplied as it is consumed or at least every two weeks. The soil should be moist before application.

(3) Human Health Risk Assessment

(a) Toxicological Endpoints

No toxicological endpoints are identified.

(b) Human Exposure

All data requirements have been fulfilled for the active ingredient. The toxicity of iron salts is low; doses < 20 mg/kg (computed as elemental iron) are considered nontoxic. Mild to moderate iron toxicity is seen with doses of 20-60 mg/kg, and severe iron toxicity and death are associated with doses of 200-300 mg/kg. Iron phosphate occurs naturally as a mineral, and is added to food, such as bread, for nutritional fortification. Iron is an essential nutrient for humans and all other vertebrates; the average human diet contains 10-15 mg of iron a day.

The submitted acute toxicity studies indicate Toxicity Category III for NEU 1165M Slug and Snail Bait for eye irritation potential. The acute oral toxicity, dermal, and dermal irritation studies for NEW 1165M Slug and Snail Bait

classified the product as Toxicity Category IV. Acute inhalation, dermal sensitization, genotoxicity, immunotoxicity, developmental toxicity and 90-day oral toxicity studies were waived because of its GRAS status, the abundance of iron in nature, its low toxicity, its use as a nutritional supplement, and its low water-solubility, which would decrease its absorption across the intestinal epithelium. Further, the nature of the inert ingredients is such that Toxicity Category IV can be assumed.

(c) Risk Assessment

BPPD has considered iron phosphate in light of the nine safety factors listed in the Food Quality Protection Act (FQPA), and has made a determination of reasonable certainty of no harm. In short, BPPD has not identified any subchronic, chronic, immune, endocrine, or nondietary cumulative exposure issues as they may affect infants and children and the general population.

(4) Ecological Risk Assessment

(a) Ecological Toxicity Endpoints

No unreasonable adverse ecological or environmental fate effects on avian, aquatic or other nontarget organisms were identified.

(b) Ecological Exposure

Iron is one of the earth's most abundant elements, and it is immobilized at the pH range of 5-9. Runoff to aquatic systems is unlikely, since the parent compounds convert very rapidly to less soluble forms in the environment, and bind tightly to the soil under the turf. Iron phosphate is insoluble in water; therefore, exposure to aquatic species should be relatively low.

Due to the composition of the end-use product (pasta noodle-like consistency and appearance) and its use pattern, there should be no significant honey bee exposure. There will likely be exposure to ground-feeding nontarget insects and earthworms. Submitted studies involving ground beetles, rove beetles and earthworms demonstrate that the product will not affect these organisms at up to twice the maximum application rate.

Because of its insolubility in water and the known lack of toxicity to birds and data submitted that demonstrated a lack of toxicity to nontarget insects and earthworms, waiver requests were approved for the acute avian dietary, freshwater fish, and freshwater invertebrates studies. A waiver was granted for honeybees

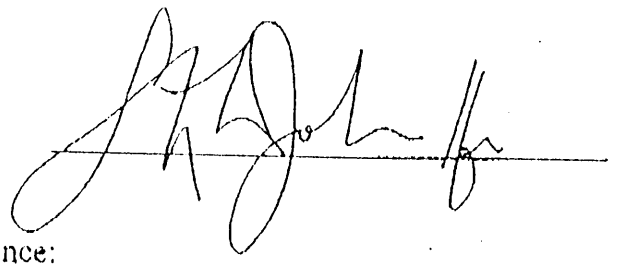
based on the lack of significant exposure due to the composition of the product and its use pattern.

(c) Risk Assessment

No unreasonable adverse ecological or environmental fate effects were identified.

OFFICE DIRECTOR CONCURRENCE

The Biopesticides and Pollution Prevention Division (BPPD) recommends that the pesticide end-use product, NEU 1165M Slug and Snail Bait, containing the new active ingredient, iron phosphate (PC Code 34903), be unconditionally registered under 3(c)(5) of FIFRA for the specified terrestrial, noncommercial food crops (vegetables, berries, fruit trees, including citrus), domestic outdoor ornamental, lawn and garden use, and noncommercial greenhouses for the control of slugs and snails.

Concurrence: 

Non Concurrence: _____

Date: 8/13/97

Iron Phosphate
(PC Code 34903)

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I. Executive Summary

A. IDENTITY

NEU 1165M Slug and Snail Bait (EPA File Symbol No. 67702-G) is the first product containing the active ingredient iron phosphate (PC Code 34903). The product contains the active ingredient at a concentration of 1% incorporated into a solid matrix, which is odorless and has a white-to-buff color, and noodle-like appearance.

B. USE/USAGE

The end-use involves spreading the bait granules on the soil around or near the plants to be protected, at a rate of approximately 1 lb. per 1,000 square feet (0.15 oz., or 1 level teaspoon per square yard). The bait should be scattered on the soil around the perimeter of domestic or non-commercial garden plots, at the base of the plants and between rows where slugs and snails are a problem. The product may be reapplied as it is consumed or at least every two weeks. The soil should be moist before application.

C. RISK ASSESSMENT

There is a reasonable certainty that no harm will result from aggregate exposure to NEU 1165M Slug and Snail Bait. This includes all anticipated dietary exposures and all other exposures for which there is reliable information.

1. Human Health Risk Assessment

a. Toxicological Endpoints

No toxicological endpoints are identified.

b. Human Exposure

All data requirements have been fulfilled for the active ingredient. The toxicity of iron salts is low; doses < 20 mg/kg (computed as elemental iron) are considered nontoxic. Mild to moderate iron toxicity is seen with doses of 20-60 mg/kg, and severe iron toxicity and death are associated with doses of 200-300 mg/kg. Iron phosphate occurs naturally as a mineral, and is added to food, such as bread, for nutritional fortification. Iron is an essential nutrient for humans and all other vertebrates; the average human diet contains 10-15 mg of iron a day.

The submitted acute toxicity studies indicate Toxicity Category III for NEU 1165M Slug and Snail Bait for eye irritation potential. The acute oral toxicity,

dermal, and dermal irritation studies for NEU 1165M Slug and Snail Bait classified the product as Toxicity Category IV. Acute inhalation, dermal sensitization, genotoxicity, immunotoxicity, developmental toxicity and 90-day oral toxicity studies were waived because of its GRAS status, the abundance of iron in nature, its low toxicity, its use as a nutritional supplement, and its low water-solubility, which would decrease its absorption across the intestinal epithelium. Further, the nature of the inert ingredients is such that Toxicity Category IV can be assumed.

c. Risk Assessment

We have considered iron phosphate in light of the nine safety factors listed in the Food Quality Protection Act (FQPA) and have made a determination of reasonable certainty of no harm. In short, BPPD has not identified any subchronic, chronic, immune, endocrine, or nondietary cumulative exposure issues as they may affect infants and children and the general population.

2. Ecological Risk Assessment

a. Ecological Toxicity Endpoints

No unreasonable adverse ecological or environmental fate effects on avian, aquatic or other nontarget organisms were identified.

b. Ecological Exposure

Iron is one of the earth's most abundant elements, and it is immobilized at the pH range of 5-9. Runoff to aquatic systems is unlikely, since the parent compounds convert very rapidly to less soluble forms in the environment. Iron phosphate is insoluble in water, and therefore, exposure to aquatic species should be relatively low. Furthermore, the oxidized iron compounds bind tightly to soil under turf.

Due to the composition of the end-use product and its use pattern, there should be no significant honey bee exposure. There will likely be exposure to ground-feeding nontarget insects and earthworms. Submitted studies involving ground beetles, rove beetles and earthworms demonstrate that the product will not affect these organisms at up to two times the maximum application rate.

Because of its insolubility in water and the known lack of toxicity to birds and data submitted that demonstrated a lack of toxicity to nontarget insects and earthworms, waiver requests were approved for the acute avian dietary, freshwater fish, and freshwater invertebrates studies. A waiver was granted

for honeybees based on the lack of significant exposure due to the composition of the product and its use pattern.

c. Risk Assessment

No unreasonable adverse ecological or environmental fate effects were identified.

D. DATA GAPS / LABELING RESTRICTIONS

There are no data gaps.

A. ACTIVE INGREDIENT OVERVIEW

Common Name: iron phosphate ($FePO_4 \cdot 2H_2O$)

Trade and Other Names: NEU 1165M Slug and Snail Bait, iron orthophosphate, iron phosphate

CAS Registry Number: 10045-86-0

OPP Chemical Code: 34903

Basic Manufacturer: W. Neudorff GmbH KG
An der Muhle 3
D-31860 Emmerthal, Germany

B. USE PROFILE

The following is information on the proposed uses with an overview of use sites and application methods.

Type of Pesticide: Molluscicide

Use Sites: Terrestrial, noncommercial food crops (vegetables, berries, fruit trees, including citrus), domestic outdoor ornamental, lawn and garden use, and noncommercial greenhouses.

Target Pests: Slugs and snails.

Formulation Type : Bait/granular formulation

Method and Rates of Application: The slug bait granules should be scattered on the soil around or near the plants to be protected. Bait should be applied evenly at a rate of 1 lb. per 1,000 square feet (0.15 oz., or about 1 level teaspoon per square yard), and reapplied as the bait is consumed or at least every two weeks, or when the area is heavily watered or after periods of heavy rain.

All areas of infestation should be treated, especially the perimeter of garden plots, flower gardens, rockeries, hedges, dichondra lawns, citrus groves, ivy patches, and other ground cover.

For vegetables and berries, the bait should be scattered around the perimeter of the plot at approximately 1 lb. per 1,000 square feet, and if slugs or snails are inside the

rows, then the bait should be scattered on the soil around the base of the plants and between the rows.

For non-commercial fruit tree seedlings and ornamentals, the bait should be applied at 0.15 oz., or 1 level teaspoon, per square yard, in a six-inch circular band around the base of the plants to be protected. For older trees, the bait should be spread around the base of the tree at approximately 1 lb. per 1,000 square feet.

For non-commercial greenhouse use, the bait is applied at the rate of 1/2 teaspoon per 9 inch pot.

For domestic lawns, the bait is applied at approximately 1 lb. per 1,000 square feet.

Type of Treatment: Granular

Equipment: By hand or with a granular spreader.

Timing: Evening is the best time of day to apply the bait, as slugs and snails travel and feed mostly by night or early morning.

Use Practice Limitations: NEU 1165M Slug and Snail Bait should be applied to moist soil, but with little or no standing water.

C. ESTIMATED USAGE

Yet to be used since these will be the first registered products.

D. DATA REQUIREMENTS

For NEU 1165M Slug and Snail Bait, the mammalian toxicology data requirements for the technical product have been fulfilled. Product analysis data requirements are adequately satisfied. All ecological effects data requirements for NEU 1165M Slug and Snail Bait have been adequately fulfilled. The data requirements for granting this registration under Section 3(c)(5) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) have been reviewed by the Biopesticides and Pollution Prevention Division (BPPD). Based on available information, the Agency foresees no unreasonable adverse effects to human health and the environment from the use of this chemical and recommends an unconditional registration of NEU 1165M Slug and Snail Bait, containing the new active ingredient, iron phosphate, for the proposed uses.

Safety factors from the Food Quality Protection Act of 1996 (FQPA) were considered. Given the low toxicity of iron phosphate, its ubiquity in the environment, and a history of safe use of iron phosphate as a nutritional supplement and food additive, a determination of

reasonable certainty of no harm for the general population as well as subgroups including infants and children was made.

E. REGULATORY HISTORY

This action registers the first pesticide product using iron phosphate as the active ingredient. In June, 1996, the Agency received an application from W. Neudorff GmbH KG to register one end-use product containing iron phosphate as the active pesticidal ingredient. A notice of receipt of the application for registration of iron phosphate as a new active ingredient was published in the ***Federal Register*** (61 FR 3287) on January 22, 1997, with a 30-day comment period. No comments were received as a result of this publication.

The registrant did not initially submit a petition for an exemption from the requirement of tolerance, based on the argument that the use pattern and nature of the active ingredient would not fall within the terrestrial food-crop general use pattern. The product is not applied directly or indirectly to growing crops, only around crops, and the registrant argued that due to the physical and chemical properties of iron, residues of this product will not occur in crops. However, the Health Effects Division (R. W. Cook memo, October 4, 1996) determined that based upon the proposed uses, this product would be considered a "food use" pesticide product, and thus be subject to regulation under FFDCA and FIFRA, as amended. The suggestion was made that if the use of the bait was clearly limited to home gardens (i.e., crops which would not move in commerce), then the product would not be subject to the tolerance or exemption from tolerance requirements of FFDCA and FIFRA, as amended.

The registrant submitted an amendment (OPP identifier number 248352) on November 27, 1996, requesting removal of food uses from the label, thereby eliminating the need for a tolerance or an exemption from the requirement for a tolerance.

A petition for exemption from the requirement of tolerance (PP 7F4804) was received December 16, 1996, and a notice of filing of this petition was published in the *Federal Register* (62 FR 32331-32336) on June 13, 1997. The registrant has indicated they will request an amendment to add the agricultural uses to their label after the comment period for the notice of filing has expired on July 13, 1997, barring any comments or objections from the public concerning an exemption from the requirement of a tolerance for iron phosphate when used on growing crops.

F. FOOD CLEARANCES/TOLERANCES

The use of NEU 1165M Slug and Snail Bait is limited to home gardens, i.e., crops which would not move in commerce. Therefore, a tolerance establishment/exemption is not an issue for the proposed uses.

III. Science Assessment

A. PHYSICAL/CHEMICAL PROPERTIES ASSESSMENT

All product chemistry data requirements for NEU 1165M Slug and Snail Bait are satisfied.

1. Product Identity and Mode of Action

NEU 1165M Slug and Snail Bait (EPA File Symbol No. 067702-G) is the first pesticide product containing the active ingredient iron phosphate (PC Code 34903). The product contains the active ingredient at a concentration of 1% incorporated into a solid matrix, which is odorless and has a white-to-buff color, noodle-like appearance.

The bait is a strong attractant to slugs and snails, which consume the bait product. The iron phosphate accumulates in the calcium spherules of their digestive glands; this interferes with calcium metabolism, and in turn, disrupts feeding and mucus production. The slugs and snails will stop feeding, and death due to starvation will occur three-to-six days later.

2. Food Clearances/Tolerances

The use of NEU 1165M Slug and Snail Bait is limited to home gardens, i.e., crops which would be sold commercially. Therefore, a tolerance establishment/exemption is not an issue for the proposed uses.

Safety factors from FQPA were evaluated. BPPD has considered, among other relevant factors, available information concerning the aggregate exposure levels of consumers and major identifiable subgroups of consumers to the pesticide chemical residue and to other related substances. These considerations include exposure from nonoccupational sources. Given the low toxicity of iron phosphate, and a history of safe use of this and other iron salts, a determination of reasonable certainty of no harm for the general population as well as subgroups including infants and children was made.

3. Physical and Chemical Properties Assessment

Chemistry data that support the registration of NEU 1165M Slug and Snail Bait are summarized in tables 1 and 2, below. Boiling point, vapor pressure, pH, and octanol/water partition coefficient data requirements were waived, based on the general abundance in the environment of iron salts, their low toxicity, occurrence in the normal diet, use as a dietary food supplement, and GRAS status.

Table 1

Guideline		Classification	
151-17	Physical Properties	A	
63-2	Color	A	white to buff
63-3	Physical State	A	solid or dry powder
63-4	Odor	A	odorless
63-5	Melting Point	N/A	loses H_2O at > 140°C and degrades to Fe_2O_3
63-6	Boiling Point	Waived	
63-7	Density	A	2.87 MI 12: 4074
63-8	Solubility	N/A	insoluble
63-9	Vapor Pressure	Waived	does not volatilize
63-10	Dissociation Constant	N/A	does not dissolve in water
63-11	Octanol / Water Partition Coefficient	Waived	does not dissolve in water
63-12	pH (when ground and diluted)	N/A	not miscible with water
63-13	Stability	N/A	stable
63-14	Oxidizing or Reducing	N/A	
63-15	Flammability (Flashpoint)	N/A	
63-16	Explodability	N/A	
63-17	Storage Stability	A	no change after 1 year
63-18	Viscosity	N/A	
63-19	Miscibility	N/A	not an emulsifiable liquid
63-20	Corrosion Characteristics	N/A	
63-21	Dielectric Breakdown Voltage	N/A	for products used near electrical equipment

A= Acceptable N/A = Not Applicable, end use product in solid matrix

Table 2

Guideline	Study	Results	MRID #
151-10	Product Identity	The end-use product contains the a.i., $FePO_4$, in a solid, noodle-like material.	440706-01
151-11	Manufacturing Process	Using materials obtained from suppliers that are nonreacting, manufacturing is carried out batchwise in a mixer used to mix dry powders and water. The product is extruded to form short, noodle-like granules, which is stored in a nonreactive container or packaged for eventual distribution.	440706-01
151-12	Formation of Impurities	N/A. Essentially pure (99.9%) $FePO_4 \cdot 2H_20$; trace metals <100 ppm	440706-01
151-13	Analysis of Samples	Acceptable study	440427-01
151-15	Certification of Limits	Limits are acceptable	440427-01
151-16	Validation of Methods Analysis	Acceptable study	440427-01
151-17	Physical & Chemical Properties/Storage Stability	Storage: stable for 1 year, room temp. other properties (pH, etc.) in table above	440427-02

B. HUMAN HEALTH ASSESSMENT

Mammalian toxicology data have been submitted and adequately satisfy the requirements as set forth in 40 CFR 158.690 for biochemical pesticides for non-commercial food, non-food, domestic outdoor uses.

1. Toxicology Assessment

No toxicological endpoints are identified. All data requirements have been fulfilled for the active ingredient. Iron phosphate occurs naturally as a mineral, and is added to food, such as bread, for nutritional fortification. Iron is an essential nutrient for humans and all other vertebrates; the average human diet contains 10-15 mg of iron a day.

a. Acute Toxicity

The required acute mammalian toxicology studies or requests for waivers of data have been submitted. The submitted acute toxicity studies indicate Toxicity Category III for NEU 1165M Slug and Snail Bait for eye irritation potential. The acute oral toxicity, dermal, and dermal irritation studies for NEU 1165M Slug and Snail Bait classifed the product as Toxicity Category IV. Acute inhalation and dermal sensitization were waived because the abundance of iron and iron salts in nature, its low toxicity, its use as a nutritional supplement, and the low water-solubility of iron phosphate, which would decrease its absorption across the intestinal epithelium. Further, the nature of the inert ingredients is such that Toxicity Category IV can be assumed.

b. Subchronic and Chronic Tests

Immune response, teratogenicity, mutagenicity and subchronic oral toxicity were not required because of the abundance of iron in nature, its GRAS status, its low toxicity, its use as a nutritional supplement, and the low water-solubility of iron phosphate, which would limit its absorption across the intestinal epithelium. The following table summarizes the acute toxicity data submitted for NEU 1165M Slug and Snail Bait:

Table 3

Guideline	STUDY	RESULTS	MRID #
152-10	Acute Oral Toxicity	Toxicity Category IV	440427-04
152-11	Acute Dermal Toxicity	Toxicity Category IV	440427-05
152-12	Acute Inhalation	Waived	
152-13	Primary Eye Irritation	Toxicity Category III	440427-06
152-14	Primary Dermal Irritation	Toxicity Category IV	440427-07
152-15	Hypersensitivity	Waived	
	Literature Review- Iron Phosphate Toxicity	Acute toxicity of iron salts is low, and requires relatively large doses to induce effects. Initial symptoms include vomiting, hemorrhagic gastritis, and diarrhea. Hematemesis, perforation of the GI tract, lethargy, coma, convulsions, pulmonary edema, cyanosis, and/or vascular collapse may occur 12-24 hours later and death may result.	440578-01

c. Effects on the Immune and Endocrine Systems

The Agency is not requiring information on the endocrine effects of this biochemical pesticide at this time; Congress has allowed three years after August 3, 1996, for the Agency to implement a screening program with respect to endocrine effects. However, BPPD has considered, among other relevant factors, available information concerning whether iron phosphate may have an effect in humans similar to an effect produced by a naturally occurring estrogen or other endocrine effects. There is no known metabolite of iron phosphate that acts as an "endocrine disrupter" or an immunotoxicant. Therefore, no adverse effects to the endocrine or immune systems are known or expected.

2. Dietary Exposure and Risk Characterization

The proposed use pattern for NEU 1165M Slug and Snail Bait will result in dietary exposure with possible residues on food grown in the home garden setting. However, in the absence of any toxicological endpoints, risk from the consumption of treated commodities is not expected for both the general population and infants and children. Acute exposure could occur from the proposed outdoor use sites, but would be very low because of the low applications rates. The application rate is 1 lb. per 1,000 square feet, with no maximum number of applications. No residue data were required since the use is for terrestrial, non-commercial food crops (vegetables, berries, fruit trees, including citrus), domestic outdoor ornamentals, lawns, gardens, and non-commercial greenhouses.

3. Occupational, Residential, School and Daycare Exposure and Risk Characterization

a. Occupational Exposure and Risk Characterization

Based on the application methods listed on the product label, the potential for dermal and eye exposures for pesticide handlers exists. Because of the domestic, nonagricultural use of the product, worker exposure data (i.e., occupational exposure data) to the active ingredient is not required at this time. However, due to the primary eye irritation response (Toxicity Category III for NEU 1165M Slug and Snail Bait), the Agency is requiring appropriate Signal Word and Precautionary Statements as indicated in Section IV C, under Labeling Rationale. It is the Agency's position that these exposures and subsequent risks are negligible because: (1) the product labeling stipulated in Section IV C will adequately mitigate the risks to handlers of the product; and (2) the toxicity of iron phosphate is very low in humans and animals. The risks are expected to be minimal based on evaluations of submitted acute toxicity tests and the ubiquity in nature and low toxicity of iron salts.

b. Residential, School and Daycare Exposure and Risk Characterization

No indoor residential, school or daycare uses currently appear on the label. The use sites are terrestrial, non-commercial food crops (vegetables, berries, fruit trees, including citrus), domestic outdoor ornamentals, lawns, gardens, and non-commercial greenhouses. Nondietary exposure to these sites could occur where children are present, but the health risk is expected to be minimal to nonexistent based on evaluations of the submitted studies and the low toxicity of iron salts.

4. Drinking Water Exposure and Risk Characterization

Although the potential exists for a minimal amount of iron phosphate to enter ground water or other drinking water sources, phosphate has an extremely low solubility in

water. Thus, the amount would, in all probability, be undetectable or more than several orders of magnitude lower than those levels considered necessary for safety. Both percolation through soil and municipal treatment of drinking water would reduce the possibility of exposure to iron phosphate through drinking water. Therefore, the potential of significant transfer to drinking water is minimal to nonexistent.

5. Acute and Chronic Dietary Risks for Sensitive Subpopulations Particularly Infants and Children

A battery of acute toxicity/pathogenicity studies is considered sufficient by the Agency to perform a risk assessment for biochemical pesticides.

In considering health risk from iron phosphate, it is important to keep the ubiquitous nature of this mineral in mind. Despite decades of widespread use of iron as a nutritional supplement, there have been no confirmed reports of immediate or delayed allergic reactions with significant oral exposure.

6. Aggregate Exposure from Multiple Routes Including Oral, Dermal and Inhalation

Oral exposure would only occur if the product itself is eaten. Since the acute oral toxicity study demonstrated no adverse effects, it is the Agency's opinion that exposure by the oral route should not pose a significant threat to human health.

Since the acute dermal toxicity and acute dermal irritation study demonstrated no adverse effects, it is the Agency's opinion that exposure to the skin should not pose a risk to health.

Exposure by the inhalation route would be nonexistent, due to the formulation of the substance, being of a noodle-like consistency. In addition, iron phosphate is not volatile. In summary, the potential aggregate exposure, derived from oral, dermal and inhalation exposure should be minimal.

C. ENVIRONMENTAL ASSESSMENT

1. Ecological Effects Hazard Assessment

A number of ecological effects toxicology data requirements are waived based on the known lack of toxicity of iron phosphate to birds, fish and non-target insects, its low solubility in water, conversion to less soluble form in the environment (soil), and its use pattern (soil application). Based on these factors, the data requirements for the toxicity studies in Mallard duck, rainbow trout, freshwater invertebrates, and

nontarget insect/honeybees are waived. The table below summarizes results of the studies that were performed.

Table 4

Guideline	Study	Results	MRID #
154-6	Avian Acute Oral - Bobwhite quail	LD_{50} and NOEL>2000 mg/kg; practically nontoxic.	440427-08
154-11	Nontarget Insect - ground beetle	No effect up to 2 times the maximum application rate.	441716-01
154-11	Nontarget Insect - ground beetle	No effect up to 2 times the maximum application rate.	441716-02
154-11	Nontarget - Earthworms	No effect up to 2 times the maximum application rate.	441716-03

2. Environmental Fate and Ground Water Data

Exposure assessments on this type of product (biochemical pesticide) are not performed unless human health or ecological effects issues arise in the toxicity studies for either of these disciplines (40 CFR §158.740(d)(2)(vi)). Since no endpoints of concern were identified, there is no requirement for environmental fate data.

3. Ecological Exposure and Risk Characterization

Exposure to daphnids and other aquatic invertebrates would not occur based on current label use directions. Exposure to honeybees is also not expected to occur, due to the composition of the end-use product (noodle-like material) and its use pattern (soil application). Nontarget insects, such as ground beetles and earthworms, could encounter the end-use product; however, in tests of rove beetles, ground beetles and earthworms, no effects were observed at up to twice the maximum application rate. Thus, the acute risk to aquatic invertebrates, nontarget insects, and earthworms is considered minimal to nonexistent.

D. EFFICACY DATA

No efficacy data were required to be submitted to the Agency since no public health uses are involved.

IV. Risk Management Decision

A. DETERMINATION OF ELIGIBILITY FOR REGISTRATION

Section 3(c)(5) of FIFRA provides for the registration of new active ingredients if it is determined that (A) its composition is such as to warrant the proposed claims for it; (B) its labeling and other materials required to be submitted comply with the requirements of FIFRA; (C) it will perform its intended function without unreasonable adverse effects on the environment; and (D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment.

To satisfy criteria "A" above, iron phosphate is an effective biological molluscicide for the control of slubs and snails. Criteria "B" is satisfied by the current label and by the data presented in this document. It is believed that this new active ingredient will not cause any unreasonable adverse effects and does provide protection as claimed, satisfying Criteria "C". Criteria "D" is satisfied in that the toxicological properties of this product indicate that it is less toxic than other conventional pesticide products currently in use for this purpose.

Therefore, NEU 1165M Slug and Snail Bait is eligible for registration. The only uses are for terrestrial, non-commercial food crops (vegetables, berries, fruit trees, including citrus), domestic outdoor ornamentals, lawns, gardens, and non-commercial greenhouses. These are listed in Appendix A.

B. REGULATORY POSITION

1. Conditional/Unconditional Registration

All data requirements are fulfilled and the Biopesticides and Pollution Prevention Division recommends unconditional registration of NEU 1165M Slug and Snail Bait.

2. Tolerance Reassessment

There is no tolerance for the active ingredient, iron phosphate. A tolerance or exemption from tolerance is not applicable, due to the domestic, non-commercial uses of this product.

3. CODEX Harmonization

There is currently no Codex tolerance for iron phosphate or iron phosphate residues.

4. Non-food Registrations

There are no non-food issues at this time.

5. Risk Mitigation

Since there are no risk issues, no risk mitigation measures are required at this time for dietary risk, occupational and residential risk, risks to nontarget organisms (plants and wildlife), or ground and surface water contamination for this product.

6. Endangered Species Statement

Currently, the Agency is developing a program (Endangered Species Protection Program) to identify all pesticides whose use may cause potential adverse impacts on endangered and threatened species and their habitats. To aid in the identification of threatened and endangered species and their habitats, several companies have formed an Endangered Species Task Force (EST) under the direction of the American Crop Protection Association (ACPA). Moreover, the EST will assist in providing species location information at the subcounty level, and particularly if an endangered species occurs in areas where pesticides would be used. This information will be useful once the Endangered Species Protection Program has been implemented.

Prior to the implementation of the Endangered Species Protection Program, the Agency will not impose specific labeling on those pesticides that pose risks to threatened and endangered species and their habitats but will defer imposing specific labeling language until the implementation of the program.

C. LABELING RATIONALE

1. Human Health Hazard

a. Worker Protection Standard

This product does not fall under the Worker Protection Standard (WPS); therefore, there are no human health hazard labeling issues associated with the WPS.

b. Non-Worker Protection Standard

There are no non-WPS human health hazard issues.

c. Precautionary Labeling

The Agency has examined the toxicological data base for NEU 1165M Slug and Snail Bait, and concluded that the precautionary statements must be, "CAUTION. Causes moderate eye irritation. Avoid contact with eyes or clothing." Exposure is expected to be minimal since the label directs that personal protective equipment (long sleeved-shirt, and long pants, shoes plus socks, and protective eyewear) must be worn.

d. Spray Drift Advisory

A spray drift advisory statement is not needed on the labeling for the registered uses of NEU 1165M Slug and Snail Bait, due to the composition of the end-use product and its domestic, non-commercial use pattern.

2. Environmental Hazards Labeling

Provided the following statement is placed into the environmental hazards statement, the risk of iron phosphate is minimal to nonexistent to nontarget organisms including endangered species:

"Do not apply directly to water. Do not contaminate water when disposing of equipment washwaters or rinsate."

3. Application Rate

It is the Agency's position that the label for the pesticide products containing iron phosphate as the active ingredient complies with the current pesticide labeling requirements. The Agency has not required a maximum number of applications for the active ingredient.

D. LABELING

(1) Product name: **NEU 1165M Slug and Snail Bait**

Active Ingredient (by weight):

Iron Phosphate	1.0%
Inert Ingredients	99.9%
Total	100.0%

Signal word is "Caution," based on the eye irritation (toxicity category III). Use of an eye irritation statement is appropriate.

V. Actions Required by Registrants

Reporting adverse effects to humans or domestic animals under FIFRA, Section 6(a)2 and incidents of hypersensitivity are required under 40 CFR Part 158.690(c), guideline reference number 152-16.

VI. Appendix A

The following table lists the use sites for the product. The label for the product is also attached.

NEU 1165M Slug and Snail Bait Non-commercial Use Sites - domestic garden or non-commercial vegetables including but not limited to artichokes, asparagus, beans, beets, blackeyed peas, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, corn, cucumbers, eggplants, garlic, lettuce, onions, peas, peppers, potatoes, radishes, rutabagas, spinach, squash, Swiss chard, tomatoes and turnips; non-commercial fruit including (but not limited to): apples, avocados, apricots, cherries, grapes, melons, peaches, plums, citrus, pears; non-commercial berries including (but not limited to): strawberries, blackberries, blueberries, boysenberries, loganberries, raspberries; domestic or non-commercial outdoor ornamentals; domestic lawns; citrus groves; ivy patches and other ground cover; greenhouses.	Official Date: registered AUG 14 1997

NEU 1165M
SLUG AND SNAIL BAIT

Active Ingredient:	By weight
Iron phosphate	1.0%
Inert Ingredients:	99.0%
Total	100.0%

KEEP OUT OF REACH OF CHILDREN

CAUTION

NET WEIGHT 20 LBS

EPA registration #67702- **EPA establishment #67702-WG-1**

STATEMENT OF PRACTICAL TREATMENT
If in eyes: Flush eyes with plenty of water. Call a physician if irritation persists.

PRECAUTIONARY STATEMENTS
Hazards to Humans and Domestic Animals: Caution. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling.

Environmental Hazards: For terrestrial uses. Do not apply directly to water. Do not contaminate water when disposing of equipment washwaters or rinsate.

DIRECTIONS FOR USE
It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

The slugs and snails controlled by this product include (but are not limited to): *Deroceras reticulatum* (Field slug), *Deroceras laeve* (Smooth slug), *Arion subfuscus* (Dusky slug), *Arion circumscriptus* (Gray garden slug), *Arion hortensis* (Black field slug), *Arion rufus* (Large red slug), *Arion ater* (Large black slug), *Limax flavus* (Spotted garden slug), *Limax tenellus* (Slender slug), *Ariolimax columbianus* (Banana slug), *Helix* spp., spp., *Helicella* spp., and *Cepaea* spp.

Home And Garden

HOW TO APPLY: The slug and snail bait granules should be scattered on the soil around or near the plants to be protected in domestic garden plots. Apply bait evenly at approximately 1 lb. per 1000 square feet (0.15 oz., or about 1 level tablespoon, per square yard) and reapply as the bait is consumed or at least every two weeks. Do not place in piles. If the ground is dry, wet it before applying bait. The soil should be moist but with little or no standing water.

Reapply as the bait is consumed or at least every two weeks. Apply more heavily if the infestation is severe, if the area is heavily watered or after long periods of heavy rain. See specific directions for different plant types and for inside non-commercial greenhouses.

WHEN TO APPLY: Evening is the best time to apply the bait, as slugs and snails travel and feed mostly by night or early morning.

WHERE TO APPLY: All likely areas of infestation should be treated, especially around the perimeter of domestic garden plots because these pests travel into plant areas from daytime refuges. They favor damp places around vegetable plants such as beans, tomatoes, lettuce, cabbage, celery and squash. Other favorite areas are domestic flower gardens, rockeries, hedges, dichondra lawns, non-commercial citrus groves, ivy patches, and other ground cover where they obtain shelter by day.

Non-Commercial Vegetables

The bait can be used to protect any domestic garden (or non-commercial) vegetables from slug and snail damage, including (but not limited to): artichokes, asparagus, beans, beets, blackeyed peas, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, corn, cucumbers, eggplants, garlic, lettuce, onions, peas, peppers, potatoes, radishes, rutabagas, spinach, squash, Swiss chard, tomatoes and turnips. Scatter the bait around the perimeter of the vegetable plot at approximately 1 lb. per 1000 square feet to provide a protective "barrier" for slugs entering the garden plot. If slugs or snails are inside the rows, then scatter the bait on the soil around the base of the plants and between the rows.

Non-Commercial Fruits Including Citrus

The bait can be used to protect non-commercial fruits from slugs and snails, including (but not limited to): apples, avocados, apricots, cherries, grapes, melons, peaches, plums, citrus, pears. For seedlings spread the bait around the base of the stem: Apply at 0.15 oz., or 1 level tablespoon, per square yard, in a 6 inch circular band around the base of the plants to be protected. For older

trees, spread the bait around the base of the tree to intercept slugs and snails traveling to the trunk. Apply the bait at approximately 1 lb. per 1000 square feet and scatter by hand or with granular spreaders.

Non-Commercial Berries

The bait can be used to protect non-commercial berries from slugs and snails, including (but not limited to): strawberries, blackberries, blueberries, boysenberries, loganberries, raspberries. Spread the bait around the perimeter of the plot to intercept slugs and snails migrating toward the berries. Use a rate of approximately 1 lb. per 1000 square feet and scatter by hand or with granular spreaders. If slugs and snails are already in the plots, then carefully spread bait between the furrows near the base of the plants. For small plots, treat around the base of the plants to be protected. Do not spread over the entire area but apply selectively.

Domestic or Non-Commercial Outdoor Ornamentals

Scatter bait in a 6 inch circular band around the base of the plants to be protected at 0.15 oz., or 1 level tablespoon, per square yard. If plants are next to a grassy area, spread the bait between the ornamentals and the grass. Slugs traveling to the plants will encounter the bait before reaching the plant. Scatter the bait around the perimeter of the plot at approximately 1 lb. per 1000 square feet to intercept snails and slugs traveling to the plot.

Non-Commercial Greenhouses

Where snails are a problem in non-commercial greenhouses, scatter the bait in the plant pots of plants being damaged or around pots on greenhouse benches. Apply about ½ teaspoon per 9 inch pot.

Domestic Lawns

The bait can be used to protect lawns. When slugs or snails are detected, scatter the bait at a rate of approximately 1 lb. per 1000 square feet and scatter by hand or with a granular spreader where the slugs or snails are observed.

STORAGE AND DISPOSAL
Do not contaminate water, food or feed by storage or disposal.

PESTICIDE STORAGE: Store this product in its original container and keep in a secure storage area out of reach of children and domestic animals.

CONTAINER DISPOSAL: Do not reuse container. Securely wrap original container in several layers of newspaper and discard in trash.

WARRANTY

Seller warrants that this product conforms to the chemical description on this label and is reasonably fit for purposes stated on this label only when used in accordance with directions under normal use conditions. This warranty does not extend to use of this product contrary to label directions, or under abnormal use conditions, or under conditions not reasonably foreseeable to seller. Buyer assumes all risk of any such use. Seller makes no other warranties, either expressed or implied.

[The following claims and product information may be presented on the product's label or labeling:
-NOTE: This package is sold by weight. Contents may have settled during shipment.
-US Patent number 5,437,870.
-This container is made from XX% recycled materials.]

GENERAL INFORMATION (WHY SLUG AND SNAIL BAIT IS SO EFFECTIVE)

This product is a unique blend of an iron phosphate active ingredient, originating from soil, with slug and snail bait additives. It is used as an ingredient in fertilizers. The bait which is not ingested by snails and slugs will degrade and become part of the soil in your garden.

The bait is extremely (highly) attractive to slugs and snails and lures them from their hiding places and plants. Ingestion, even in small amounts, will cause them to cease feeding. This physiological effect of the bait gives immediate protection to the plants even though the slugs and snails may remain in the area. After eating the bait, the slugs and snails cease feeding, become less mobile and begin to die within three to six days. Dead slugs and snails may not be visible as they often crawl away to secluded places to die. Plant protection will be observed in the dramatic decrease in plant damage.

This product is effective against a wide variety of slugs and snails and will give protection to home lawns, gardens, greenhouses, outdoor ornamentals, vegetable gardens, fruits, berries, citrus and crop plants. The bait can be scattered on the lawn or on the soil around any vegetable plants, flowers or fruit trees or bushes to be protected.

Registrant: W. Neudorff GmbH KG, Postfach 1209, an der Mühle 3,
D-31860 Emmerthal, Germany

BIOLOGY, THIRD EDITION

Helena Curtis

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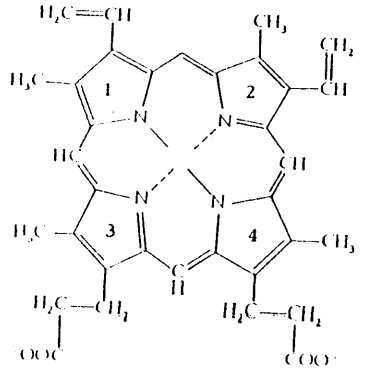
3-27
The heme group of hemoglobin. It contains an iron atom (Fe) held in a porphyrin ring. The porphyrin ring consists of four nitrogen containing rings, which are numbered in the diagram. Each heme group is attached to a long polypeptide chain that wraps around it. The oxygen molecule is held flat against the heme.



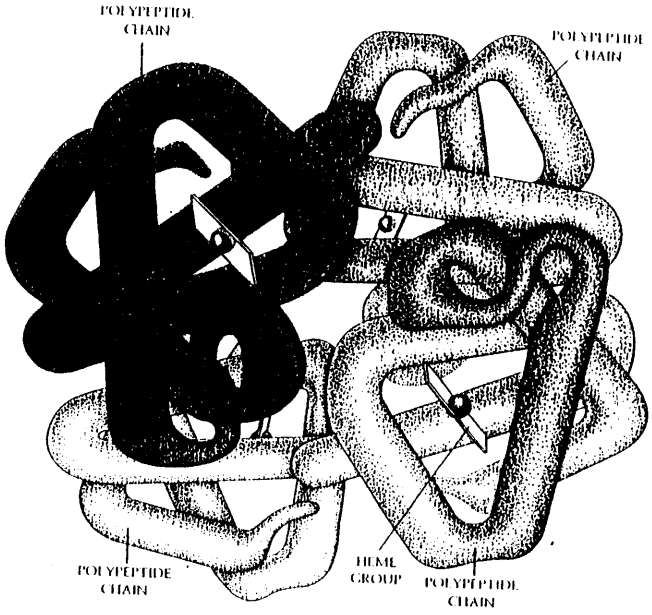
3-28
The hemoglobin molecule consists of four heme groups with their polypeptide chains intertwined in a quaternary structure. The outside of the molecule and the hole through the middle are lined by charged amino acids, and the uncharged amino acids are packed inside. Each molecule can hold up to four oxygen molecules. The sequence of the amino acids in each chain is its primary structure. The helical form assumed by any part of the chain as a consequence of hydrogen bonding between nearby C=O and NH groups is its secondary structure. The folding of the chains in three-dimensional shapes is the tertiary structure, and the combination of the four chains into a single functional molecule is the quaternary structure. (Adapted with permission from R. E. Dickerson and I. Geis, The Structure and Action of Proteins, W. A. Benjamin, Inc., Menlo Park, Calif., 1969. Copyright 1969 by Dickerson and Geis.)

Hemoglobin: An Example of Specificity

Fibrous proteins, like structural polysaccharides, are usually molecules with a relatively small variety of monomers in a repetitive sequence. Many proteins, by contrast, have extremely complex, irregular amino acid sequences, as complex and irregular as the sequence of letters in a sentence on this page. Just as these sentences make sense (if they do) because the letters are the right ones and in the right order, the proteins make sense, biologically speaking, because their amino acids are the right ones in the right order.

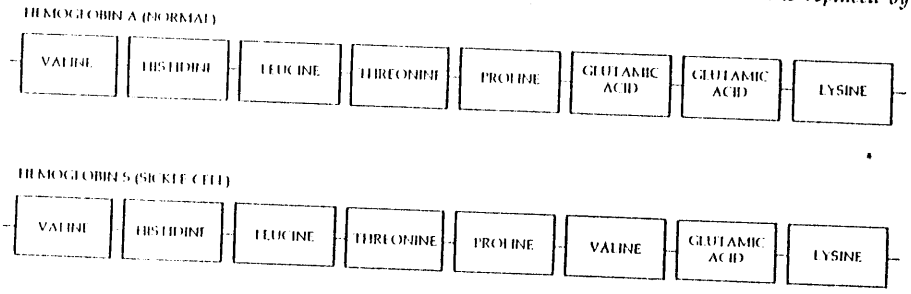
Hemoglobin, for example, has a quaternary structure that consists of four polypeptide chains, each of which is combined with an iron-containing molecule known as *heme*. In heme, an iron atom is held in the center of a ring of nitrogen-containing atoms known as a porphyrin ring (Figure 3-27). Hemoglobin has two identical alpha chains and two identical beta chains, each about 150 amino acids long, for a total of about 600 amino acids in all. In man, hemoglobin molecules are manufactured and carried in the red blood cells. A mature red blood cell contains about 265 million molecules of hemoglobin. These molecules possess the special property of being able to combine loosely with oxygen so that they can collect oxygen in the lungs and release it in the tissues.

Sickle cell anemia is a disease in which the hemoglobin molecules are defective. When oxygen is removed, the defective molecules change shape and combine with one another to form stiffened rodlike structures. Red cells containing large proportions of these molecules become stiff and deformed, taking on the characteristic sickle shape. The deformed cells may clog the smallest blood vessels (capillaries), cutting off the local blood supply and resulting in anemia. The disease is usually painful and often fatal.



3-29

An example of the remarkable precision of the "language" of proteins. Portions of the beta chains of the hemoglobin A (normal) molecule and the hemoglobin S (sickle cell) molecule are shown. The hemoglobin molecule is composed of two identical alpha chains and two identical beta chains, each chain consisting of about 150 amino acids, or a total of 600 amino acids in the molecule. The entire structural difference between the normal molecule and the sickle cell molecule (literally, a life-and-death difference) consists of one change in the sequence of each beta chain: One glutamic acid is replaced by one valine.



3-30

Scanning electron micrographs of (a) red blood cell containing normal hemoglobin, and (b) red blood cells containing the abnormal hemoglobin associated with sickle cell anemia. In these sickle cells, so called because of their shape, the hemoglobin molecules stick together.

(a)

(b)

Analysis of the hemoglobin molecules of patients with sickle cell anemia reveals that the only difference between normal and sickle cell hemoglobin is that in a precise location in each beta chain, one glutamic acid is replaced by one valine.

When one considers that this difference of two amino acids in a total of almost 600 is actually the difference between life and death, one begins to get an idea of the meaning of specificity and of the precision and the importance of the arrangement of amino acids in a precise sequence in a protein.

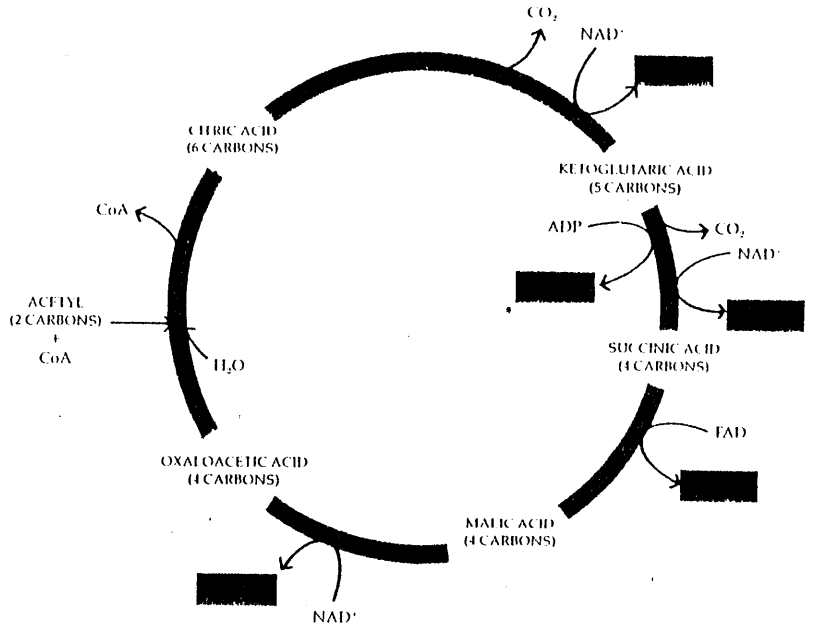
LEVELS OF ORGANIZATION

In the last three chapters we have progressed from a brief consideration of subatomic particles to an examination of large proteins, among the most complex of all molecules. Although the neutrons, protons, and electrons of which atoms are composed are all the same, the elements differ greatly from one another. Mercury is a heavy metallic liquid, chlorine is a green gas, sulfur is a yellow powder, pure carbon can take the form of a hard solid—a diamond—and so on. The differences lie not in the nature of the subatomic particles, but rather in their number and arrangement—in their organization.

And just as subatomic particles combine to form atoms, atoms, as we have seen, combine to form molecules. At each level of organization, new properties appear. Water, for instance, as we have seen, is not the sum of the properties of hydrogen and oxygen; it is something more and also something different. In a molecule such as hemoglobin, we see how amino acids, with their diverse properties, become organized into a polypeptide and how polypeptide chains combine in a new level of organization, the quaternary structure of the complete molecule. Only at this level of organization do the complex properties of the molecule emerge, and only then can the molecule assume its function.

Living systems, as we noted earlier, obey the laws of physics and chemistry. Are we then "nothing but" a collection of atoms and molcules? There are recognizable differences between "life" and "nonlife." What is the basis of these differences? According to biologists, the differences are to be found not in the atoms and molecules themselves, but in their organization.

8-10
Summary of the Krebs cycle. One molecule of ATP, three molecules of NADH, and one molecule of $FADH_2$ represent the energy yield of the cycle.



The Electron Transport Chain

The carbon atoms of the glucose molecule are now completely oxidized. Some of the energy of glucose has been used to produce ATP from ADP. Most of its energy, however, remains in electrons removed from the C—C and C—H bonds and passed to the electron carriers NAD^+ and FAD. These electrons are still at a high energy level.

In the final stage of the oxidation of glucose, these high-energy-level electrons are passed step-by-step to the low energy level of oxygen. The energy they yield in the course of this passage regenerates ATP from ADP. This step-by-step passage is made possible by a series of electron carriers, each of which holds the electrons at a slightly lower level.

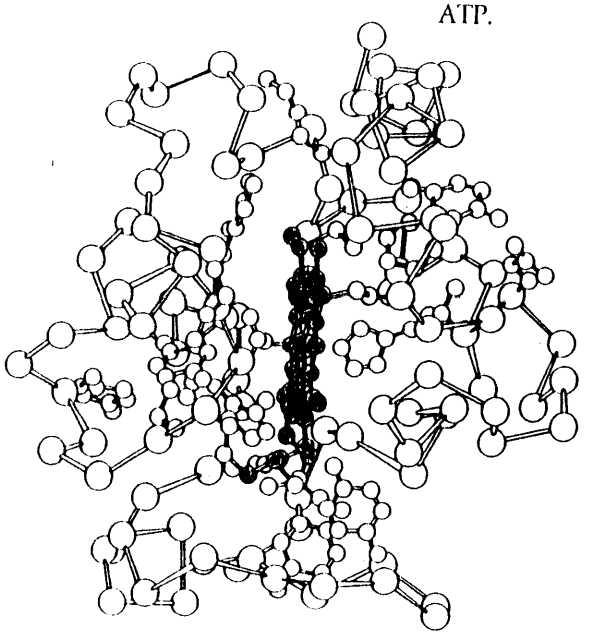
These carriers make up what is known as an *electron transport chain*. At the top of the energy hill the electrons are held by NADH and $FADH_2$. Most of the energy of the glucose molecule now resides in these electron acceptors. The Krebs cycle yielded two molecules of $FADH_2$ and six molecules of NADH for each molecule of glucose. The oxidation of pyruvic acid to acetyl CoA yielded two molecules of NADH. Also, you will recall, two molecules of NADH were produced in glycolysis. In the presence of oxygen, the electrons held by these two NADH molecules are also transported into the mitochondrion where they are accepted by FMN (flavin mononucleotide; see Figure 8-9) and fed into the electron transport chain.

The principal components of the electron transport chain are molecules known as cytochromes (Figure 8-11). These molecules consist of a porphyrin ring, similar to that of heme, enclosing an atom of iron. Each iron atom alternately accepts and

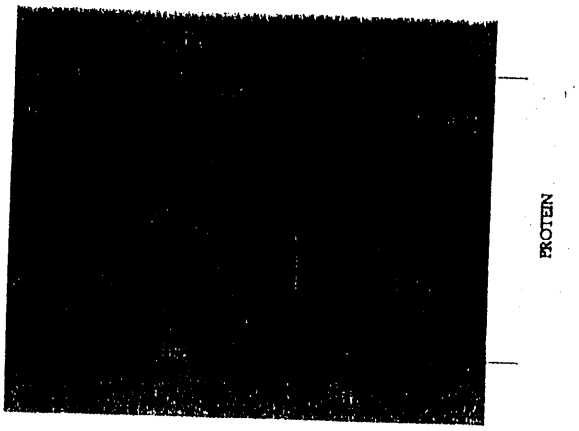
releases an electron, passing it along to the next cytochrome at a slightly lower energy level until the electrons, their energy spent, are accepted by oxygen. The energy released in this downhill passage of electrons is used to form ATP molecules from ADP. Such ATP formation is known as *oxidative phosphorylation.* At the end of the chain, the electrons are accepted by oxygen, which then combines with protons (hydrogen ions) from the solution to produce water. Calculations show that each time two electrons pass from NADH to oxygen, three molecules of ATP are formed from ADP and phosphate. Each time a pair of electrons passes from $FADH_2$, which holds them at a slightly lower energy level than NADH, two molecules of ATP are formed. In oxidative phosphorylation the electron transfer potential of NADH and $FADH_2$ is converted to the phosphate transfer potential of ATP.

8-11

(a) Cytochromes are molecules in which a heme group is held in an intricate protein structure. In the cytochrome c structure shown here, the heme group is in color. (b) The heme group of cytochrome c. In the cytochromes, an atom of iron (Fe) is held in a nitrogen-containing ring (a porphyrin ring). Cytochromes are involved in electron transfer. It is the iron within the molecule that actually combines with the electrons.



(a)



CYTOCHROME *c*

(b)

8-12

The electron transport chain. Flavin mononucleotide (FMN) and coenzyme Q transfer electrons and protons. The cytochromes transfer only electrons. The electrons carried by NADH enter the chain when they are transferred to FMN; those carried by $FADH_2$ enter the chain farther down the line at coenzyme Q. Each time two electrons from NADH pass down the chain, three molecules of ATP are formed from ADP; each time two electrons from $FADH_2$ pass down the chain, two molecules of ATP are formed.

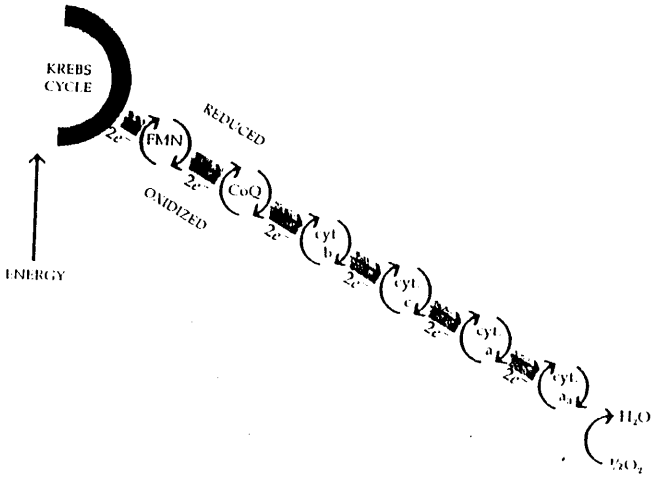
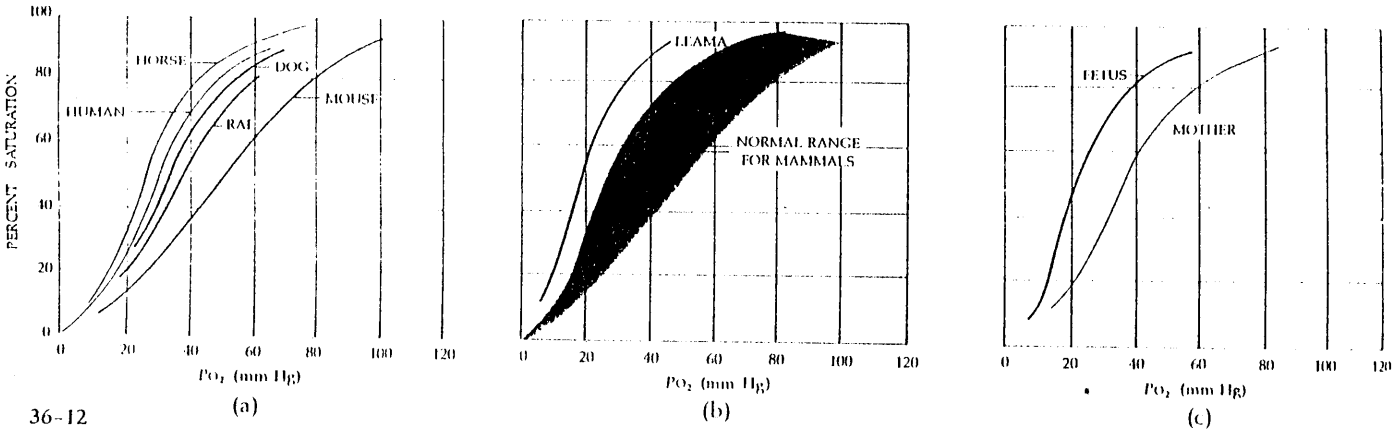


Table 29-1 *A Summary of Mineral Elements Required by Plants*

ELEMENT	FORM IN WHICH ABSORBED	APPROXIMATE CONCENTRATION IN WHOLE PLANT (AS % OF DRY WEIGHT)	SOME FUNCTIONS
Macronutrients			
Nitrogen	NO_3^- (or NH_4^+)	1–3%	Component of amino acids, proteins, nucleotides, nucleic acids, chlorophyll, and coenzymes.
Potassium	K^+	0.3–6%	Osmoregulation. Activator of many enzymes. Involved in opening and closing of stomata.
Calcium	Ca^{2+}	0.1–3.5%	Component of cell walls. Enzyme cofactor. Involved in cell membrane permeability.
Phosphorus	$H_2PO_4^-$ or HPO_4^{2-}	0.05–1.0%	Formation of "high-energy" phosphate compounds (ATP and ADP). Component of nucleic acids and of several essential coenzymes.
Magnesium	Mg^{2+}	0.05–0.7%	Part of the chlorophyll molecule. Activator of many enzymes.
Sulfur	SO_4^{2-}	0.05–1.5%	Component of some amino acids, proteins, and coenzyme A.
Micronutrients			
Iron	Fe^{2+}, Fe^{3+}	10–1,500 parts per million (ppm)	Required for chloroplast development. Component of cytochromes.
Chlorine	Cl^-	100–10,000 ppm	Involved in osmosis and ionic balance; probably essential in photosynthesis in the reactions in which oxygen is produced.
Copper	Cu^{2+}	2–75 ppm	Activator of some enzymes.
Manganese	Mn^{2+}	5–1,500 ppm	Activator of some enzymes. Required for oxygen release in photosynthesis.
Zinc	Zn^{2+}	3–150 ppm	Activator of many enzymes.
Molybdenum	MoO_4^{2-}	0.1–5.0 ppm	Nitrate reduction and nitrogen fixation.
Boron	BO^{3-} or $B_4O_7^{2-}$ (borate or tetraborate)	2–75 ppm	Functions unknown. Possibly involved in carbohydrate transport.
Elements Essential to Some Plants or Organisms			
Cobalt	Co^{2+}	Trace	Required by nitrogen-fixing microorganisms.
Sodium	Na^+	Trace	Involved in osmotic and ionic balance, probably for many plants not essential. Required by some desert and salt-marsh species and may be required by all plants that utilize C_4 photosynthesis.

equivalent of 2 million barrels of oil a day is required for the production of nitrogen-containing fertilizers.

On a worldwide basis, most nitrogen fixation is carried out by a few types of free-living microorganisms, including blue-green algae, some free-living bacteria, and some species of bacteria that live in symbiosis with plants. Of these various classes of nitrogen-fixing organisms, the symbiotic bacteria are by far the most important in terms of total amounts of nitrogen fixed.



36-12

These curves show how the amount of oxygen carried by the hemoglobin is related to oxygen pressure. When oxygen pressure reaches 100 mm Hg—the pressure usually present in the human lung—the hemoglobin becomes totally saturated with oxygen. As the pressure drops, the oxygen bound to the hemoglobin molecule is given up. Therefore, when blood carrying oxygen reaches the capillaries, where pressure is only about 40 mm Hg or less, it gives up some of its oxygen to the tissues. A curve located to the right signifies that the oxygen is given up more readily at a given pressure. (a) *Small animals have higher metabolic rates and so need more oxygen per gram of tissue than larger animals. Therefore, they have blood that gives up oxygen more readily.* (b) *The llama, which lives in the high Andes of South America, has a hemoglobin that enables its blood to take up oxygen more readily at the low atmospheric pressures.* (c) *The fetus must take up all its oxygen from the maternal blood. The hemoglobin of mammalian fetuses has a greater affinity for oxygen than does the hemoglobin of adult mammals, and so the oxygen tends to leave the maternal blood and enter the fetal blood.*

humans, the partial pressure of oxygen in the blood as it leaves the lungs is about 100 millimeters of mercury (100 mm Hg); at this pressure, the hemoglobin is saturated with oxygen. As the hemoglobin molecules travel through the bloodstream, the Po_2 drops, and as it drops, the oxygen bound to the hemoglobin molecules is given up. Little oxygen is yielded as the Po_2 drops from 100 mm Hg to 60 mm Hg. This is a built-in safety factor that protects individuals at high altitudes or those who have heart or lung diseases that decrease blood Po_2. However, as the partial pressure drops below 60 mm Hg, oxygen is given up much more readily (Figure 36-12).

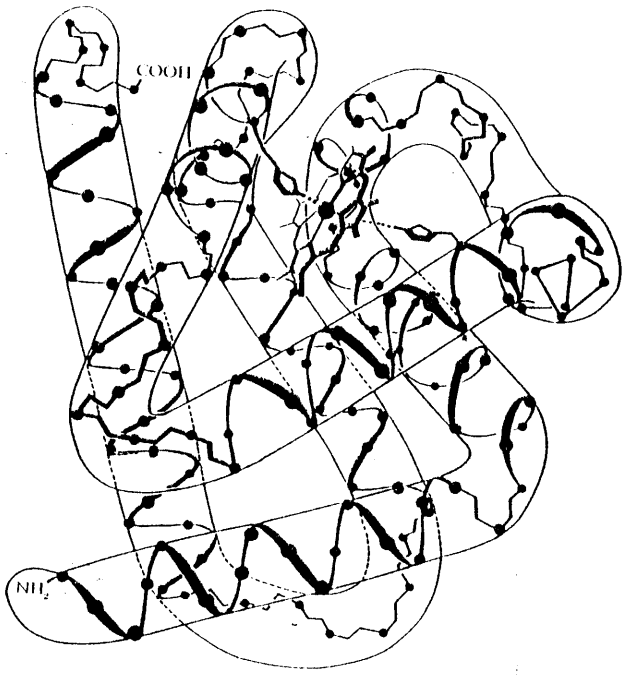
The Po_2 of the blood in the tissue capillaries is normally about 40 mm Hg. As a consequence, when the blood leaves the capillaries, its hemoglobin is still usually 70 percent saturated. This extra O_2 represents a reserve supply of oxygen should the demand increase—as a result, for example, of exercise.

Myoglobin and Its Function

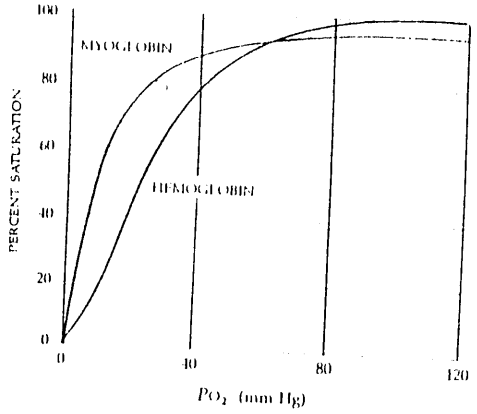
Myoglobin is a protein molecule with an iron-containing (heme) group (Figure 36-13); in its structure, it resembles a single unit of the hemoglobin molecule (Figure 3-27, page 69). Myoglobin is found in skeletal muscle. It has a greater affinity for oxygen than hemoglobin does and begins to release significant amounts

Table 36-2 *Composition of Respiratory Gas at Standard Atmospheric Pressure*

GAS	INSPIRED AIR		EXPIRED AIR		ALVEOLAR AIR	
	% OF VOLUME	PARTIAL PRESSURE (mm OF Hg)	% OF VOLUME	PARTIAL PRESSURE (mm OF Hg)	% OF VOLUME	PARTIAL PRESSURE (mm OF Hg)
O_2	20.71	157	14.6	111	13.2	100
CO_2	0.04	0.3	4.0	30	5.3	40
H_2O	1.25	9.5	5.9	45	5.9	45
N_2	78.00	593	75.5	574	75.6	574



36–13
Tertiary structure of myoglobin, as deduced from x-ray diffraction analyses. Myoglobin closely resembles a single chain of the four chain hemoglobin molecule. The heme portion is shown in color.



36–14
Comparison of the oxygen dissociation curves of myoglobin and hemoglobin. Note that myoglobin remains 80 percent saturated with oxygen until the partial pressure of oxygen falls below 20 mm Hg. Therefore, myoglobin retains its oxygen in the resting cell and relinquishes it only when strenuous muscle activity uses up the available oxygen provided by hemoglobin.

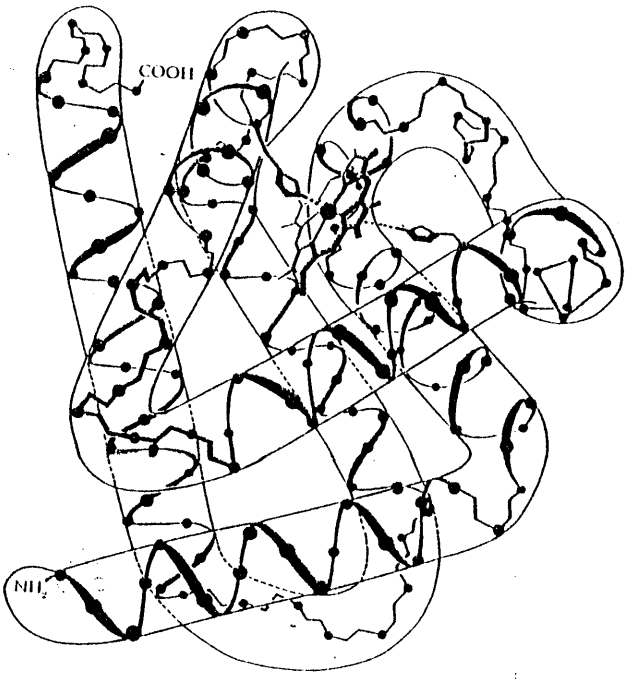
of oxygen only when the Po_2 falls below 20 mm Hg (Figure 36–14). Thus, when the muscle is at rest or engaged in only moderate activity, the myoglobin holds on to its oxygen. During strenuous exercise, however, when muscle cells are using oxygen rapidly and the partial pressure of oxygen in the muscle cells drops toward zero, myoglobin gives up its oxygen. Thus myoglobin provides an additional reserve of oxygen for active muscles.

Carbon Dioxide

A small amount of carbon dioxide is carried in the blood in the form of dissolved CO_2. Some (about 25 percent) is bound to hemoglobin molecules. Carbon dioxide does not combine with the heme units of the hemoglobin molecule, as oxygen does, but rather with the amino groups of the hemoglobin molecule. However, most of the carbon dioxide (about 65 percent) is carried in the blood as bicarbonate. Bicarbonate is produced in a two-stage reaction. First, carbon dioxide combines with water to form carbonic acid. This reaction is catalyzed by the enzyme carbonic anhydrase found in red blood cells. Carbonic acid, a weak acid, dissociates to yield bicarbonate and hydrogen ions:

$$CO_2 + H_2O \xrightleftharpoons{\text{carbonic anhydrase}} H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

As more carbon dioxide is taken up by the blood, the blood becomes increasingly acidic. As the acidity increases, hemoglobin gives up its oxygen more readily. Thus, as carbon dioxide enters the capillaries, the acidity of the blood increases and the yield of oxygen increases.



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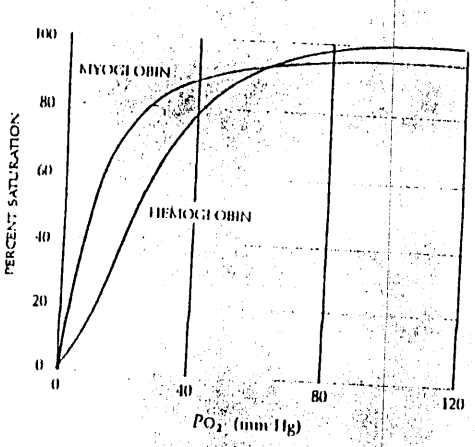

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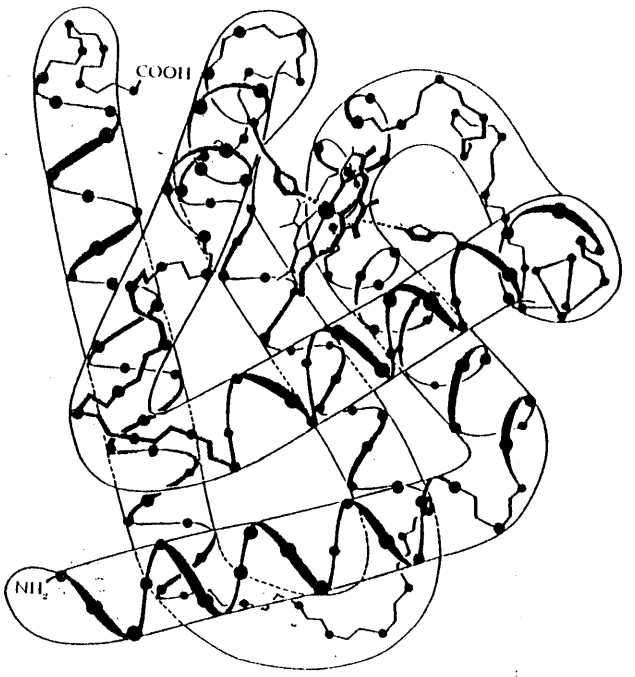

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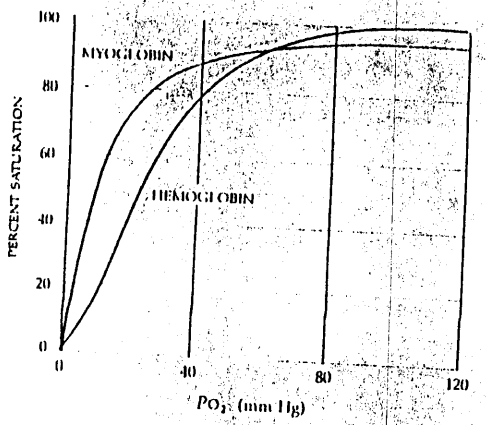

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FAO SOILS BULLETIN

48

micronutrients and the nutrient status of soils:

a global study

by
mikko sillanpää

sponsored by
the government of finland
executed at
the institute of soil science
agricultural research centre
jokioinen, finland
and
soil resources, management
and conservation service
land and water development division
FAO

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
Rome 1982

APPENDIX 2. National mean values of basic analytical data on original wheat plants and respective soils. For analytical methods, see Section 11.3. Only basic (uncorrected) results for soil micronutrients are given: hot water B, AAAc-EDTA extr. Cu and Fe, DTPA extr. Mn and Zn, AO-OA extr. Mo.

Country		GENERAL SOIL PROPERTIES: Particle-size distr. Sand 2.0–0.05 mm	Silt 0.05–0.002 mm	Clay <0.002 mm	Texture class	CEC meq/100 g	pH H2O	pH CaCl2	CaCO3 equiv. %	Org. C %	Volume weight g/cm³	SOIL MACRONUTRIENTS: N (total) %	P mg/l	K (extractable) mg/l	Ca mg/l	Mg mg/l	SOIL MICRONUTRIENTS: Na mg/l	B mg/l	Ca (extractable) mg/l	Fe mg/l	Mn mg/l	Mo mg/l	Zn mg/l	NUTRIENT CONTENTS OF ORIGINAL WHEAT PLANTS: N %	P %	K %	Ca %	Mg %	B ppm	Cu ppm	Fe ppm	Mn ppm	Mo ppm	Zn ppm
EUROPE AND OCEANIA																																		
BELGIUM	mean	12	72	15	0	36	16.4	6.55	6.08	1.5	.4	.9	1.23	.103	1272	83.7	213	1868	92	15	.54	5.1	262	48.7	.253	5.17	3.95	.501	3.95	.358	0.088	4.18	7.3	40.7	.30	29.7
(n = 21)	± s	4	11	13	0	4	2.3	.60	.66	.5	1.5	.2	.03	.013	150	23.3	58	983	29	6	.18	2.7	76	22.2	.087	2.10	.61	.102	.55	.076	.018	1.62	1.1	25.3	.20	10.5
	min.	8	44	53	0	29	12.8	5.70	5.00	.7	.0	.6	1.19	.081	983	45.6	122	805	46	9	.26	2.4	130	18.4	.089	2.79	2.68	.330	2.94	.239	.057	2.43	4.7	14.6	.09	22.4
	max.	19	84	45	0	43	21.1	7.90	7.40	1.9	7.1	1.2	1.28	.129	1552	121.6	369	5045	146	33	1.09	13.1	425	94.4	.489	10.53	5.04	.668	4.76	.493	.132	9.43	9.0	124.2	.83	72.8
FINLAND	mean	28	48	25	0	45	31.8	5.73	5.21	1.6	.0	3.9	.99	.288	2711	61.0	205	1521	207	13	.56	4.3	563	21.4	.540	2.77	5.03	.429	4.33	.399	.142	8.98	7.1	69.9	.37	27.0
(n = 94)	± s	21	19	21	0	18	13.9	.52	.52	.7	.0	2.8	.13	.160	1058	32.5	100	969	213	8	.29	2.6	361	14.3	.357	2.64	.76	.093	.59	.094	.038	5.86	1.7	49.5	.33	5.6
	min.	1	11	2	0	16	12.5	4.60	4.10	.6	.0	1.4	.66	.106	1181	14.2	40	190	10	2	.14	.9	130	1.0	.086	.34	2.64	.230	3.26	.224	.076	3.48	4.3	19.5	.01	17.4
	max.	81	89	74	0	86	89.7	7.30	6.90	3.9	.4	17.5	1.22	1.023	7169	208.0	632	8800	1075	47	1.88	16.5	1995	63.2	2.071	13.13	7.17	.752	6.70	.652	.285	37.30	13.1	423.1	1.88	43.3
HUNGARY	mean	29	52	19	0	47	29.8	7.25	6.83	2.2	4.1	1.6	1.20	.183	2176	32.7	217	4910	437	45	.98	5.5	148	34.1	.133	1.18	5.46	.490	4.15	.529	.177	4.28	8.5	75.8	.29	25.9
(n = 144)	± s	12	15	20	0	11	9.9	.79	.83	1.1	6.6	.5	.07	.054	592	20.3	122	1893	310	97	.46	2.5	83	27.9	.100	1.09	.78	.127	.86	.107	.048	1.46	1.8	31.3	.25	7.0
	min.	4	1	1	0	15	6.9	4.80	4.25	.5	.0	.5	1.06	.052	753	5.6	46	520	30	0	.11	1.6	61	8.9	.030	.34	2.72	.256	1.50	.304	.105	2.27	5.1	26.7	.03	14.2
	max.	69	76	94	0	78	57.1	8.35	7.90	8.3	45.0	3.6	1.45	.331	3511	130.0	843	8850	1826	795	2.68	14.6	605	150.0	.634	8.75	7.45	.829	6.55	.769	.399	12.87	13.6	175.9	1.87	48.4
ITALY	mean	36	37	25	3	49	27.6	7.62	7.22	6.0	11.4	1.3	1.19	.142	1684	19.6	334	6598	341	42	.87	11.3	197	20.8	.213	2.31	4.55	.424	3.55	.505	.140	4.47	8.6	54.3	.74	30.6
(n = 118)	± s	19	13	18	11	17	10.9	.58	.57	9.0	11.5	.7	.10	.057	643	17.8	279	4229	306	56	.60	13.8	119	24.3	.215	6.18	1.03	.114	.75	.214	.081	1.87	2.7	40.4	.69	15.6
	min.	9	6	1	0	19	9.4	5.61	4.96	.6	.0	.5	.96	.065	798	3.2	40	820	45	2	.24	1.4	30	4.0	.007	.17	1.99	.175	2.05	.182	.065	2.41	4.0	13.0	.04	10.7
	max.	85	79	93	58	89	74.9	8.28	7.82	57.0	57.4	5.7	1.75	.422	4696	116.4	1720	21930	1889	395	4.17	87.5	690	222.3	1.311	47.57	7.22	.781	5.30	1.302	.876	15.36	20.1	268.0	5.12	128.3
MALTA	mean	28	39	33	0	43	22.2	7.91	7.54	5.9	58.6	1.3	1.17	.145	1711	80.4	365	6518	271	202	1.14	7.2	35	7.5	.112	10.29	3.07	.533	4.21	.491	.102	3.40	7.4	37.0	.89	57.9
(n = 25)	± s	10	7	10	0	9	4.4	.10	.05	2.4	5.7	.3	.02	.034	414	51.3	226	744	47	143	.53	2.5	11	2.0	.057	12.51	.75	.148	.84	.132	.013	.70	1.5	6.7	.36	11.9
	min.	18	25	20	0	32	17.9	7.78	7.48	3.2	52.0	.8	1.13	.115	1364	20.7	186	5640	207	52	.63	5.0	22	4.9	.021	2.02	1.63	.422	2.87	.308	.075	2.45	4.5	26.0	.40	38.8
	max.	51	53	51	0	61	29.8	8.08	7.64	9.1	68.4	2.1	1.20	.212	2536	171.8	789	8090	335	441	2.20	12.9	52	11.3	.217	39.40	4.70	.800	5.93	.836	.126	4.75	9.5	51.2	1.70	81.1
NEW ZEALAND	mean	30	58	13	0	48	35.1	5.87	5.33	1.3	.0	3.2	1.04	.340	3435	24.7	210	1916	169	28	.67	2.3	290	16.6	.148	1.45	4.68	.392	3.48	.384	.153	4.56	8.4	54.7	.15	26.5
	± s	10	11	11	0	12	14.9	.25	.26	.5	.0	1.3	.08	.139	1072	7.8	165	753	176	15	.23	1.6	233	12.0	.104	1.66	.59	.049	.68	.128	.038	1.08	1.8	30.9	.09	8.1
	min.	[illegible]					[illegible]	5.02	.6	.0	2.0	.87	.221	2443	15.2	68	1170	48	11	.38	.6	112	6.3	.035	.28	3.78	.321	2.47	.262	.109	2.29	4.2	20.9	.03	16.8
	max.	69	78	43	0	78	66.3	6.41	5.90	2.2	.0	6.2	1.14	.701	6096	41.6	699	3610	638	51	1.20	6.7	960	51.2	.419	5.18	5.51	.484	5.12	.672	.249	6.04	11.4	141.4	.35	42.7
LATIN AMERICA																																		
ARGENTINA	mean	22	59	19	0	42	27.2	6.11	5.49	1.4	.0	1.9	1.04	.199	2067	24.4	784	1993	296	27	.72	3.2	287	39.7	.387	2.03	4.71	.419	4.74	.385	.158	3.98	7.6	64.3	.71	27.1
(n = 119)	± s	4	12	13	0	5	5.3	.31	.34	2.2	.1	.7	.07	.066	713	22.8	198	632	72	47	.22	.7	73	11.5	.222	1.66	.88	.134	.69	.084	.032	1.58	1.9	27.4	.67	6.5
	min.	11	24	2	0	25	17.0	5.42	4.85	.5	.0	.8	.89	.111	1175	5.4	420	1020	175	4	.42	1.7	105	13.1	.132	.41	2.78	.168	3.21	.208	.096	1.83	2.7	18.2	.69	15.5
	max.	31	73	64	0	50	45.3	7.41	6.96	24.4	.7	4.1	1.20	.425	4309	200.0	1649	5480	584	292	1.82	5.4	460	75.2	1.949	12.04	6.42	.800	6.42	.591	.244	10.96	12.5	137.5	5.37	49.4
BRAZIL	mean	59	21	20	0	67	27.1	5.66	5.10	.9	.0	2.0	1.12	.184	2028	10.9	170	1004	227	4	.64	17.5	166	108.1	.199	3.81	3.96	.418	4.42	.338	.223	6.15	14.5	107.3	.24	34.9
(n = 71)	± s	19	10	20	0	17	8.5	.50	.57	.3	.0	.8	.10	.057	578	9.6	111	782	137	3	.19	16.0	111	85.3	.072	14.88	.91	.117	1.20	.111	.056	1.96	11.0	43.5	.19	12.0
	min.	7	3	2	0	17	6.4	4.55	3.97	.4	.0	.6	.92	.051	742	2.4	37	180	40	0	.26	1.4	42	2.4	.049	.20	2.10	.227	1.49	.158	.140	2.88	6.9	37.4	.02	17.6
	max.	83	50	90	0	88	46.8	6.77	6.30	2.0	.0	4.7	1.46	.325	3778	74.2	632	5730	1031	18	1.21	81.1	700	286.0	.458	123.90	6.04	.752	6.83	.661	.449	12.66	99.9	231.3	.95	77.7
ECUADOR	mean						21.5	6.76	6.22	10.7	.1	1.4	1.20	.209	2349	17.7	280	1884	421	32	.42			24.1	.249	1.41	3.47	.432	4.31	.247	.145	2.33	7.7	34.3	.40	23.8
(n = 16)	± s						9.6	.73	.82	6.6	.2	.6	.11	.162	1905	16.3	93	1082	287	29	.20			20.8	.232	.82	1.07	.058	.84	.053	.050	.62	1.7	18.8	.40	6.1
	min.						9.7	5.33	4.66	3.1	.0	.6	.98	.049	664	2.4	134	590	78	8	.16			1.2	.048	.24	2.21	.326	3.35	.170	.096	1.45	5.1	15.0	.13	12.5
	max.						42.1	8.00	7.65	27.2	.6	2.3	1.45	.747	8844	67.6	472	4110	1038	108	.95			76.7	.870	2.90	6.43	.547	5.95	.321	.267	3.90	10.8	91.8	1.50	34.9

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APPENDIX 2 (cont.)

Country		GENERAL SOIL PROPERTIES: Particle size distrib. Sand 2–0.05 mm	Silt 0.05–0.002 mm	Clay <0.002 mm	Tex. incl.	CEC	pH H_2O	pH $CaCl_2$	EL cond.	$CaCO_3$ equiv.	Org. C	Volume weight	SOIL MACRONUTRIENTS: N (total)	P	K (extractable)	Ca (extractable)	Mg	SOIL MICRONUTRIENTS: Na	B	Cu (extractable)	Fe (extractable)	Mn	Mo	Zn	NUTRIENT CONTENTS OF ORIGINAL WHEAT PLANTS: N	P	K	Ca	Mg	B	Cu	Fe	Mn	Mo	Zn
		%	%	%		mval/100 g			10^{-6} mho/cm	%	%	g/cm³	%	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	%	%	%	%	%	ppm	ppm	ppm	ppm	ppm	ppm
(n = 100)	mean	46	40	25	C	C	30.7	6.11	7.64	5.1	10.1	.5	1.19	.100	1183	14.7	693	7023	720	726	1.16	3.9	.49	12.9	.200	.58	4.88	.378	4.77	.402	.185	10.81	11.1	100.6	1.25	37.8
	± s	17	15	15	C	C	12.2	.52	.23	6.1	15.3	.5	.06	.029	325	28.5	518	5000	576	352	.72	1.5	31	6.4	.168	1.75	.87	.120	.67	.131	.037	10.47	2.1	30.5	1.19	12.4
	min.	9	7	2	C	C	11.0	4.77	6.48	.7	.1	.3	1.02	.044	563	2.4	168	1970	151	4	.19	.9	10	4.8	.028	.22	2.28	.182	2.91	.231	.118	2.94	5.4	48.7	.11	14.0
	max.	77	78	82	3	83	80.3	8.85	8.09	42.8	59.8	1.8	1.44	.209	2358	271.4	2019	19980	1587	2358	3.45	8.7	170	44.5	1.080	14.83	6.46	1.020	6.30	.912	.307	83.53	17.4	223.5	6.18	76.9
PERU	mean	25	32	29	14	38	25.3	6.99	6.58	1.8	4.6	1.2	1.23	.144	1786	10.6	178	4067	387	23	.54	4.2	134	27.5	.224	3.66	2.94	.382	2.89	.332	.131	4.37	9.2	48.8	.88	37.3
(n = 13)	± s	10	14	11	18	12	6.9	.94	.92	.7	6.0	.5	.15	.056	809	8.2	65	2016	265	17	.29	1.7	59	13.9	.136	8.07	.62	.095	.77	.124	.045	2.14	3.6	17.0	1.16	19.6
	min.	14	13	6	0	22	15.3	5.33	4.98	.8	.0	.5	1.01	.084	893	2.8	78	1220	133	7	.22	1.9	65	9.1	.053	.42	1.84	.167	1.38	.157	.085	1.59	3.9	26.7	.11	15.4
	max.	46	57	52	44	61	35.0	8.00	7.57	3.0	16.7	2.2	1.48	.285	3959	27.4	273	6490	1073	70	1.20	7.9	239	52.8	.481	30.21	4.24	.486	4.34	.490	.194	8.42	18.4	93.0	4.22	76.1
FAR EAST																																				
INDIA	mean	18	47	35	0	36	18.4	8.06	7.56	2.9	2.8	.5	1.26	.071	881	9.3	186	3530	448	175	.50	4.3	145	13.4	.122	1.16	3.31	.323	3.83	.356	.187	4.83	8.8	53.9	1.11	23.3
(n = 188)	± s	15	17	23	1	14	16.2	.52	.50	2.7	7.3	.2	.08	.021	232	8.1	119	2795	383	197	.40	2.4	170	6.1	.107	3.04	1.51	.131	1.30	.159	.072	4.50	3.7	29.1	.98	9.2
	min.	2	9	1	0	16	5.1	6.02	5.14	.3	.0	.2	.95	.009	95	1.2	42	380	49	1	.07	.6	28	3.8	.014	.10	.60	.048	.94	.113	.052	1.68	2.5	8.6	.04	3.1
	max.	62	91	86	8	73	76.5	9.10	8.32	23.1	40.4	1.3	1.50	.142	1722	54.0	856	12040	3298	1295	2.10	18.9	885	48.7	.936	38.83	6.14	.608	6.22	.926	.407	42.78	18.0	160.1	6.31	55.7
KOREA	mean	20	47	33	0	37	16.9	6.10	5.61	1.7	.2	1.2	1.15	.118	1327	45.4	131	1068	194	32	.39	4.5	217	41.6	.295	10.97	5.27	.430	3.98	.386	.184	4.15	6.9	85.7	.41	33.0
(n = 50)	± s	10	11	19	0	11	4.2	.70	.73	.8	.2	.4	.07	.041	398	28.2	48	312	81	39	.31	4.1	192	36.3	.518	34.33	1.07	.129	.72	.092	.048	3.16	2.3	45.2	.29	11.0
	min.	5	18	5	0	18	8.2	5.00	4.20	.5	.0	.3	.98	.035	451	6.7	45	400	48	5	.08	.6	35	3.5	.066	.47	2.99	.203	2.20	.244	.108	1.40	3.4	25.5	.07	18.1
	max.	41	68	77	0	56	34.3	7.30	6.85	4.1	.9	2.6	1.32	.270	2641	116.3	256	2220	357	198	1.92	24.6	905	149.5	3.241	186.45	7.09	.777	5.77	.591	.314	18.55	16.4	244.4	1.36	74.1
NEPAL	mean	18	54	27	0	37	19.7	6.75	6.16	1.1	1.0	1.0	1.14	.119	1332	21.6	80	1766	205	27	.19	5.7	334	21.5	.084	.75	4.19	.400	3.70	.477	.196	2.99	10.7	69.1	.43	33.8
(n = 50)	± s	8	14	17	1	9	5.7	.84	.91	.5	3.8	.4	.11	.042	390	26.6	48	1173	111	24	.07	7.2	237	15.8	.039	1.08	1.07	.111	.89	.134	.059	.97	2.8	29.3	.44	9.6
	min.	5	22	3	0	23	9.5	5.19	4.50	.3	.0	.4	.84	.061	770	1.2	23	220	38	0	.10	1.0	48	3.7	.023	.11	2.24	.217	2.23	.230	.109	1.75	5.7	21.9	.03	18.6
	max.	40	76	67	10	57	36.5	8.20	7.59	2.5	26.3	2.0	1.36	.222	2191	121.4	323	4660	458	100	.43	40.4	1125	74.1	.204	6.72	6.34	.756	6.48	.756	.358	8.28	17.8	140.5	2.08	60.9
PAKISTAN	mean	20	60	20	0	40	17.3	8.38	7.83	5.0	6.9	.7	1.23	.082	.993	7.1	245	4516	362	349	.69	4.8	127	8.5	.198	.82	4.56	.372	4.81	.393	.189	7.60	12.6	78.0	2.24	27.3
(n = 156)	± s	9	13	16	0	8	4.6	.27	.21	7.7	4.0	.2	.08	.026	275	6.9	127	770	154	554	.68	2.3	64	2.3	.164	1.47	.82	.100	.90	.134	.044	6.18	10.2	33.4	1.17	8.2
	min.	4	10	1	0	19	7.6	7.89	7.40	1.0	.7	.2	1.04	.033	465	1.4	55	1200	78	5	.08	1.3	28	3.6	.022	.10	2.19	.120	2.17	.134	.106	1.74	5.9	25.7	.35	11.8
	max.	50	79	82	0	65	32.4	9.25	8.56	57.5	18.1	1.4	1.43	.169	1785	51.6	945	7240	924	2765	4.42	22.7	371	14.3	1.049	12.10	6.25	.719	6.84	.780	.358	33.78	100.6	228.2	7.99	61.0
NEAR EAST																																				
EGYPT	mean	47	37	15	0	60	44.5	8.01	7.68	7.8	4.4	1.2	1.19	.132	1559	18.7	722	7463	1580	746	.87	12.1	195	13.4	.144	1.31	4.31	.356	4.04	.355	.184	5.93	11.1	56.8	.94	31.1
(n = 100)	± s	15	12	21	0	14	10.3	.19	.13	5.5	1.8	.3	.06	.030	316	13.8	308	1319	525	686	.37	3.9	89	4.5	.045	.92	.58	.071	.64	.108	.031	3.39	2.0	20.8	.33	7.9
	min.	5	1	2	0	15	10.2	7.52	7.38	1.6	1.3	.4	1.08	.061	825	4.2	228	1640	395	98	.30	3.3	49	7.3	.042	.46	2.81	.191	2.98	.184	.130	2.99	7.0	27.4	.41	17.0
	max.	78	60	94	0	84	58.5	8.43	8.05	26.5	16.3	1.8	1.51	.221	2537	85.8	2097	9920	2946	3398	2.74	26.4	458	39.9	.304	7.50	5.76	.584	5.80	.839	.280	32.40	17.5	164.1	2.16	61.5
IRAQ	mean	35	51	13	0	52	26.9	8.04	7.69	8.3	25.2	.8	1.17	.097	1130	8.3	341	7315	678	329	1.36	4.8	110	9.1	.123	.28	3.39	.300	3.48	.375	.162	12.89	9.6	84.1	1.19	21.2
(n = 119)	± s	12	11	13	3	10	7.4	.15	.15	10.1	6.4	.3	.07	.035	400	10.2	141	1608	334	439	1.37	1.2	45	2.9	.114	.32	.79	.082	.61	.094	.045	14.63	12.2	40.9	.98	5.9
	min.	7	9	1	0	18	11.0	7.68	7.22	1.2	2.1	.3	1.04	.031	354	1.2	130	4400	190	4	.16	2.1	32	3.6	.019	.07	1.90	.172	1.83	.192	.075	2.36	4.6	26.4	.05	9.9
	max.	63	79	84	28	74	43.8	8.44	8.00	53.5	43.5	1.8	1.38	.239	2993	69.7	1028	15431	1555	2224	8.90	9.8	215	19.1	.656	3.56	5.16	.524	4.84	.776	.272	95.44	99.9	261.4	4.45	46.0
SYRIA	mean	45	35	18	3	57	37.8	7.94	7.53	3.8	27.5	1.1	1.23	.121	1466	19.5	465	9159	911	116	1.04	5.1	83	14.9	.114	1.21	4.14	.375	3.98	.413	.162	5.44	8.5	74.5	.74	26.5
(n = 20)	± s	19	15	20	6	17	13.6	.21	.13	4.2	15.7	.8	.07	.078	896	24.6	226	3391	586	139	.67	2.2	46	13.1	.073	1.73	.76	.087	.70	.100	.051	4.47	1.5	37.2	.54	7.0
	min.	7	9	2	0	18	9.3	7.61	7.36	1.6	6.8	.3	1.14	.040	558	2.0	166	4900	108	20	.31	1.9	29	5.8	.024	.10	2.82	.239	3.04	.220	.109	2.65	5.4	28.8	.03	12.0
	max.	74	58	84	20	80	62.9	8.51	7.84	18.2	59.2	3.9	1.39	.379	4442	111.9	965	17700	2620	486	3.18	12.8	185	67.0	.290	7.45	5.55	.560	5.57	.624	.315	22.27	11.4	148.7	2.11	42.7

APPENDIX 2 (cont.)

Country		GENERAL SOIL PROPERTIES: Particle size distr. 2–0.2 mm	Particle size distr. 0.2–0.02 mm	Particle size distr. 0.02–0.002 mm	Tex. cl.	CEC	pH H_2O	pH $CaCl_2$	EC cond.	$CaCO_3$ equiv.	Org. C	Volume weight	SOIL MACRONUTRIENTS: N (total)	P	K (extractable)	Ca (extractable)	Mg	SOIL MICRONUTRIENTS: Na	B	Cu (extractable)	Fe (extractable)	Mn	Mo	Zn	NUTRIENT CONTENTS OF CROP: N	P	K	Ca	Mg	B	Cu	Fe	Mn	Mo	Zn
													%	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	mg/l	%	%	%	%	%	ppm	ppm	ppm	ppm	ppm	ppm
TURKEY (n = 209)	mean	36	28	36	0	68	16.5	6.83	7.29	.45	11.8	.9	1.21	.494	1124	10.6	411	6408	495	62	1.16	.53	.89	15.2	.111	.59	4.12	.395	3.33	.543	.174	9.50	8.6	55.6	4.3	18.1
	± s	20	15	19	0	17	10.5	1.05	.75	.45	11.5	.3	.07	.084	577	7.9	210	2140	305	24	1.13	.24	.65	12.9	.126	.34	.78	.087	.61	.218	.069	12.67	2.1	37.0	3.95	6.32
	min.	3	12	1	0	9	9.7	5.90	5.30	.5	.0	.2	1.00	.026	357	1.0	58	660	70	3	.06	.9	13	3.4	.020	.12	1.02	.141	1.80	.214	.067	1.61	4.9	22.0	.05	7.6
	max.	77	67	75	0	84	64.2	8.90	8.55	2.0	54.2	2.8	1.47	.288	3192	69.6	1338	13160	1755	2625	9.99	15.5	558	84.0	.956	3.65	6.73	.572	5.36	1.677	.948	99.19	16.6	225.8	8.57	41.7
AFRICA																																				
ETHIOPIA (n = 54)	mean	58	32	10	0	48	56.7	6.63	5.97	.8	.2	2.0	1.12	.176	1905	10.0	740	5662	718	31	.55	6.0	237	85.8	.537	2.07	3.05	.314	3.77	.307	.108	2.51	6.7	65.1	1.34	25.4
	± s	14	9	9	1	12	12.5	.25	.90	.5	.4	.9	.08	.093	905	9.6	260	3261	394	42	.19	2.2	133	51.0	.398	1.99	.77	.077	.81	.085	.017	.49	1.6	29.5	1.87	5.5
	min.	15	20	1	0	28	34.8	5.90	4.60	.3	.0	.8	.92	.056	678	3.0	127	1250	189	0	.28	1.1	74	11.5	.106	.49	1.94	.226	2.59	.158	.075	1.39	1.5	24.6	.02	12.9
	max.	76	63	47	9	82	79.0	8.35	7.60	2.2	1.8	3.6	1.25	.360	3826	57.8	1336	11550	1432	283	1.09	14.3	700	193.0	2.600	9.90	5.43	.557	6.43	.553	.162	3.94	10.0	166.0	10.04	43.9
NIGERIA (n = 42)	mean	23	36	41	0	38	16.4	6.54	6.12	2.5	1.3	.7	1.29	.083	1058	16.7	207	2009	345	172	.25	2.1	162	27.3	.175	.78	4.28	.343	4.54	.461	.231	3.31	9.7	114.4	.71	33.3
	± s	21	15	23	0	18	10.9	1.86	1.06	2.4	5.3	.4	.11	.041	499	13.1	134	1952	362	443	.24	1.7	161	17.2	.244	.51	.72	.112	.71	.167	.072	1.28	2.0	65.3	.93	12.7
	min.	2	1	6	0	12	5.1	4.57	4.13	.5	.0	.1	1.06	.030	486	1.2	50	320	49	5	.03	.2	22	4.5	.016	.28	2.44	.206	2.98	.260	.126	1.47	5.7	47.8	.07	16.6
	max.	69	67	97	0	77	44.9	9.17	7.96	10.5	26.8	2.3	1.62	.227	3132	56.4	633	7000	1795	1880	1.31	7.0	870	81.0	1.248	3.12	5.95	.732	6.01	1.102	.483	7.00	14.0	364.7	4.13	84.8
TANZANIA (n = 5)	mean	38	13	49	0	47	19.0	5.66	4.99	.6	.0	1.9	1.07	.153	1635	3.2	65	420	82	6	.36	4.0	58	25.0	.094	.48	4.54	.296	4.54	.386	.219	2.24	10.8	60.6	.25	42.9
	± s	2	2	2	0	2	3.7	.19	.26	.3	.0	.4	.03	.042	433	1.2	29	407	44	2	.05	1.2	19	10.7	.034	.14	.39	.090	.52	.091	.057	.32	1.1	19.7	.29	17.6
	min.	36	10	45	0	45	14.8	5.48	4.79	.4	.0	1.5	1.04	.104	1100	1.9	20	110	41	3	.28	2.7	38	17.4	.063	.26	3.98	.199	3.99	.251	.141	1.92	9.8	48.3	.04	28.5
	max.	41	15	52	0	50	23.2	5.96	5.41	1.1	.0	2.5	1.10	.202	2141	4.9	97	1110	153	8	.40	5.2	88	43.2	.150	.65	5.04	.415	5.38	.470	.274	2.74	12.6	95.6	.76	69.2
WHOLE INTERNAT. MATERIAL (n = 1768)	mean	31	45	24	0	47	27.8	7.38	6.91	3.5	7.4	1.3	1.18	.133	1506	20.2	365	4671	489	162	.81	6.1	172	25.2	.204	1.77	4.28	.375	4.03	.428	.172	6.56	9.4	73.6	.94	27.4
	± s	18	17	19	4	15	13.6	1.82	1.07	5.4	12.0	1.1	.11	.084	779	24.7	283	3076	437	357	.75	6.4	175	33.1	.229	7.30	1.15	.125	.97	.166	.060	7.80	5.7	39.8	1.03	11.3
	min.	1	1	1	0	12	5.1	4.55	3.97	.3	.0	.1	.66	.009	95	1.0	20	110	10	0	.03	.2	10	1.0	.007	.07	.60	.048	.94	.113	.044	1.39	1.5	8.6	.01	3.1
	max.	85	91	97	58	89	89.7	9.25	8.56	57.5	68.4	17.5	1.75	1.023	8844	271.4	2097	21930	3298	3398	9.99	87.5	1995	286.0	3.241	186.45	7.45	1.020	6.84	1.677	.948	99.19	100.6	423.1	11.04	128.3

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APPENDIX 3. National mean values of basic analytical data on original maize plants and respective soils.
For analytical methods see Appendix 2 and Section 1.3.

Country		GENERAL SOIL PROPERTIES										SOIL MACRONUTRIENTS				SOIL MICRONUTRIENTS							NUTRIENT CONTENTS OF ORIGINAL MAIZE PLANTS									
		Particle size distr.			Tex. cl.	CEC	pH		El. cond.	$CaCO_3$ equiv.	Org. C	Volume weight	N (total)	P	K (extractable)	Ca	Mg	Na	B	Ca (extractable)	Fe	Mn	Mo	Zn	N	P	K	Ca	Mg	B	Ca	Fe	Mn	Mo	Zn
		2-0.2 mm	0.2-0.02 mm	<0.02 mm			H_2O	$CaCl_2$	10^{-3}																								
		%	%	%		mval/100 g			mS/cm	%	%	g/l	%	ppm	ppm	ppm	%	ppm	ppm	ppm	ppm	ppm	ppm	ppm	%	%	%	%	%	ppm	%	ppm	ppm	ppm	ppm
EUROPE AND OCEANIA																																			
BELGIUM	mean	7	35	57	0	23	19.8	5.91	6.52	2.5	.2	1.5	1.26	.134	1674	119.3	232	1240	76	19	.48	4.5	401	31.0	.170	19.23	5.81	.535	4.35	.618	.124	4.61	10.5	137.6	.54	168.1
(n = 20)	± s	5	24	29	0	9	3.0	.71	.77	.6	.5	.4	.07	.023	271	59.3	94	866	31	19	.25	2.2	180	31.0	.049	11.72	7.28	.104	.51	.111	.040	.85	2.1	107.7	.22	106.8
	min.	2	12	6	0	15	13.4	4.85	4.45	1.2	.0	.6	1.15	.088	1033	43.2	108	490	35	0	.23	2.2	115	4.0	.101	2.75	4.43	.369	3.23	.415	.083	3.20	7.6	43.7	.10	22.8
	max.	15	79	85	0	39	24.5	7.30	7.05	3.9	2.4	2.1	1.37	.171	2223	187.0	406	4050	135	71	1.09	9.3	750	104.6	.250	44.06	5.54	.778	5.02	.864	.250	6.66	15.3	517.1	1.09	403.7
HUNGARY	mean	30	52	18	0	47	29.5	7.32	6.96	2.7	3.6	1.6	1.22	.169	2826	38.9	241	4858	481	39	1.09	5.2	145	44.2	.138	1.83	4.72	.502	4.13	.768	.385	6.14	15.0	115.8	.37	30.8
(n = 106)	± s	13	15	21	0	13	11.6	.89	.95	1.1	3.9	.6	.06	.061	655	34.0	136	2094	262	41	.48	2.4	85	33.2	.130	.91	.50	.105	.89	.262	.138	1.74	4.1	56.2	.41	11.9
	min.	13	12	1	0	16	4.6	5.00	4.20	.5	.0	.4	.99	.036	508	7.8	50	165	115	2	.12	.6	52	7.5	.040	.34	2.93	.262	1.48	.326	.144	3.05	7.7	43.1	.01	16.5
	max.	77	73	83	0	84	64.2	8.40	8.00	8.7	42.2	3.9	1.42	.404	4252	322.0	956	8270	1352	1446	3.09	13.1	567	154.0	1.161	5.96	5.87	1.038	6.02	1.880	1.073	10.69	25.6	429.1	2.86	77.9
ITALY	mean	28	43	27	2	44	25.5	7.37	7.00	3.6	8.4	1.3	1.16	.178	2051	32.5	210	4990	392	21	.68	19.2	236	21.8	.184	2.63	4.88	.363	3.09	.685	.292	9.53	14.5	76.5	.45	32.9
(n = 70)	± s	16	12	17	7	15	10.8	.76	.76	3.3	10.2	.6	.08	.141	1739	23.0	189	2566	413	17	.36	20.2	120	21.5	.162	3.16	.69	.079	.96	.172	.103	3.88	4.0	31.2	.49	11.4
	min.	9	3	1	0	23	9.9	5.18	4.65	1.0	.0	.7	.97	.096	1110	2.8	24	730	59	2	.15	2.5	88	2.7	.047	.39	2.11	.150	.76	.330	.145	4.02	2.5	19.4	.03	15.6
	max.	71	76	67	48	80	58.9	8.10	7.77	22.0	37.8	4.3	1.31	1.169	14729	105.0	1121	11130	2100	94	1.85	96.0	820	127.0	1.224	18.97	5.73	.591	5.22	1.204	.711	24.06	27.4	144.8	2.72	64.1
NEW	mean	45	39	16	0	58	60.0	5.83	5.42	2.6	.1	6.2	.92	.481	3944	40.0	500	3215	518	46	.77	16.3	589	67.0	.195	3.70	3.68	.355	3.52	.340	.179	10.55	9.5	64.7	.08	40.3
ZEALAND	± s	20	12	12	0	16	17.2	.73	.71	1.1	.5	9.0	.16	.340	1418	33.1	317	2025	395	27	.43	17.6	452	50.6	.192	3.52	.89	.088	.80	.064	.053	4.07	2.4	34.5	.10	23.0
(n = 24)	min.	11	21	2	0	32	29.7	4.00	3.62	.8	.0	2.1	.47	.211	2287	4.8	76	1070	41	14	.31	.3	75	2.7	.036	.38	1.71	.229	2.13	.237	.106	3.71	5.4	26.1	.01	15.8
	max.	75	63	35	0	82	99.7	7.07	6.77	5.2	2.6	39.1	1.09	1.657	8378	157.4	1063	7120	1264	117	1.78	42.9	2275	237.0	.940	18.29	5.40	.507	4.85	.471	.291	19.14	13.6	144.9	.50	102.8
LATIN AMERICA																																			
ARGENTINA	mean	23	67	10	0	44	28.4	6.08	5.45	1.6	.0	1.9	1.06	.207	2189	23.7	790	2090	297	18	.78	3.2	201	71.8	.357	2.97	3.81	.326	4.10	.596	.242	7.45	12.0	85.6	.46	25.4
(n = 90)	± s	3	6	7	0	4	5.6	.29	.27	.7	.1	.8	.03	.074	758	16.1	196	309	46	27	.24	.7	74	18.6	.218	4.35	.46	.073	.51	.291	.094	3.37	9.8	27.3	.48	4.2
	min.	15	46	2	0	22	20.4	5.24	4.79.	.7	.0	1.1	.96	.124	1289	.7	479	1100	191	4	.41	1.9	110	31.8	.182	.61	2.52	.189	2.85	.184	.117	3.22	4.7	34.2	.05	14.2
	max.	36	81	29	0	54	44.9	6.72	6.08	4.3	.4	4.3	1.16	.433	4434	105.4	1649	2990	537	200	1.91	7.0	506	123.9	1.633	28.69	4.95	.537	5.61	1.218	.474	23.07	99.6	153.7	3.26	39.1
MEXICO	mean	35	36	29	0	49	32.8	7.37	6.89	2.2	1.3	1.0	1.18	.100	1154	19.4	548	4363	651	237	1.30	4.0	80	35.4	.183	1.73	2.86	.308	2.71	.383	.186	10.90	9.6	65.1	.73	28.5
	± s	15	15	22	2	18	16.0	.93	.93	1.7	2.4	.4	.11	.045	435	17.5	338	2519	381	443	1.68	4.8	66	29.9	.160	3.62	.70	.080	.70	.140	.051	7.30	2.5	26.9	.65	20.7
	min.	1	6	1	0	10	.2	4.60	4.10	.3	.0	.1	.88	.011	176	2.5	51	290	25	2	.07	.3	14	.9	.020	.16	1.40	.131	.98	.163	.087	2.91	3.2	16.6	.01	6.2
	max.	76	75	82	19	82	79.1	8.80	8.25	9.2	24.8	3.3	1.60	.342	3068	90.4	1918	14880	1829	2748	9.99	54.4	535	163.2	1.151	26.95	4.67	.629	4.32	1.024	.336	43.13	15.5	180.6	4.76	224.5
PERU	mean	24	29	38	10	36	26.1	7.30	6.92	3.0	3.8	1.5	1.24	.175	2117	20.9	230	4556	324	29	.67	5.8	167	25.8	.237	2.26	3.24	.332	2.85	.511	.241	8.05	11.6	54.7	1.02	30.7
(n = 57)	± s	15	10	16	14	14	11.3	.82	.82	2.2	7.3	.7	.13	.076	794	16.8	144	2491	188	29	.46	3.9	92	25.3	.292	4.61	.56	.089	1.32	.205	.126	3.34	2.9	15.6	.96	13.2
	min.	2	12	1	0	9	13.5	4.54	4.00	.4	.0	.3	.98	.053	664	2.4	56	280	49	2	.21	.4	30	6.3	.046	.29	1.99	.107	.85	.213	.093	3.90	6.6	25.9	.07	16.0
	max.	61	54	73	55	69	66.1	8.14	7.70	13.7	47.0	3.4	1.58	.420	4402	79.8	777	10840	909	127	2.60	23.0	394	138.0	1.853	34.35	5.33	.514	4.68	1.024	.723	21.54	19.2	107.6	5.24	104.2
FAR EAST																																			
INDIA	mean	11	55	33	0	31	13.6	8.07	7.55	1.8	5.2	.6	1.26	.073	910	8.6	126	2660	269	70	.37	4.4	183	16.0	.105	.90	2.62	.310	2.35	.556	.313	7.99	11.8	63.6	2.70	25.2
(n = 107)	± s	5	18	19	0	6	3.5	.52	.49	1.8	11.0	.2	.08	.017	171	7.1	78	1271	134	123	.26	7.8	227	10.3	.067	4.02	.62	.067	.99	.259	.133	4.04	4.4	27.7	2.75	18.9
	min.	3	11	5	0	15	5.1	6.04	5.54	.5	.0	.2	1.01	.042	571	1.9	41	470	36	3	.05	.7	31	4.5	.010	.09	1.57	.156	.96	.194	.057	1.88	5.7	24.9	.03	8.6
	max.	28	87	86	0	48	26.0	8.90	8.55	15.4	39.6	1.1	1.43	.128	3443	46.2	517	5330	600	816	1.61	82.0	930	55.9	.482	41.89	4.34	.480	4.34	1.159	.823	25.90	33.3	180.7	16.76	195.2
KOREA,	mean	18	44	38	0	35	17.8	6.02	5.58	2.6	1.3	1.3	1.10	.144	2553	44.0	190	1390	262	10	.34	3.0	134	39.1	.196	1.67	3.95	.369	3.39	.442	.270	6.48	10.4	103.5	.37	34.2
REP. OF	± s	10	15	22	0	11	5.2	1.06	1.09	1.7	6.1	.5	.11	.043	382	32.2	104	831	266	6	.20	1.5	59	37.5	.109	1.02	.41	.076	.78	.115	.085	6.26	2.4	93.5	.37	14.3
(n = 50)	min.	3	18	4	0	19	6.7	4.40	4.10	.7	.0	.4	.88	.041	529	5.0	52	300	42	2	.14	.5	25	3.3	.018	.32	2.90	.213	1.87	.211	.147	3.24	6.0	21.8	.01	18.5
	max.	42	81	76	0	56	36.0	8.00	7.50	10.0	42.9	2.3	1.31	.231	2318	140.0	492	4000	1832	34	1.20	6.2	310	148.0	.624	5.68	4.69	.507	5.30	.777	.471	31.03	15.8	453.8	1.94	109.0

Reference e
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APPENDIX 3 (cont.)

Country		GENERAL SOIL PROPERTIES: Particle size distr. 2–0.2 mm (%)	0.2–0.02 mm (%)	0.02–0.002 mm (%)	Tot. vol. (%)	CEC (meq/100 g)	pH H_2O	pH $CaCl_2$	EC (mmhos/cm)	$CaCO_3$ equiv. (%)	Org. C (%)	Volume weight (g/cm³)	SOIL MACRONUTRIENTS: N (total) (%)	P (mg/l)	K (extractable) (mg/l)	Ca (extractable) (mg/l)	Mg (mg/l)	SOIL MICRONUTRIENTS: Na (mg/l)	B (mg/l)	Cu (extractable) (mg/l)	Fe (mg/l)	Mn (mg/l)	Mo (mg/l)	Zn (mg/l)	NUTRIENT CONTENTS OF ORIGINAL MAIZE PLANTS: N (%)	P (%)	K (%)	Ca (%)	Mg (%)	B (ppm)	Cu (ppm)	Fe (ppm)	Mn (ppm)	Mo (ppm)	Zn (ppm)
	mean	18	24	19	0	48	14.6	6.37	6.07	2.5	20.0	3.2	1.37	.139	1771	41.0	510	7160	615	1329	1.45	9.5	200	57.3	505	3.04	4.67	.522	5.52	1.620	.652	49.42	26.3		218.4	9.01	59.2
PHILIPPINES	± s	21	16	19	2	18	12.8	1.76	1.71	1.5	5.0	1.3	1.08	.098	1471	18.5	212	3839	811	56	.28	13.4	273	45.0	.228	3.26	2.99	.287	2.46	.524	.340	6.93	12.3		54.9	.56	32.6
(n = 197)	min.	3	9	0	0	17	6.7	4.56	4.63	.4	.0	.3	.80	.039	487	1.5	18	1100	177	87	.15	10.6	131	35.8	.189	15.89	.51	.071	.81	.162	.174	3.35	2.6		26.7	.76	17.0
	max.	87	77	81	22	91	67.2	8.10	7.55	11.6	16.0	4.8	1.42	.527	4313	138.6	1997	12800	6490	681	.86	93.0	840	226.0	1.585	185.20	4.50	.600	4.39	1.114	1.125	26.57	20.8		221.1	6.36	183.0
	mean	23	11	64	2	31	14.2	6.21	6.02	1.0	.1	1.2	1.28	.122	1553	14.0	144	1159	181	10	.34	3.9	156	64.6	.196	3.78	2.82	.322	3.51	.412	.231	6.22	9.8		94.2	.17	27.8
SRI LANKA	± s	11	5	14	8	10	4.3	.75	.85	.4	.2	.7	.08	.061	727	12.3	59	586	136	13	.19	2.7	104	52.5	.132	11.27	.76	.097	.80	.126	.098	1.91	2.4		39.1	.27	11.8
(n = 21)	min.	3	3	40	0	13	6.8	5.15	4.38	.5	.0	.5	1.07	.025	1028	2.2	21	300	35	0	.16	.9	50	3.8	.065	.55	1.56	.167	2.02	.216	.106	4.00	4.9		26.8	.02	15.6
	max.	47	20	94	33	55	24.6	8.02	7.60	1.8	.8	3.9	1.45	.363	4400	48.4	258	3700	574	66	.85	10.7	470	203.0	.510	52.81	4.17	.537	4.80	.704	.499	10.34	13.2		167.9	1.27	57.9
THAILAND	mean	44	34	21	1	56	41.8	7.31	6.80	1.3	4.8	1.6	1.21	.157	1884	11.7	216	6444	440	18	.42	6.3	140	52.5	.305	1.60	3.27	.294	3.01	.321	.182	6.21	10.5		49.6	.46	27.9
(n = 150)	± s	16	12	15	4	14	17.0	.76	.80	.9	10.1	.5	.07	.047	513	18.8	131	4244	305	40	.15	8.8	104	34.2	.454	2.66	.52	.073	.60	.096	.059	1.24	1.9		12.2	.44	6.4
	min.	6	9	1	0	12	11.8	5.30	4.50	.3	.0	.7	1.00	.076	1045	.1	40	600	39	0	.16	.2	22	10.0	.026	.20	1.52	.143	1.30	.157	.081	3.78	4.0		26.4	.03	12.8
	max.	81	63	84	25	85	82.8	8.20	7.70	10.5	50.0	3.7	1.43	.380	4134	165.2	849	15390	1762	441	.83	99.7	775	162.0	3.326	20.51	4.63	.474	4.75	.637	.424	9.70	15.0		88.6	2.66	54.3
NEAR EAST																																				
EGYPT	mean	45	35	20	0	57	41.8	8.29	7.81	4.8	4.6	1.2	1.17	.117	1358	15.8	635	6348	1208	595	1.00	11.0	191	10.6	.140	1.04	3.02	.302	3.31	.330	.263	13.63	10.9		59.6	.74	31.6
(n = 100)	± s	14	13	21	0	14	10.6	.19	.12	3.6	2.9	.3	.06	.022	291	13.4	306	986	372	435	.39	3.3	97	4.1	.042	1.12	.45	.054	.49	.075	.071	5.21	2.1		12.8	.21	6.6
	min.	5	3	1	0	15	5.9	7.75	7.60	1.2	1.0	.4	1.07	.044	642	3.4	82	3450	363	48	.32	2.5	44	5.6	.023	.29	1.72	.166	2.37	.131	.156	7.69	5.6		32.0	.30	15.1
	max.	82	54	92	0	87	57.2	8.95	8.20	32.0	24.1	1.8	1.46	.208	2314	101.1	2325	8098	1998	2053	2.86	21.3	675	36.9	.224	9.18	3.83	.527	4.64	.593	.691	40.18	15.6		105.7	1.40	49.8
IRAQ	mean	33	56	11	0	51	23.6	8.16	7.83	13.5	25.8	.7	1.16	.087	1011	7.5	304	6456	688	739	2.08	4.7	121	9.6	.134	.27	3.14	.276	3.52	.487	.291	38.23	14.0		102.5	1.27	22.8
(n = 31)	± s	8	9	9	0	7	5.4	.16	.17	16.7	4.7	.2	.08	.032	405	4.6	126	2851	245	1002	2.24	1.2	38	3.7	.096	.10	.40	.060	.45	.084	.089	26.53	4.7		33.6	.71	8.9
	min.	14	34	1	0	36	13.6	7.87	7.65	1.4	15.6	.3	1.00	.041	464	.7	120	4200	237	10	.37	2.5	38	3.6	.034	.13	2.50	.165	2.34	.337	.160	7.16	8.7		44.5	.23	9.7
	max.	49	77	39	0	63	40.8	8.65	8.55	73.0	42.5	1.1	1.34	.197	2634	20.9	645	17995	1272	4058	10.02	7.7	220	21.2	.439	.60	4.12	.405	4.45	.654	.483	100.04	24.5		193.4	2.90	44.6
					0	60	38.3	7.80	7.44	3.9	17.1	.9	1.20	.057	1158	42.5	354	7789	545	44	.54	6.0	98	17.9	.077	.85	3.43	.359	3.32	.497	.219	10.43	13.0		85.8	.30	26.2
(n = 16)	± s	17	10	11	0	13	9.4	.37	.29	3.6	20.7	.3	.04	.023	287	31.0	234	1919	412	31	.16	2.0	37	11.5	.068	.42	.73	.061	.54	.153	.075	3.94	3.4		24.1	.32	5.1
	min.	15	19	1	0	38	23.8	7.10	6.95	1.5	.4	.4	1.10	.051	736	5.3	101	5000	177	15	.34	4.1	24	6.8	.014	.21	1.83	.246	2.21	.220	.143	6.38	7.9		57.3	.05	14.7
	max.	78	70	33	0	84	61.9	8.10	7.75	13.5	67.1	1.3	1.26	.357	1722	104.6	1070	11950	1553	126	.97	11.5	156	37.9	.250	1.67	4.69	.425	4.15	.854	.406	22.12	22.4		139.2	1.33	34.1
SYRIA	mean	36	40	18	6	50	39.6	8.05	7.66	3.4	23.8	1.3	.....	.134	1494	16.6	418	7618	1006	126	1.12	4.5	91	15.1	.125	1.21	2.98	.284	3.10	.499	.263	19.62	9.8		86.3	.76	32.1
(n = 18)	± s	18	18	15	13	15	12.7	.25	.24	2.6	15.3	1.2	.12	.101	877	19.1	249	2763	510	124	.80	1.5	86	20.9	.121	2.60	.83	.070	1.10	.151	.099	15.05	2.8		34.7	.75	16.1
	min.	9	9	4	0	23	22.2	7.28	6.90	1.3	1.4	1.5	.86	.023	304	4.4	136	3310	268	29	.22	2.0	25	2.8	.027	.24	1.41	.198	2.18	.282	.159	4.79	4.7		8.3	.12	14.5
	max.	75	72	66	43	82	74.3	8.38	7.92	12.6	61.4	5.6	1.34	.486	4128	82.0	887	15910	2359	538	3.45	6.4	380	97.5	.529	11.36	4.22	.422	5.30	.854	.476	56.72	14.1		135.7	3.17	80.6
TURKEY	mean	31	36	33	0	45	28.3	7.36	6.79	1.5	3.5	1.2	1.20	.119	1407	17.5	213	5411	469	30	.78	7.7	210	46.1	.168	1.72	3.28	.303	2.74	.569	.290	7.82	12.2		64.9	.34	26.6
(n = 50)	± s	15	12	19	0	14	12.2	.76	.74	.9	5.5	.5	.06	.047	507	14.4	115	2282	363	19	.45	4.5	103	38.5	.120	2.73	.63	.060	.79	.140	.131	2.85	2.9		19.6	.35	8.2
	min.	10	12	1	0	25	7.7	5.60	5.20	.3	.0	.4	1.08	.047	560	3.0	46	1290	95	6	.08	1.8	65	9.6	.035	.27	1.59	.173	1.00	.326	.134	3.62	6.6		33.8	.03	15.6
	max.	79	59	72	0	85	58.2	8.30	7.60	4.7	24.8	2.7	1.40	.270	2905	73.0	556	10375	1742	95	2.20	20.2	540	167.0	.504	16.16	4.56	.460	4.18	.895	.614	18.25	19.0		111.6	1.64	47.9

Reference e
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APPENDIX 3 (cont.)

Country		GENERAL SOIL PROPERTIES: Particle size distr. Sand 2-.05 mm %	Silt .05-.002 mm %	Clay <.002 mm %	Fine Earth %	Tex. cl.	CEC me/100 g	pH H_2O	pH $CaCl_2$	El. cond. 10^{-3} S/cm	$CaCO_3$ equiv. %	Org. C %	Volume weight g/cm³	SOIL MACRONUTRIENTS: N (total) %	P mg/l	K (extractable) mg/l	Ca mg/l	Mg mg/l	SOIL MICRONUTRIENTS: Na mg/l	B mg/l	Cu (extractable) mg/l	Fe (extractable) mg/l	Mn mg/l	Mo mg/l	Zn mg/l	NUTRIENT CONTENTS OF ORIGINAL MAIZE PLANTS: N %	P %	K %	Ca %	Mg %	B ppm	Cu ppm	Fe ppm	Mn ppm	Mo ppm	Zn ppm
AFRICA																																				
ETHIOPIA	mean	45	35	23	0	66	41.5	6.23	5.46	1.6	.1	2.2	2.01	.200	1967	13.7	540	2292	417	31	.54	3.3	.199	89.7	.771	4.88	3.90	.304	3.65	.396	.210	5.67	10.6	78.8	.71	45.7
(n = 71)	± s	20	12	15	1	17	10.9	.75	.81	.6	.4	.5	.11	.068	611	43.0	390	1608	295	59	.26	2.9	123	50.4	.580	6.52	.87	.120	.77	.112	.069	1.80	3.5	32.4	1.76	30.5
	min.	5	12	2	0	20	16.2	4.60	4.10	.3	.0	.9	.76	.064	775	1.2	87	510	87	0	.16	.1	49	6.5	.093	.23	1.59	.126	2.14	.191	.074	3.10	2.0	32.3	.03	15.5
	max.	79	62	66	11	84	64.5	8.30	7.65	9.2	1.8	4.0	1.25	.394	5767	311.0	2077	7680	1753	393	1.24	11.5	825	213.5	3.560	43.63	6.51	.814	5.16	.707	.449	10.21	17.0	238.5	14.33	156.2
GHANA	mean	18	19	58	5	30	14.7	6.34	5.85	.9	.1	1.3	1.30	.132	1692	8.2	129	1145	215	6	.57	1.9	94	62.3	.681	1.06	2.80	.318	3.10	.329	.283	9.15	9.4	68.0	.38	23.9
(n = 93)	± s	8	12	18	10	9	6.0	.55	.66	.4	.1	.5	.10	.056	663	10.7	70	520	183	9	.22	1.2	37	27.4	.028	.95	.41	.071	.46	.057	.043	2.05	1.9	17.6	.43	6.3
	min.	4	7	17	0	13	4.9	4.80	4.35	.3	.0	.6	1.08	.053	727	1.8	34	71	72	0	.24	.4	32	13.6	.033	.16	1.58	.174	1.87	.159	.119	4.36	3.9	35.8	.01	12.8
	max.	37	50	88	56	55	41.2	7.37	7.05	2.3	.5	2.7	1.52	.333	3770	95.8	321	3150	1455	71	1.37	5.7	225	138.1	.160	4.36	3.84	.513	4.43	.498	.316	15.84	13.6	119.9	2.68	43.1
MALAWI	mean	24	17	59	0	35	17.7	5.91	5.38	2.6	.1	1.3	1.29	.115	1461	39.4	227	1534	222	4	.29	3.3	131	86.4	.184	1.59	2.72	.393	2.92	.477	.215	4.84	12.7	94.2	.40	17.0
(n = 100)	± s	11	8	14	1	10	8.3	.56	.51	3.0	.2	.6	.12	.041	457	26.3	144	889	156	4	.11	2.7	67	53.7	.101	.94	.80	.153	.98	.142	.078	.84	4.5	61.0	.49	4.5
	min.	4	8	8	0	15	5.9	4.89	4.58	.3	.0	.3	.76	.039	298	2.6	38	200	17	0	.12	.3	39	18.7	.049	.17	1.18	.206	1.00	.180	.096	2.61	5.4	18.2	.03	9.2
	max.	49	47	87	8	61	41.1	7.30	6.80	16.7	.8	3.3	1.51	.257	2864	113.4	693	3838	769	19	.69	22.3	316	378.4	.748	4.10	4.32	.926	5.09	.939	.595	6.30	27.0	322.8	2.98	32.9
NIGERIA	mean	14	20	64	1	26	14.0	6.23	5.62	1.1	.1	1.0	1.36	.092	1211	21.7	191	1099	180	11	.30	1.9	89	37.3	.112	3.33	2.48	.315	3.42	.437	.232	5.38	10.8	76.1	1.53	29.6
(n = 103)	± s	12	16	24	7	12	6.7	.94	1.09	.8	.6	.6	.15	.049	564	41.4	175	1107	258	8	.17	1.7	65	32.4	.064	8.04	.52	.096	.80	.145	.075	1.58	2.8	35.0	2.79	12.9
	min.	3	2	5	0	13	2.4	4.70	3.95	.2	.0	.2	1.03	.041	607	1.2	35	65	15	1	.05	.3	15	2.9	.011	.17	1.31	.138	1.78	.174	.080	2.17	5.9	28.9	.03	13.3
	max.	78	63	93	45	83	47.1	8.20	7.60	4.8	5.4	4.9	1.77	.392	4500	303.2	1042	4880	2468	56	.86	13.4	376	203.0	.384	57.19	3.80	.593	6.02	.789	.530	10.48	22.1	232.8	21.03	81.3
SIERRA LEONE	mean	21	18	61	0	33	20.9	5.72	4.90	.8	.0	2.5	1.09	.198	2086	12.3	108	585	92	6	.38	1.1	123	7.8	.039	1.52	2.83	.266	3.65	.289	.168	6.59	10.2	62.1	.28	49.7
(n = 49)	± s	9	10	15	0	8	7.6	.50	.58	.6	.2	1.0	.09	.091	768	21.1	55	547	67	6	.14	.6	71	7.1	.017	1.91	.53	.064	.72	.073	.033	.91	3.1	14.4	.17	41.9
	min.	11	6	25	0	13	10.7	4.85	4.10	.3	.0	.8	.88	.103	1231	3.0	47	100	15	2	.17	.3	33	1.4	.017	.29	1.72	.166	1.61	.169	.111	4.42	3.8	39.5	.09	15.0
	max.	48	46	82	0	58	44.7	7.50	7.10	3.0	.9	5.7	1.22	.492	4512	152.0	280	2840	411	25	.81	3.1	400	45.5	.099	11.15	4.14	.472	5.20	.454	.267	8.60	25.0	115.7	.93	256.3
TANZANIA	mean	29	16	55	0	39	23.4	6.83	6.30	1.0	.4	1.3	1.26	.116	1356	32.7	639	2104	368	29	.80	4.6	114	52.1	.307	1.64	2.16	.317	3.05	.434	.223	16.49	10.8	103.0	1.63	80.7
(n = 175)	± s	22	9	26	4	20	15.6	.66	.75	.6	.8	.9	.19	.077	768	66.6	737	1727	263	74	.53	4.5	96	31.8	.396	1.99	.45	.109	.93	.168	.113	10.86	4.4	60.4	1.49	128.9
	min.	2	2	3	0	13	3.1	5.20	4.39	.1	.0	.2	.90	.014	237	.8	18	155	23	0	.15	.2	20	7.9	.019	.12	.88	.050	1.03	.091	.036	4.06	2.8	22.1	.03	13.0
	max.	85	46	93	54	88	60.0	8.30	7.80	4.7	7.6	4.8	1.72	.425	4747	656.0	5598	9265	1355	570	2.97	24.8	570	161.2	2.724	15.95	3.50	.596	6.71	.990	.772	99.99	25.0	316.3	7.60	915.6
[illegible]	mean	15	18	66	0	27	11.4	5.72	5.02	1.1	.0	.8	1.36	.073	957	28.8	145	665	123	4	.25	2.4	72	53.4	.110	.88	3.16	.400	2.09	.485	.200	4.02	13.5	128.3	.29	24.3
(n = 45)	± s	11	9	17	2	11	6.2	.63	.73	1.7	.1	.4	.12	.035	385	20.4	202	570	132	5	.10	3.3	57	36.7	.094	1.26	.41	.095	.49	.139	.052	1.00	3.6	116.8	.29	11.0
	min.	1	1	28	0	11	3.4	4.85	4.18	.2	.0	.2	1.10	.027	448	2.8	18	10	2	0	.10	.1	20	8.1	.019	.17	2.29	.189	.94	.274	.111	2.78	7.3	27.5	.02	12.0
	max.	44	41	97	11	55	28.2	7.64	7.14	11.5	.5	2.0	1.66	.180	2136	114.5	1272	2650	466	34	.66	12.5	350	200.0	.460	8.19	3.94	.587	3.15	.815	.369	7.62	21.2	488.5	1.34	78.7
WHOLE	mean	28	36	35	1	42	27.0	6.92	6.40	2.1	2.8	1.3	1.20	.135	1547	22.5	330	3450	446	86	.65	6.0	160	43.2	.212	2.14	3.14	.330	3.13	.470	.251	9.24	11.6	77.6	.86	35.7
INTERNAT.	± s	18	20	26	5	17	15.4	1.05	1.11	3.2	7.1	1.3	.14	.088	793	33.0	356	2815	462	260	.71	7.9	139	38.4	.273	6.49	.87	.104	.96	.205	.119	8.00	4.2	47.8	1.35	47.2
MATERIAL	min.	1	1	0	0	9	.2	4.00	3.62	.1	.0	.1	.47	.008	97	.1	18	10	2	0	.05	.1	14	.9	.010	.09	.88	.050	.58	.091	.036	1.88	2.0	8.3	.01	6.2
(n = 1976)	max.	87	87	97	56	91	99.7	8.95	8.55	73.0	67.1	39.1	1.77	1.657	14729	656.0	5598	17995	6490	4058	10.02	99.7	2275	378.4	3.560	185.20	6.51	1.038	6.71	1.880	1.125	100.04	99.6	517.1	21.03	915.6

Reference e
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Weed Science:

PRINCIPLES AND PRACTICES

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Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

FAO Food and Agriculture Organization of the United Nations

IPCS International Programme on Chemical Safety

ILSI Press

IRON OXIDE YELLOW

INS:	172iii
Chemical names:	HYDRATED FERRIC OXIDE; HYDRATED IRON (III) OXIDE
Synonyms:	C.I. PIGMENT YELLOW 42 AND 43
Functional class:	COLOUR
Colour class:	INORGANIC PIGMENT
Colour code:	C.I. (1975) No. 77492
Latest evaluation:	1979
ADI:	0-0.5
Report:	TRS 648-JECFA 23/13
Specs/residues:	FNP 49-JECFA 35/26 (1989); COMPENDIUM/799
Tox monograph:	FAS 6/NMRS 54A-JECFA 18/100 (1974)
Previous status:	1984, FNP 31/1-JECFA 28/99, R 1979, FNP 12-JECFA 23/53, R 1978, TRS 631-JECFA 22/20, FNP 7-JECFA 22/36, ADI NOT SPECIFIED (TEMPORARY), NS/TE, R,T 1974, NMRS 54/TRS 557-JECFA 18/17, FAS 7/NMRS 54B-JECFA 18/61, FAS 6/NMRS 54A-JECFA 18/100, ADI NOT SPECIFIED (TEMPORARY), NS/TE, R 1959, NMRS VOL. II-IV/19, N

IRON PALMITATE

Latest evaluation:	1985
ADI:	NOT SPECIFIED
Report:	TRS 733-JECFA 29/12
Specs/residues:	NOT PREPARED
Tox monograph:	NOT PREPARED

IRON PHOSPHATE

Latest evaluation:	1985
ADI:	70
Comments:	Also includes the free acid, PMTDI of 0.8 mg/kg of body weight for iron applies to iron from all sources except for iron oxides used as colouring agents and supplemental iron
Report:	TRS 733-JECFA 29/12
Specs/residues:	NOT PREPARED
Tox monograph:	NOT PREPARED

IRON SILICATE

Latest evaluation:	1985
ADI:	NOT SPECIFIED
Comments:	Also includes the free acid; this salt is insoluble in water and is not expected to provide a significant level of available silicate to the diet
Report:	TRS 733-JECFA 29/12
Specs/residues:	NOT PREPARED
Tox monograph:	NOT PREPARED

IRON SORBATE

Latest evaluation:	1985
ADI:	0-25
Comments:	Also includes the free acid
Report:	TRS 733-JECFA 29/12
Specs/residues:	NOT PREPARED
Tox monograph:	NOT PREPARED

IRON STEARATE

Latest evaluation:	1985
ADI:	NOT SPECIFIED
Report:	TRS 733-JECFA 29/12
Specs/residues:	NOT PREPARED
Tox monograph:	NOT PREPARED

ADI

The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 165 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of health manpower, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activities, such as developing systems of primary health care that reach the whole population of Member countries; promoting the health of mothers and children; combating malnutrition; controlling malaria and other communicable diseases including tuberculosis and leprosy; having achieved the eradication of smallpox, promoting mass immunization against a number of other preventable diseases; improving mental health; providing safe water supplies; and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides, and pharmaceuticals; formulating environmental health criteria; recommending international nonproprietary names for drugs; administering the International Health Regulations; revising the International Classification of Diseases, Injuries, and Causes of Death; and collecting and disseminating health statistical information.

Further information on many aspects of WHO's work is presented in the Organization's publications.

* * *

The *WHO Technical Report Series* makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration in their personal capacities rather than as representatives of governments or other bodies. An annual subscription to this series, comprising 15 to 20 such reports, costs Sw. fr. 80.–.

Summaries of these reports and of all other WHO publications are included regularly in the *WHO Chronicle*, a periodical review of the Organization's activities, published in Arabic, Chinese, English, French, Russian, and Spanish; annual subscription Sw. fr. 25.–.

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization or of the Food and Agriculture Organization of the United Nations

Evaluation of certain food additives and contaminants

Twenty-ninth Report of the
Joint FAO/WHO Expert Committee on
Food Additives

World Health Organization
Technical Report Series
733

World Health Organization, Geneva 1986

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ADI

studies on the immobilized enzyme preparation to assess the safety of the enzyme component, but studies would also be needed to establish the safety of the immobilizing agent.

Evaluation of microbial enzyme preparations

The Committee recognized that three separate situations must be considered with respect to the enzymes described in categories 4 and 5 of the guidelines for evaluating the toxicity of enzymes.[1] These situations are as follows:

(*a*) enzyme preparations added directly to the food but not re ed;

(*b*) enzyme preparations added to the food but removed from the final product according to good manufacturing practice; and

(*c*) immobilized enzyme preparations that are in contact with food only during processing.

For (*a*) above, the Committee concluded that an acceptable daily intake (ADI) should be established to ensure that levels of the enzyme preparation present in food are safe. For (*b*), the Committee concluded that an ADI "not specified" may be established, provided that there is a large margin of safety between possible residues and their acceptable intake. For (*c*), the Committee concluded that it may not be necessary to set an ADI for enzyme residues that might occur in food as a result of using the immobilized form of the enzyme. The Committee endorsed the concept that immobilized enzymes are acceptable for use in food processing.

The Committee was aware that new techniques in genetic ... ering could be used in the production of some enzyme preparations that are used in food processing. Evaluation of preparations containing enzymes produced by modified gene

[1] Full guidelines for evaluating enzyme preparations used in food processing are given in the twenty-sixth report of the Joint FAO/WHO Expert Committee (Annex 1, reference *59*, p. 49). Categories 4 and 5 of the guidelines for toxicological evaluation are reproduced below for ease of reference:

(4) Enzymes derived from nonpathogenic microorganisms commonly found as contaminants of foods. These materials are not considered as foods. It is necessary to establish chemical and microbiological specifications and to conduct short-term toxicity experiments to ensure the absence of toxicity. Each preparation must be evaluated individually and an ADI must be established.

(5) Enzymes derived from microorganisms that are less well known. These materials also require chemical and microbiological specifications and more extensive toxicological studies, including a long-term study in a rodent species.

complexes might entail an expansion of some of the principles enunciated by the Committee in its twenty-sixth report. New guidelines will be developed as such enzyme preparations are brought to the attention of the Committee.

Immobilizing agents

The Committee was informed that a number of procedures involving different chemical substances are used to immobilize enzymes. These procedures include microencapsulation (e.g., entrapment in gelatin), addition of glutaraldehyde, entrapment in a porous ceramic carrier, and formation of complexes with agents such as diethylaminoethyl cellulose or polyethylenimine. Several agents may be used in the immobilizing process.

Substances derived from the immobilizing agent may be found in the final food product if it contains impurities or if the immobilized enzyme system breaks down, but the levels of residue are normally extremely low.

Safety data will be required for the immobilizing agent, the type of data depending on the chemical nature of the substance. Some of the substances used to prepare immobilized enzyme systems are extremely toxic. The levels of these substances, or their toxic contaminants, permitted in the final product should be as low as technically feasible, and must be below levels that cause toxicological concern. ADIs will not be established for immobilizing agents.

2.2.2 *Inorganic and organic acids and their salts*

The Committee evaluated a list of food salts referred to it by the Codex Committee on Food Additives (see section 3.4. for details).

The Committee had in the past evaluated a large number of food acids and salts, and was of the opinion that ADIs for ionizable salts should be based on previously accepted recommendations for the constituent cations and anions (Annex 1, references *11* and *50*). Therefore, in order to aid future evaluations of ionizable salts, the Committee prepared Table 1, which gives acceptable daily intakes for a large number of combinations of cations and anions.

The ADIs listed in Table 1 are indicative of the general level of safety of the main classes of salts. Evaluations of specific salts may result in ADIs that differ from those listed in the table. In such cases, the results of evaluations of the individual salts supersede the ADIs

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ADI

Table 1. Acceptable daily intake for various anions and cations[a]

Cations	Anions	Acceptable daily intake (ADI)	References
	Acetate[b]	Not specified	11, 32
	Adipate[b]	0–5 mg/kg body wt	11, 44
	Caprate	Not specified	
	Caprylate	Not specified	
Aluminium (59)[c]	Carbonate	Not specified	11, 59
	Chloride[d,e]	Not specified	11, 50
Ammonium (11,50)[b]	Citrate[b]	Not specified	7, 13, 32
	Fumarate[b]	0–6 mg/kg body wt	11, 35
	Gluconate[b]	0–50 mg/kg body wt	13, 35, 50
Calcium (11,50)[b,e]	Guanylate[b]	Not specified	35
	Hydrogen carbonate	Not specified	11, 50, 59
Iron (62)[e,f]	Inosinate[b]	Not specified	35
	Laurate	Not specified	
	DL-malate[b,e]	Not specified	11, 13, 50
Magnesium (11,50)[e]	Myristate	Not specified	19, 32
	Oleate	Not specified	
	Palmitate	Not specified	
Potassium (11,50)[b]	Phosphate[g,h]	70 mg/kg body wt[i]	19, 32 59
	Silicate[j]	Not specified[k]	19, 32
Sodium (11,50)[b,e]	Sorbate[b]	0–25 mg/kg body wt	32
	Stearate	Not specified	19, 32
	Succinate	Not specified	
	Sulfate[l]	Not specified	47
	Sulfite[l]	0–0.7 mg/kg body wt	32, 62

[a]This table consolidates information presented in a previous report (Annex 1, reference 50) as well as information about compounds referred to the present Committee: the table applies only to the compounds for which the Committee has developed specifications.

[b]Temporary ADI of 0–6 mg/kg of body weight for sodium aluminium phosphate should be expanded to include all added aluminium salts and the ADI should be based on the aluminium content (0–0.6 mg/kg).

[c]No restriction provided that the contribution made to food is assessed and considered acceptable.

[d]Maximum tolerable daily intake allocated was 70 mg/kg of body weight (expressed as phosphorus) which applies to the sum of phosphates and polyphosphates in food. In the case of calcium salts, the Expert Committee had previously expressed concern about the calcium: phosphorus ratio in the diet and the desirability of maintaining nutritionally sound ratios (Annex 1, reference 59).

[e]For use in infant foods (Annex 1, reference 26, sections 3.4 and 5.4 in Annex 3).

[f]Provisional maximum tolerable intake for iron of 0.8 mg/kg of body weight per day applies to iron from all sources except for iron oxides used as colouring agents, supplemental iron taken during pregnancy and lactation, and supplemental iron for specific clinical requirements.

[g]Intake limited by laxative action.

[h]Also includes the free acids.

[i]Not to be added to the diet of very young infants.

[j]See recommendations on sulfite given in the seventeenth and twenty-seventh reports of the Committee (Annex 1, references 32 and 62, respectively).

[k]An ADI was not specified because these salts are insoluble in water and are not expected to provide a significant level of available silicate to the diet. Asbestiform fibres would be subject to special consideration (Annex 1, reference 47).

for the main classes of salt. For example, no information was available to the present Committee to indicate whether certain salts that were under review are being manufactured or used as food-grade materials and therefore, even though ADIs have been

allocated to the classes of salt to which these chemicals belong (as indicated in Table 1), no ADIs could be allocated to the specific salts.

With respect to the cations ammonium, calcium, potassium, and sodium, the Committee concurred with the ninth report (Annex 1, reference *11*) in placing no restrictions on their use, provided that their contribution to the diet is assessed and considered acceptable. In the case of calcium salts, the desirability of maintaining nutritionally sound ratios of calcium and phosphorous in the diet was stressed in accordance with the twenty-sixth report (Annex 1, reference *59*). The Committee agreed with the recommendations concerning the use of sodium chloride and calcium phosphate salts in infant foods given in the fifteenth report (Annex 1, reference *26*).

The Committee had specific reservations about the use of aluminium and magnesium salts, as discussed below.

(a) Cations

Aluminium. The Committee has previously expressed concern about the use of aluminium salts (Annex 1, reference *59*). These were that there was (*a*) insufficient information on the aluminium content of the diet, and (*b*) a need for additional safety data including absorption and metabolic studies in man, short-term feeding studies, and a multigeneration reproduction study. The Committee was informed that information on levels of aluminium in the diet is limited. Reported levels range from a few mg to 100 mg/day. However, with the refinement of analytical methods, more meaningful data are being obtained.

Limited new information was presented on the absorption of ingested aluminium. In one recent study in man, in which the levels of dietary aluminium were of the same order as that reported in food, some absorption occurred which resulted in a very slight increase in serum aluminium levels and increased excretion in the urine. No accumulation in tissue was reported, since all the administered aluminium was recovered in the urine and faeces. The Committee noted that (*a*) accumulation of aluminium ions is increased in individuals with chronic renal diseases and that their intake of aluminium should therefore be reduced; (*b*) aluminium has been implicated in the etiology of certain neurotoxic disorders, but definitive studies relating diet to these conditions are lacking; and (*c*) other dietary factors, such as citrate, phosphate, and fluoride, affect

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the absorption of aluminium. The studies requested by the Committee in 1982 (Annex 1, reference 59) had not been submitted. The Committee concluded that the temporary ADI of 0–6 mg/kg of body weight (equivalent to 0–0.6 mg/kg of body weight expressed as aluminium) allocated to sodium aluminium phosphate until its review in 1986 should be used for all aluminium salts added to food. The Committee also recommended that aluminium be subjected to a detailed review at a future meeting.

Magnesium. Magnesium is an essential ion that occurs in a wide range of foods. The estimated daily intake ranges from 180 to 4[illegible] mg/day. The recommended daily dietary requirement is 50–250 mg/day for infants, and 200–350 mg/day for adults.[1,2]

The Committee was concerned that the use of magnesium salts as food additives may have a laxative effect. The effect may be caused by osmotic absorption of water into the intestinal lumen or, more likely, by release of the gastrointestinal hormone cholecystokinin-pancreozymin, which stimulates motor and secretory activity in the gastrointestinal tract. The minimum effective dose is approximately 1000 mg of the magnesium moiety in the magnesium salt; however, the laxative effect is observed only when the magnesium salt is administered as a single dose. It is not known whether lower doses have other effects on hormonal activity. It was also noted that infants are particularly sensitive to the sedative effects of magnesium salts, and that individuals with chronic renal impairment retained 15–30% of administered magnesium, which could cause toxicity problems. The Committee concluded that the use of magnesium salts [illegible]d additives is acceptable provided that the above caveats are [illegible]n into consideration.

Iron. Iron compounds were considered by the Committee in 1983 (Annex 1, reference 62), when a provisional maximum tolerable daily intake of 0.8 mg iron/kg of body weight was established. The Committee reiterated its view that "this evaluation applies to iron from all sources except for iron oxides and hydrated iron oxides used as colouring agents and iron supplements taken during pregnancy

[1] *Recommended dietary allowances*, revised edition. Washington, DC, National Academy of Sciences, 1980.

[2] *Handbook of human nutritional requirements*. Geneva, World Health Organization, 1974 (Monograph series, No. 61).

ADI

and lactation or for specific clinical requirements" (Annex 1, reference 62).

(b) Anions (acids)

Fatty acids. The Committee has previously established ADIs "not specified" for myristic, palmitic, and stearic acids. The Committee extended the list of acceptable fatty acids to include capric, caprylic, lauric, and oleic acids. Their safety is based on their occurrence in edible fats and oils that have a long history of use as foods or food components. In addition, the even-chain fatty acids from C_2 to C_{18} have been shown to undergo oxidation to give acetoacetic acid and ketone bodies. The metabolic products are utilized and excreted.

Succinates. Succinic acid is a natural constituent of plants and animals that are commonly used as food. Experimental animals can tolerate high dietary concentrations of succinic acid. Succinic acid does not represent a hazard at the levels at which it is likely to be used as a food additive because of its normal role in metabolism. An ADI "not specified" was established for the succinate moiety.

Sulfates. Sulfates are natural constituents of food and are products of sulfur metabolism in animals. There is no information to suggest that their use as food additives has any toxic effects at normal dietary exposure. An ADI "not specified" was established for the sulfate moiety.

The other acids in Table 1 have been previously considered and ADIs established. The Committee concluded that their use would be safe, based on the information provided in Table 1.

2.2.3 *Limitation of the ADI imposed by lack of observed toxicity*

A number of food additives do not produce adverse effects in feeding studies, even when the maximum possible amount that is consistent with reasonable nutrition is added to the diet; the only effects arise from the physical properties of the additives, such as their bulk and hydrophilic properties. In such cases, the application of the conventional safety factor of 100 to the no-effect level obtained from a feeding study provides an ADI that underestimates the amount of additive that could be safety ingested by human consumers.

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Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides and pharmaceuticals; formulating environmental health criteria; recommending international nonproprietary names for drugs; administering the International Health Regulations; revising the International Classification of Diseases, Injuries, and Causes of Death; and collecting and disseminating health statistical information.

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toxicological consideration that arises is concerned with the maximum tolerable daily intake of bromide,[1] which should be dealt with at a subsequent meeting in the light of more recent studies than those that were available to the Committee at the time of its seventh report.

The Committee decided to change the previous acceptance of potassium bromate for the treatment of flour used for baking products to a temporary acceptance with a maximum treatment level of 75 mg potassium bromate per kg of flour, provided that bakery products prepared from such treated flour contain negligible residues of potassium bromate. For other foods, no acceptable level of treatment was proposed. Further work was required to establish residual levels of potassium bromate in foods treated with it.

A toxicological monograph was prepared, and the existing specifications were revised.

L-(+)-Tartaric acid, ammonium, calcium, and magnesium salts

L-(+)-Tartaric acid and its potassium, sodium, and mixed potassium-sodium salts were evaluated in the twenty-first report of the Committee (Annex 1, reference *43*). Consideration of the additional salts was requested by the Codex Committee on Food Additives. However, since no specifications were prepared, no ADI was allocated.

No toxicological monograph was prepared.

DL-(±)-Tartaric acid, ammonium, calcium, and magnesium salts

The Committee took this opportunity to revise the specifications for DL-(±)-tartaric acid. The existing tentative specifications were revised and the Committee agreed to delete the "tentative" qualification. The Committee was not aware of the use of ammonium, calcium, or magnesium salts of DL-(±)-Tartaric acid as food additives and requested additional information in this regard.

No toxicological monograph was prepared, and no ADI was allocated.

[1] In 1966, the joint report of the FAO Working Party on Pesticide Residues and the WHO Expert Committee on Pesticide Residues established an ADI for man for inorganic bromide, from all sources, of 0–1.0 mg/kg of body weight (WHO Technical Report Series, No. 370, 1967; FAO. PL:CP/15; and WHO/Food Add./67.32).

3.2 Contaminants

3.2.1 *Metals*

Arsenic

In the tenth report of the Committee (Annex 1, reference *12*) a maximum acceptable daily limit for arsenic was set at 0.05 mg/kg of body weight. The present Committee withdrew this limit since new data available to suggested that the limit is too high for inorganic arsenic.

The Committee recognized that inorganic and organic forms of arsenic present different problems. Epidemiological studies indicate that ingested inorganic arsenic may be carcinogenic in man at doses that produce signs of chronic arsenic toxicity, but accurate quantification of an acceptable exposure level is not possible owing to complicating factors in the populations that were exposed to drinking-water containing high concentrations of arsenic or to arsenical therapy. Animal models so far employed have not been useful for studying the question of the carcinogenic effect of inorganic arsenic.

There is evidence that organic arsenical compounds occur in a wide variety of foods and that relatively high concentrations may be present in some foods, particularly in certain sea foods. However, little is known about the chemical nature of these arsenical compounds and their relative distribution in foods. Work is therefore needed on the identification, metabolism, and potential toxicity of these compounds. However, there is no evidence to suggest that people who regularly consume large amounts of fish suffer ill-effects from its content of organic arsenic; the limited amount of animal data that are available also support the conclusion that ingestion of such fish does not constitute a hazard.

On the basis of the data available, the Committee could arrive at only an estimate of 0.002 mg/kg of body weight as a provisional maximum tolerable daily intake for ingested inorganic arsenic; no figure could be arrived at for organic arsenicals in foods. A toxicological monograph was prepared.

Iron

Although iron is an essential nutrient and an unavoidable constituent of foods, it may also be present as a contaminant. It has not been previously considered by the Committee in this context, but

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some iron-containing compounds have been accepted for food additive use. In the twenty-second (Annex 1, reference *48*) and twenty-third (Annex 1, reference *51*) reports of the Committee, "iron oxides and hydrated iron oxides" were evaluated for use as food colouring agents. The iron in these compounds is in the ferric form and has low bioavailability, and the results of feeding experiments with high levels did not result in any adverse effects. Hence, an ADI of 0–0.5 mg/kg of body weight for iron oxides and hydrated iron oxides (expressed as iron) was established (Annex 1, reference *51*). In its nineteenth (Annex 1, reference *37*) report, the Committee considered ferrous gluconate as a food colouring agent with a limited use, and established an ADI "not specified" provided that the ADI for gluconic acid was not exceeded.

A considerable body of information about iron is available from biochemical, physiological, and epidemiological studies, as well as from studies particularly oriented to toxicological aspects. The nutritional requirement for iron depends on age and sex. Recommended daily dietary requirements for iron range from 10 mg for adult men and post-menopausal women to 20 mg for women of child-bearing age. Adequate guidelines for nutritional requirements for iron have been published.[1,2]

There is still some uncertainty with regard to the maximum level of iron that can be tolerated. Normal individuals have taken daily supplements of 50 mg of iron per day (ferrous iron) for long periods without any adverse effects. The body has a considerable capacity to store iron, and chronic iron toxicity occurs only when the stores have been overloaded. This may occur in a number of disorders of ption, distribution, and utilization of iron.

the basis of the data available, the Committee allocated a provisional maximum tolerable daily intake to iron of 0.8 mg/kg of body weight. This evaluation applies to iron from all sources except for iron oxides and hydrated iron oxides used as colouring agents and iron supplements taken during pregnancy and lactation or for specific clinical requirements.

The Committee reiterated the view, expressed in the twenty-sixth report, that the tolerable daily intake should not be used as a

[1] *Recommended dietary allowances*, revised edition. Washington, DC, National Academy of Sciences, 1980.

[2] *Handbook of human nutritional requirements*. Geneva, World Health Organization, 1974 (Monograph Series, No. 61).

guideline for fortifying processed food (Annex 1, reference *60*, section 2.8).

A toxicological monograph was prepared.

3.2.2 *Xenobiotic anabolic agents*

The use of hormones and substances with hormonal activity in animal husbandry was considered in the twenty-sixth report of the Committee (Annex 1, reference *60*). In that report the Committee had recommended some general principles with respect to the evaluation of xenobiotic anabolic agents for use in the raising of animals for food. The data requirements included: "(*a*) adequate, relevant toxicological data; and (*b*) comprehensive data about the kinds and levels of residue when substances are used according to good animal husbandry practice." The Committee was aware of the extensive use of trenboline acetate and zeranol as anabolic agents in cattle.

Evaluating the toxicological data submitted to it, the Committee encountered several problems. Some of the data on residues were from studies in which the xenobiotic agents were used in combination with natural hormones (or their derivatives) and no toxicological studies of these combinations were available. The Committee also encountered problems with regard to the design of the necessary toxicological studies and to the potential tumorigenic activity of these compounds. The main problem was that the side-effects of the hormones used made the interpretation of results obtained difficult in the long-term studies with high doses. Furthermore, it was difficult to rule out completely some slight hormonal activity of even the lowest doses administered in the animal feeding studies. Therefore, the Committee had to determine whether or not the residues (or metabolites of the agents used) in animal tissue would be completely devoid of endocrinological or toxicological consequences for the consumer.

The Committee had for its consideration the results of detailed studies on the nature and levels of residues of trenbolone acetate and zeranol and their metabolites in muscle and edible organs of cattle and other animals treated with those agents. In cattle treated with trenbolone acetate according to good animal husbandry practice, the residue levels did not exceed 3 µg of α-trenbolone per kg of liver and 0.5 µg of β-trenbolone per kg of other tissues. In cattle treated with zeranol according to good animal husbandry practice, the

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limited further data were available. These were insufficient to allow for allocation of an ADI. The existing tentative specifications were revised and the "tentative" qualification was deleted.

The Committee was informed that further studies were in progress. No new toxicological monograph was prepared.

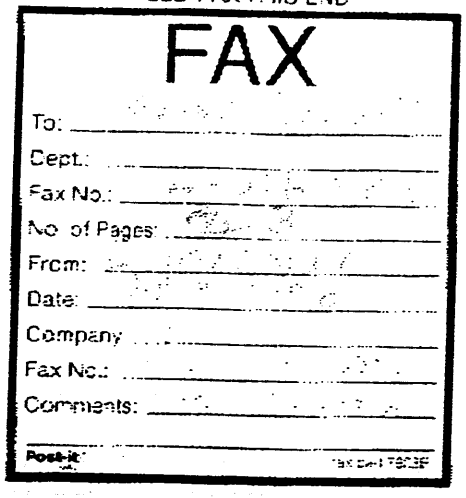
Quinoline Yellow. This compound was last evaluated by the Expert Committee in 1978 and a temporary ADI was allocated (see Annex 1, reference *48*). Some additional toxicological data were available to the present meeting, and the Committee was informed that further major studies were approaching completion. There are two quinoline yellows, the so-called "earlier" and "later" quinoline yellows; the latter is about 30% methylated, whereas the former is non-methylated.

In its nineteenth report (suggested that data from b logical evaluation of either use. This view was reitera

It was decided, therel 0–0.5 mg/kg of body weig postpone the preparation graph on Quinoline Yellow were available for evaluati

Specifications were revi methylated derivatives in as tentative.

Sunset Yellow FCF. Thi the eighth report of the E *8*) and allocated an ADI o work was considered desir studies have also been ca Committee reconsidered the earlier studies together with its consideration of the newer studies and decided to allocate a revised ADI of 0–2.5 mg/kg of body weight. The existing specifications were revised. A new toxicological monograph was prepared.



3.1.6 *Inorganic salts and buffering agents*

A number of substances on the agenda that have a variety of functions as food additives could be conveniently assembled under the heading of inorganic salts.

Phosphates and polyphosphates

Many phosphate and polyphosphate salts and phosphoric acid have been previously evaluated by the Expert Committee for acceptable daily intake (see Annex 1, references *6, 7, 8, 11, 19*, and *32*) and a toxicological monograph was published in 1974 (see Annex 1, reference 33). Some other phosphates and polyphosphates were considered for the first time by the present meeting. The list of compounds and their status in respect of toxicological evaluations and specifications is given in Annex 4.

Aluminium-containing phosphates were considered separately by the Committee. The remaining phosphates and polyphosphates were considered as a group, together with phosphate occurring naturally in food. The Committee noted the need to pay attention to the calcium/phosphorus ratio in the diet in evaluating the use of phosphates and polyphosphates as food additives (see section 2.6). The main toxicological finding in feeding studies with high levels of phosphates is nephrocalcinosis, in which respect the rat is acutely susceptible. The best estimate of the lowest level of dietary intake of phosphates (expressed as phosphorus) that might conceivably cause nephrocalcinosis in man is about 7000 mg per day.

Since phosphorus (as phosphates) is an essential nutrient and an unavoidable constituent of foods, it is neither appropriate nor feasible to give a range of values from zero to a maximum; therefore, the Committee decided to allocate a maximum tolerable daily intake (MTDI) to phosphates, rather than an ADI.

The maximum tolerable daily intake allocated was 70 mg/kg of body weight (expressed as phosphorus), which applies to the sum of phosphates and polyphosphates naturally present in food and the additives listed in Annex 4. This figure applies to diets that are nutritionally adequate in respect of calcium. However, if the calcium intake were abnormally high, the intake of phosphates could be proportionately higher than that stated above, and the reverse relationships would also apply (see also section 6.2). A revised toxicological monograph on phosphates was prepared.

Previously prepared specifications were confirmed except for calcium and potassium polyphosphates, the specifications for which were modified to include limits and a test procedure for cyclic phosphates. The Committee foresaw the need to revise the specifications for the polyphosphates in this respect. The Committee was not aware of any food additive use of ammonium polyphosphate and

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requested additional information; meanwhile tentative specifications were established, including limits and a test for cyclic phosphates. The Committee was concerned about the potential levels of fluoride, lead, and other heavy metal contaminants in bone phosphate, and was only able to establish tentative specifications until further information has been obtained.

Sodium aluminium phosphate (acidic and basic)

The main toxicological consideration in relation to these compounds is due to the aluminium component. The particular compounds on the agenda were "sodium aluminuum phosphate, basic" and "sodium aluminuum phosphate, acidic". Neither has been considered specifically by a previous meeting of the Expert Committee, but both compounds were included in a toxicological monograph on aluminium published in 1977 (see Annex 1, reference *44*). Only one recent feeding study with "sodium aluminium phosphate, acidic" was available for consideration; this was a 90-day feeding study in beagles at levels up to 3% in the diet. A temporary ADI of 0–6 mg/kg of body weight was allocated to sodium aluminium phosphate. Further work required is specified in Annex 3. A toxicological monograph on sodium aluminium phosphate was prepared. New specifications were prepared for "sodium aluminium phosphate, basic" and new tentative specifications were prepared for "sodium aluminium phosphate, acidic".

Ammonium carbonate and ammonium hydrogen carbonate (formerly ammonium bicarbonate)

Although only limited toxicological data are available for these ammonium salts, the results of studies with other ammonium salts and other carbonates and bicarbonates provide a basis for evaluation. There is a considerable amount of information on the clinical uses of ammonium chloride and sodium bicarbonate to alter acid–base balance and urinary pH. The evidence from human exposure to relatively high doses suggests that it is without significant toxic effects, except for alteration in acid–base balance. It would appear that this would be less of a problem with ammonium carbonate and bicarbonate.

In assigning the ADI for ammonium carbonate and ammonium hydrogen carbonate as "not specified", the Committee stressed the need to apply all the conditions and restraints that follow from such

a designation (see Annex 1, reference *32*). The existing specifications for the two compounds were revised. A toxicological monograph was prepared.

Magnesium silicate

This anti-caking agent was previously considered by the Expert Committee in 1969, 1973, 1976, and 1980 (see Annex 1, references *19*, *32*, *40*, and *54*). No additional information was made available to the present meeting. However, the existing tentative specifications have been revised to exclude magnesium trisilicate. Therefore, the Committee considered that the ADI for magnesium silicate should be reallocated at its former level, namely, "not specified". No new toxicological monograph was prepared. The existing specifications were revised and the Committee agreed to delete the "tentative" qualification.

3.1.7 *Sweetening agents*

Sorbitol

This substance was assigned an ADI "not specified" by the Committee in its seventeenth report (see Annex 1, reference *32*). However, this was changed to a temporary ADI in 1978 (see Annex 1, reference *48*) and confirmed as temporary in 1980 (see Annex 1, reference *54*) because of concern about the production of adrenal medullary hyperplasia in rats in a feeding study with 20% of sorbitol in the diet. The present meeting took the view that such a high level of sorbitol produced gross dietary imbalance, which may produce metabolic imbalance, and considered that the adrenal medullary hyperplasia produced by high dietary levels of sorbitol and certain other nutrients might occur as a physiological consequence of the stresses induced in aging rats. Consequently, the Committee removed the temporary status.

The Committee was aware of a multigeneration study in progress and considered that the submission of the results of this study was highly desirable. No new toxicological monograph was prepared. The existing specifications were revised.

Calcium and sodium cyclamates

Cyclamate, calcium and sodium salts, and cyclohexylamine were evaluated in the twenty-first report of the Expert Committee, when a temporary ADI of 0–4 mg/kg of body weight was allocated to

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Preventing Iron Deficiency Through Food Fortification

Richard F. Hurrell, Ph.D.

June 1997: 210–222

Excellent

One way to prevent iron deficiency anemia in developing countries is through the fortification of food products with iron. In addition to avoiding undesirable color and flavor changes, the main challenge is to protect the fortification iron from potential inhibitors of iron absorption present in commonly fortified foods.

Introduction

There is clear evidence of a high prevalence of iron deficiency anemia in developing countries and, to a lesser extent, in the more industrialized countries of the world. Most critically affected are infants, school-age children, and women of reproductive age. Approximately 50% of these populations suffer from anemia in the less-developed countries of South Asia and Africa, compared with about 25% in Latin America and approximately 10% in the industrialized countries of Europe.[1] In addition to the deleterious physiologic consequences of iron deficiency in individuals, the resulting public health consequences in developing countries can significantly impact economies in the form of health costs, wasted educational resources, and lost productivity.

Before considering an intervention strategy to prevent iron deficiency, its etiology must be understood. This is more complex in developing countries than in industrialized countries where the consumption of insufficient absorbable iron is usually the only cause or may be the major factor causing iron deficiency.[2] In developing countries, other possible causes are intestinal worm infections, malaria, and vitamin A deficiency.[3,4] The major causative factor in developing countries is not low iron intake, but, rather, low iron absorption. Iron intake is often relatively high, almost 20 mg/day,[3] and would easily meet the recommended dietary allowances for the United States (10–15 mg/day).[5] Unfortunately, much of the ingested iron is poorly bioavailable iron from plant sources or is contamination iron from soil and includes little bioavailable iron from animal tissues. Major cereals, legumes, and staple foods contain high levels of phytic acid, which is a potent inhibitor of iron absorption,[6,7] and some, such as sorghum, also contain phenolic compounds, which greatly impede iron absorption[8] by binding iron in the gut in unabsorbable complexes. The intake of foods that enhance iron absorption such as fruits and vegetables containing vitamin C[9] or muscle tissue[10] is often limited.

The fortification of foods is often regarded as the most cost-effective long-term approach to reducing the prevalence of iron deficiency.[11,12] This can be in the form of "mass medication" by fortifying foods such as cereals, milk, salt, and condiments that are widely consumed by both at-risk populations and others who have little or no need for extra iron. Alternatively, a targeted fortification program in which a food product preferentially consumed by one of the at-risk groups is fortified can be considered.

Although targeted fortification is relatively easy to design for infant foods such as formulas and commercial infant cereals, or for schoolchildren through school feeding programs including such foods as fortified drinks or cookies, it is more difficult to target a fortified food specifically for adult fertile women. For this group, the fortification of a widely consumed product would seem the best way to provide extra food iron, but other groups such as adult men and postmenopausal women, who do not require extra iron, will also consume the fortified food. In industrialized countries, there is concern that this excess iron may be detrimental and lead to increased incidence of atherosclerosis[13] and cancer[14] owing to increased oxidative stress.

In developing countries, however, where a lower intake of bioavailable iron occurs, these considerations might not apply. The prevalence of anemia in adult men has been reported to range from 2% in Europe and 4% in North America, to 13% in Latin America, 20% in Africa, and 32% in South Asia.[1]

Although widespread iron deficiency has been recognized for more than 50 years, intervention strategies including food fortification have been met with limited success. The only clear success story has been in industrialized countries, such as the United States and Sweden, where the steady drop in the prevalence of iron deficiency in infants and preschool children over the last 30 years[15] is

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considered to be the result of the consumption of iron-fortified infant formulas.[16] The current low incidence of iron deficiency anemia in fertile U.S. women, reported as 2.9% in the NHANES II survey,[17] could also be due in part to the high consumption of iron-fortified foods in the United States.[18] Fortification of products such as white bread, rolls, crackers, corn flour, corn grits, pasta, and breakfast cereals is widespread, and fortified iron from these products represented about 20% of the total iron intake as determined in NHANES II.[18,19]

Although pilot fortification trials in developing countries have given promising results, there are as yet no major success stories except perhaps for Chile.[20,21] This could be due to lack of political commitment, insufficient funding, too little technical support from local or multinational industries, poor distribution networks, or lack of nutrition education programs for the consumer, all of which are considered necessary for a successful fortification program.[22] Another reason could be that iron deficiency is due to factors other than insufficient absorbable iron. Hookworm infections, malaria, and vitamin A deficiency should be addressed simultaneously in any food fortification strategy. However, if low bioavailability of food iron is the major determinant of iron deficiency anemia in developing countries,[23] increasing the supply of absorbable food iron should decrease the prevalence of iron deficiency anemia.

This necessitates the careful selection of both the food product to be fortified and the iron fortification compound to be added. Clearly, the iron compound must be first optimized with respect to relative bioavailability.[24] However, if the food vehicle contains potent inhibitors of absorption, the added iron, like the native iron, will be poorly absorbed and will have little or no impact on the iron status of the consumer. The success of a food fortification program thus depends heavily on the absorbability of the added iron and its protection from major dietary absorption inhibitors.

This review focuses on the technical aspects governing the choice of food vehicle and iron compound with the aim of ensuring an adequate absorption of fortification iron. The optimization of the iron compound in relation to bioavailability and organoleptic problems is discussed first, followed by a description of methods that can be used to protect fortification iron from absorption inhibitors. These include the addition of ascorbic acid, the use of hemoglobin or dried blood, and the use of NaFeEDTA. Finally, the major foodstuffs that are used as iron fortification vehicles are discussed in relation to potential organoleptic problems, the presence of absorption inhibitors, and possible fortification compounds.

Optimization of the Iron Compound

Some characteristics of commonly used iron compounds are shown in Table 1.[12,24,25] They can be conveniently divided into four groups: (1) those that are freely water-soluble; (2) those that are poorly water soluble but soluble in dilute acids such as gastric juice; (3) those that are water

Table 1. Characteristics of Iron Sources Commonly Used to Fortify Food (adapted from Hurrell 1985, 1992; Bothwell & McPhail 1992)

	Approximate Fe content (%)	Average relative bioavailability		Approximate relative cost[a]
		Rat	Man	
Freely water soluble				
Ferrous sulfate $7H_2O$	20	100	100	1.0
Dried ferrous sulfate	33	100	100	0.7
Ferrous gluconate	12	97	89	5.1
Ferrous lactate	19	—	106	4.1
Ferric ammonium citrate	18	107	—	2.1
Poorly water soluble/soluble in dilute acid				
Ferrous fumarate	33	95	100	1.3
Ferrous succinate	35	119	92	4.1
Ferric saccharate	10	92	74	5.2
Water-insoluble/poorly soluble in dilute acid				
Ferric orthophosphate	28	6–46	25–32	4.1
Ferric ammonium orthophosphate (EKA Nobel, Sweden)	19	—	30–60	—
Ferric pyrophosphate	25	45–58	21–74	2.3
Elemental Fe powders: electrolytic	98	44–48	5–100	0.5
carbonyl	98	39–66	5–20	1.0
reduced	97	24–54	13–148	0.2
Protected compounds				
NaFeEDTA	14	—	28–416	6.0
Hemoglobin	0.34	—	100–700	—

Adapted from references 10, 12, and 25.
[a]Relative to ferrous sulfate $7H_2O$ = 1.0, for the same level of total iron.

insoluble but poorly soluble in dilute [illegible]; and (4) protected iron c[illegible]ds. The table gives [illegible]ideline values for relative b[illegible]ilability in rat and mar[illegible] a relative cost factor. A more detailed description of th[illegible]nd other compounds can be found in reference 25.

The cost [illegible]he more recent or experi[illegible]tal compounds such as NaFe[illegible]TA, ferric ammonium [illegible]iophosphate,[26] and hemoglobin depends to some exte[illegible]n the amounts ordered. In general, the freely water-s[illegible]le compounds are highly bioava[illegible]able in rodents and humans, as are compounds that are w[illegible]ter insoluble but soluble in dilute acids. Compounds th[illegible] are poorly soluble in dilute acid, however, have only [illegible]ow to moderate bioavailability. This is because of variable [illegible]issolution in gastric juice owing to both the characteristics [illegible]f the compound itself[27] and the meal composition.[28] Although it would be logical to always use iron compounds [illegible]hi[illegible]st bioavailability, they unfortunately often ca[illegible]p[illegible]ible color and flavor changes in many foods. [illegible]tion, therefore, means selecting the iron compound with the highest potential [illegible]n without causing subsequent organoleptic problems in the food vehicle.

Bioavailability

The absorption of fortification iron depends primarily on its solubility in gastric juice. Water-soluble compounds such as ferrous sulfate dissolve instantaneously in gastric juice, whereas more insoluble compounds, such as elemental iron, rarely dissolve completely. Once dissolved, fortification iron enters the common pool, where its absorption (like that of all pool iron) depends on the content of enhancing or inhibitory ligands in the meal and on the iron status of the subject. For example, phytate and polyphenols or a satisfactory iron status in an individual will diminish absorption, whereas vitamin C or low iron status will enhance absorption.

Because iron status and various food components may markedly affect iron absorption, the absorption of a single iron compound can vary from less than 1% to almost 100%. Therefore, when comparing different iron compounds, one must measure the bioavailability relative to a standard compound. The standard is usually ferrous sulfate, which has been designated as having a relative bioavailability (RBV) of 100. It has recently been demonstrated that the hemoglobin repletion test in rodents and the measurement of dialyzable iron in vitro are good predictors of iron bioavailability in humans.[29] The RBV of many commercial iron compounds is well known (Table 1[12,24,25]). New compounds can be screened by animal or in vitro assays, although human studies are ultimately necessary.

Compounds labeled with radioactive or stable isotopes can be prepared and used as confirmation for the more soluble compounds. For those compounds that are poorly soluble in dilute acids, however, such as phosphate and elemental iron powders, one is never absolutely sure that the labeled experimental compound made on a small scale has exactly the same physicochemical characteristics as the commercial compound. The best confirmation of the utility of these compounds is intervention studies monitoring iron status.[30]

Organoleptic Problems

In addition to causing unacceptable changes in color and flavor when added to foods, iron compounds may also provoke precipitation, such as when added to fish sauce[31] or when iron-fortified sugar is added to tea.[32] Many iron compounds are colored and cannot be used to fortify light-colored foods. In addition, the more soluble iron compounds often react with substances in foods, causing discoloration. Infant cereals have been found to turn gray or green on addition of ferrous sulfate and dark blue if bananas are present.[27] Phenolic compounds have often been implicated, and Douglas et al.[33] reported that ferrous sulfate, ferrous lactate, ferrous gluconate, and ferric ammonium citrate, as well as the less soluble ferrous fumarate and ferric citrate, produce off-colors when added to a chocolate milk drink. Similarly, salt fortified with ferrous sulfate or other soluble iron compounds becomes yellow or brown.[34]

Off-flavor can also result from the metallic taste of the soluble iron itself, particularly in beverages. However, the catalytic effect of iron on fat oxidation in cereals during storage is the major problem. As in the case of product discoloration, the water-soluble compounds, such as ferrous sulfate, promote fat oxidation and reduce product shelf life. A convenient method to measure the potential of iron fortification compounds to promote fat oxidation in cereals is to measure pentane formation in the headspace of sealed cans containing the iron-fortified product.[35]

Pentane is the major hydrocarbon formed by the oxidative degradation of linoleic acid, and its formation correlates with the production of off-flavors. Figure 1 shows the rate of pentane formation during storage at 37 °C of a precooked whole wheat flour containing various iron salts (at a concentration of 15 mg iron per 100 g flour).[27] Ferrous sulfate and ferrous gluconate rapidly generated pentane and were judged unacceptable by a taste panel after 4 to 6 weeks of storage. Ferric pyrophosphate and reduced elemental iron generated far less pentane and were still organoleptically acceptable after 7 weeks of storage. A similar oxidative rancidity can occur in milk products when iron is added.[36,37]

Freely Water-Soluble Compounds

Freely water-soluble compounds are the most bioavailable iron compounds, but also the most likely to promote unacceptable color and flavor changes. They are essential in liquid products, and there is often little difference between the compounds with respect to bioavailability, flavor, and organoleptic problems. Ferrous sulfate is the least expen-

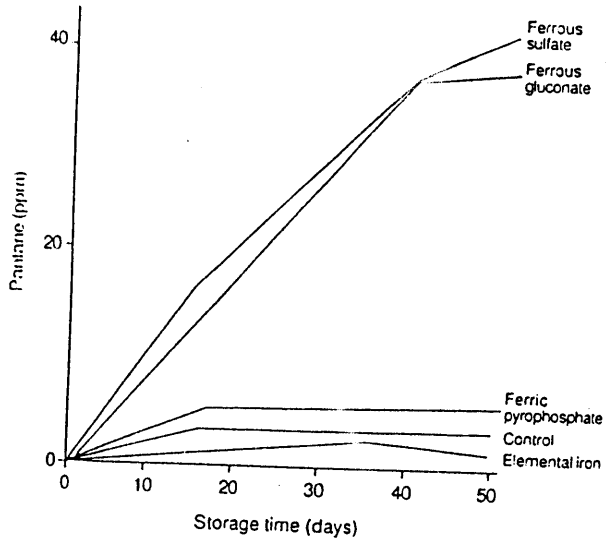

Figure 1. Pentane formation in stored wheat flour fortified with different iron compounds (adapted from reference 27).

sive compound and is widely used to fortify infant formulas and pasta and cereal flour that are stored for only short periods. Other possibilities are ferrous gluconate, ferrous lactate, and ferric ammonium citrate. Although there is no evidence that soluble ferric salts are absorbed to a lesser extent than soluble ferrous salts when iron is in an ionized form,[35] it is possible that ferric iron binds more strongly with inhibitors of absorption such as phytic acid and polyphenols.

Compounds Soluble in Dilute Acid

Recently, several compounds that are poorly soluble in water but readily soluble in dilute acids have been identified. These compounds are ferrous fumarate, ferrous succinate, and ferric saccharate. Their advantage is that they cause far fewer organoleptic problems than freely water-soluble compounds and still readily enter the common iron pool during digestion. They have been suggested for use in infant cereals[35] and chocolate drink powders.[39]

Studies have been conducted in which adult human subjects were fed a chocolate drink or an infant cereal fortified with ^{55}Fe-radiolabeled test compounds or ^{59}Fe-radiolabeled ferrous sulfate.[35,39] The chocolate drink contained 5 mg iron and 25 mg vitamin C per serving, and the infant cereal contained 7.5 mg iron and 35 mg vitamin C per serving. Absolute absorption from the ferrous sulfate control meals varied from 3% to 6%. The absorption from ferrous fumarate and ferrous succinate was at least as good if not better than from ferrous sulfate. Absorption from ferrous fumarate was twice as high as from ferrous sulfate in the chocolate milk drink, and the iron compound may have undergone some reactions during the manufacture of the chocolate drink powder, which included a vacuum drying stage. In the infant cereal, ferrous fumarate was dry-mixed into the product after processing and had an absorption equivalent to the ferrous sulfate. Ferric saccharate had a variable but moderate absorption (RBV 39–74), and ferric pyrophosphate had a variable but low absorption (RBV 20–39). It would seem that these iron compounds are less soluble in gastric juice in the presence of chocolate milk drink than in the presence of infant cereal, because the lowest absorption values were from the chocolate milk drink. Ferric pyrophosphate and ferric saccharate caused no organoleptic problems in either product. In the chocolate drink, ferrous succinate was satisfactory, but ferrous fumarate caused a color loss if the product was made with boiling water. Similarly, ferrous fumarate and ferrous succinate were organoleptically satisfactory when added to simple infant cereals, but color problems occurred in more acid fruit varieties.

Compounds Poorly Soluble in Dilute Acids

Compounds that are poorly soluble in dilute acids include ferric pyrophosphate, ferric orthophosphate, ferric ammonium orthophosphate, and the elemental iron powders made by carbonyl, electrolytic, or reduction techniques.[24,40] They are the most often-used compounds in food fortification and their main advantage is that they cause no organoleptic problems. Their disadvantage is that they have a variable absorption because they do not readily dissolve in gastric juice. Animal studies indicate that current commercial compounds are about half as well absorbed as ferrous sulfate.[35] Human studies, however, have given variable and conflicting results (Table 1[12,24,25]). This is either because the compounds tested had different physiochemical characteristics from the commercial compounds[29,41,42] or because of the influence of different meals on the dissolution of the iron compound in gastric juice. Hallberg et al.,[25] for instance, found that the RBV in humans of the same carbonyl iron powder varied from 5 to 20 and the RBV of ferric ammonium orthophosphate varied from 30 to 60[25] simply because of the composition of the meal with which they were fed. When carbonyl iron is consumed without a meal in pharmacologic (100 mg) doses, it is reported to have a relative bioavailability in humans of about 70% that of ferrous sulfate.[43]

It seems probable that the low levels of elemental iron (40 mg/kg) added to wheat flour would have little impact on iron nutrition, but the much higher levels added to commercial infant cereals (200–550 mg/kg) together with vitamin C could contribute substantially to the prevention of iron deficiency anemia.

Encapsulated Iron Compounds

Both ferrous sulfate and ferrous fumarate are available commercially in encapsulated form. Commonly, the coatings are partially hydrogenated oils, such as soybean and cottonseed, or ethyl cellulose. The coating has little influence

on the RBV as measured in rodent assa and can prevent fat oxidation changes during stora cereals or in infant formulas fortified with the easily dizable long-chain polyunsaturated fatty acids. Most tings are heat labile, however, and at temperatures abo 0–70 °C often do not prevent unwanted color reaction inc stearate is the only coating proposed that has a hi melting point (122 °C), and its bioavailability in rodent assays was reported to be 70% that of ferrous sulfate.[44]

Protecting and Enhancing the Absorption of Fortification Iron

Many food vehicles for iron fortification contain substances that inhibit iron absorption. Cereals contain phytic acid and occasionally polyphenols, milk contains calcium and casein, and chocolate drinks contain polyphenols. In addition, many diets in developing countries to which fortified salt, sugar, or other condiments are added are often high in phytate and polyphenols from cereal and legume foods. To ensure a level of absorption that is high enough to improve or maintain iron status, it is necessary to prevent the fortification iron from reacting with the absorption inhibitors. This can be accomplished by adding absorption enhancers. The most common enhancer is vitamin C. Alternatives would be bovine hemoglobin and NaFeEDTA where iron is in a protected form.

Vitamin C

Vitamin C can increase the absorption of both native iron and fortification iron severalfold when added to foods. Its effect appears to be related to both its reducing power and its chelating action. It can reduce ferric to ferrous iron and/or maintain ferrous iron in the ferrous state and so prevent or decrease the formation of insoluble complexes with absorption inhibitors or with hydroxide ion in the gut. In addition, it can form soluble complexes with iron at low pH that remain soluble and absorbable at the more alkaline duodenal pH. Thus, Layrisse et al.[45] reported a sixfold increase in iron absorption (1.4% to 7.9%) by adult peasants in Venezuela who consumed 100 g maize containing 2.8 mg iron and 70 mg added vitamin C. Similarly, Cook and Monsen[46] reported that iron absorption in young men fed a liquid formula meal containing 4.1 mg iron increased from 0.8% to 7.1% as vitamin C was increased from 25 to 1000 mg. More recently, Siegenberg et al.[47] reported that the effect of vitamin C on phytate and polyphenols was dose dependant and that as little as 30 mg vitamin C could completely overcome the effect of phytic acid (58 mg phytate phosphorus) in maize bran added to white bread, whereas >50 mg vitamin C overcame the negative effect of meals containing ≥100 mg polyphenols added as tannic acid.

Vitamin C increases the absorption of all fortification iron compounds to a similar extent.[29] Derman et al.[48] reported that iron absorption by adult women with low iron stores from infant cereal fortified with ferrous sulfate or ferrous ammonium citrate was only about 1% in the absence of vitamin C, but increased fourfold to 10-fold when vitamin C was added. Similarly, Forbes et al.[29] reported that iron absorption by adult men and women consuming a farina and milk meal containing 3 mg iron as ferrous sulfate, ferric orthophosphate, or electrolytic iron was only 1% to 4% in the absence of vitamin C but increased three- to fourfold in its presence.

In a milk-based infant formula fortified with 15 mg iron as ferrous sulfate per liter, iron absorption by infants was only 3% in the absence of vitamin C but increased to 5% with 100 mg vitamin C per liter and to 8% with 200 mg per liter.[49] The poor iron absorption from the product with no added vitamin C was cited as the reason for the relative ineffectiveness of a field trial conducted with this product,[20] but in subsequent field trials with the product containing 100 mg vitamin C per liter, the prevalence of iron deficiency anemia in children 15 months old was only 5.5% compared with 30% in infants receiving a non-iron-fortified formula.[50]

Hemoglobin

Hemoglobin is a form of food iron that is naturally protected from major inhibitors of iron absorption, such as phytic acid and polyphenols. The iron is contained within the porphyrin ring of the heme molecule, which is split from the globin moiety during digestion, and is taken up intact into the mucosal cells.[51,52] The iron is released within the mucosal cell by the action of heme oxygenase[53] and is prevented from reacting with the inhibitory and enhancing ligands within the intestinal lumen. Hemoglobin iron, however, is better absorbed than heme iron without the globin and is further enhanced in the presence of muscle tissue.[54,55] The nature of the mechanism is not fully established, but it seems to be related to protein digestion products preventing the polymerization of heme molecules, thus reducing their absorption.[51]

When used as a food additive, hemoglobin is added in the form of dried red blood cells. Its main advantage is that iron absorption is relatively high and predictable. Absorption varies little with the composition of a meal, and although it varies to some extent with the iron status of the subjects,[56] this variation is far less than with nonheme iron. Monsen et al.[57] estimated that heme iron would be 15–35% absorbed depending on the iron stores; it is thus possible that if hemoglobin-fortified products are not targeted specifically to at-risk groups, tissue iron stores will gradually accumulate in iron-replete subjects. The main disadvantage of hemoglobin iron, however, is the very low iron content (0.34%) and its intense red-brown color. In infant cereal, 5 g dried bovine red blood cells per 100 g rice flour was necessary to provide 14 mg Fe/100 g,[58] making the product dark brown. Iron absorption was 14% in 8-month-old infants, and although the globin protein is lacking in isoleucine, it is high in lysine and is reported to

provide a useful amount of addition[illegible]otein to a mixed diet.[58] Other disadvantages are the te[illegible]al difficulties of collecting, drying, and storing anima[illegible]od and of obtaining animal blood in countries where [illegible]eat is not widely consumed, as well as religions beliefs that forbid the consumption of blood.

In Latin American countries where the supply of animal blood is plentiful, two field trials demonstrated the potential usefulness of dried red blood cells as a food fortificant. In the first,[59] extruded rice containing 5% bovine hemoglobin concentrate was fed to infants 4 to 12 months old and their iron status was compared with that of infants fed regular solid foods (vegetables and meat). In the control group at 12 months, the prevalence of iron deficiency anemia was 17% compared with only 6% in infants who consumed more than 30 g fortified cereal per day. In a second study,[21] three 10 g w[illegible]eat flour cookies containing 6% bovine hemoglobin c[illegible]entrate were fed as part of the Chilean school lunch program over a period of 3 years. In a survey of 1000 participating children, significantly higher serum ferritin and hemoglobin levels were found in children who consumed the fortified cookies than in those who did not. However, the prevalence of anemia in 10- to 16-year-old schoolchildren was surprisingly low, and in girls the prevalence fell from 1.3% to 0.5%, compared with a fall from 0.8% to 0.4% in boys. The authors concluded that the program would have had a larger impact on iron status in regions where the prevalence of iron deficiency in schoolchildren is higher.

Sodium Iron EDTA

The use of NaFeEDTA as a food additive has recently been reviewed by the International Nutritional Anemia Consultative Group (INACG)[60] and was strongly recommended as the most suitable iron fortificant for use in developing countries. The provisional acceptance of the compound by the Joint FAO/WHO Expert Committee on Food Additives[61] for use in supervised fortification programs in iron-deficient populations has cleared the way for large-scale fortification trials. Other EDTA-containing compounds, i.e., Na_2EDTA and $CaNa_2EDTA$, are widely used in manufactured foods in industrialized countries as protection against metal-induced organoleptic changes. The EDTA molecule forms FeEDTA in the intestinal tract,[60] so that combinations of Na_2EDTA and ferrous sulfate or other iron compounds can also be considered for fortification purposes.

Chemistry. EDTA (ethylene diamine tetraacetic acid) is a hexadentate chelate binding through its four negatively charged carboxylic acid groups and two amine groups. It can combine with virtually every metal in the periodic table. Its effectiveness as a chelate depends on the stability constant between EDTA and the metal. This is influenced by pH and molar ratio, and any metal capable of forming a stronger complex with EDTA will at least partially displace another. Of the nutritionally important metals, Fe^{3+} has the highest stability constant log k of 25.1, followed by copper (Cu) at 18.4, zinc (Zn) at 16.1, Fe^{2+} at 14.6, calcium (Ca) at 10.7, magnesium (Mg) at 8.7, and sodium (Na) at 1.7. The less desirable metals such as mercury (Hg, 20.4), lead (Pb, 17.6), and aluminum (Al, 15.5) and perhaps manganese (Mn, 13.5) also have fairly high stability constants. The situation is somewhat complicated by having an optimum pH for complex formation between 1 and 10. The optimum pH for complex formation between Fe^{3+} and EDTA is pH 1, Cu is 3, Zn is 4, Fe^{2+} is 5, Ca is 7.5, and Mg is 10.[62]

Based on the pH optima, the predicted effect in the intestine of NaFeEDTA and $CaNa_2EDTA$ in food would be as follows. In the stomach, Fe^{3+} from NaFeEDTA would remain firmly bound to EDTA, whereas Ca and Na from $CaNa_2EDTA$ would dissociate and EDTA would bind Fe from the common pool. So even with the addition of $CaNa_2EDTA$, iron EDTA would form in the stomach. In the duodenum, the iron would be released and absorbed[63] and the EDTA would presumably bind in succession to Cu (pH 3), Zn (pH 4), and Fe^{2+} (pH 5), but most of the metals are released for absorption as <5% of the metal–EDTA complexes are absorbed (<1% FeEDTA)[64] and excreted directly in the urine. More than 95% of the EDTA molecule is excreted in the stool. Theoretically, in the ileum and colon, it could bind to Ca, which has a pH optimum of 7.5 for complex formation. Mg, with a low stability constant and a high pH optimum of 10.5, probably would not react.

Absorption of Iron from NaFeEDTA. The major advantage of NaFeEDTA over other iron fortification compounds is that it prevents iron from binding with the phytic acid present in many cereal and legume grains. Thus, in cereal foods or meals containing a considerable quantity of phytic acid, the absorption of iron from NaFeEDTA is two- to threefold that from ferrous sulfate. With less inhibitory foods, such as potato, there is little difference between the iron absorption from the two iron compounds. With neutral foods, such as sugar cane syrup, consumed on their own, iron absorption when fortified with NaFeEDTA was only 30% of that from ferrous sulfate (for detailed review see reference 60).

In a way similar to vitamin C, Na_2EDTA could be considered an absorption enhancer. It has the added advantage of being stable during processing and storage. It must, however, be added at an equivalent or slightly lower molar ratio to iron in the meal. El-Guindi et al.[65] added equimolar quantities of ferrous sulfate and Na_2EDTA to Egyptian *baladi* bread and increased iron absorption from 2.1% to 5.3%. Earlier work suggested that increasing the ratio of Na_2EDTA to iron is associated with a progressive reduction in iron absorption.[66] MacPhail and Bothwell[30] recently reported that adding Na_2EDTA to a ferrous sulfate–fortified rice meal significantly increased absorption at EDTA-to-iron ratios of 1:4 to 1:1, with a maximum absorption at

1:2. EDTA-to-iron ratios of 2:1 to 4:1 did not significantly increase or decrease iron absorption.

Possible Reactions of EDTA with Other Dietary Minerals. Considering the possible impact of EDTA from NaFeEDTA (10 mg iron per day) on the nutritional status of other minerals assumed to be in the diet at levels equivalent to their RDAs, it can be calculated that on a molar ratio basis there are 50 times more magnesium and 80 times more calcium than EDTA, so there would be no likely impact of EDTA on magnesium or calcium metabolism. With copper and zinc, however, there could be a possible effect, since on a molar basis there are eight times more EDTA than copper and equivalent amounts of EDTA and zinc.

We have investigated this effect in both rodents and adult women. In rodents, increasing levels of EDTA in the diet increased zinc absorption and, to a lesser extent, also increased copper absorption but had no effect on calcium absorption.[67] In adult women fed iron-fortified bread rolls, zinc absorption was increased from 20% with ferrous sulfate to 34% with NaFeEDTA, although there was no effect on calcium absorption. Urinary zinc excretion was also increased from 0.3% to 0.6%, but this had little or no effect on overall zinc metabolism.[68] The EDTA molecule from added NaFeEDTA can therefore increase both iron and zinc absorption from meals containing phytic acid. It might also increase the absorption of copper, as well as the potentially toxic elements Pb, Hg, Al, and Mn. However, it would be expected to have no effect on calcium and magnesium absorption.

Intervention Studies. Three intervention studies have been made with NaFeEDTA by Garby and Areekul[69] in Thailand, Viteri et al.[70,71] in Guatemala, and Ballot et al.[72] in South Africa. All were controlled studies, but only the South African study was double blinded. The number of subjects varied from approximately 600 to 17,000 and the study time from 12 to 32 months. None of the food vehicles—fish sauce, sugar, curry powder—contained phytic acid. The amounts of iron provided per day were 4.3 mg in sugar, 7.7 mg in curry powder, and 10–15 mg in fish sauce. All showed a positive effect on iron status. In the fish sauce study, packed cell volume increased in men, women, and children. In the sugar study, even with a fairly low level of fortification and a relatively modest compliance, there was an increase in serum ferritin (iron stores) in all subjects receiving the fortified product but not in subjects receiving the unfortified product. In the curry powder study, there was an increase in red cell hemoglobin levels and serum ferritin in all subjects, and anemia in women fell dramatically from 22% to 5%.

Organoleptic Considerations. Iron combined in NaFeEDTA causes fewer organoleptic problems than other water-soluble iron compounds. It can, however, cause unwanted color changes. We have found it to be unsuitable for the fortification of chocolate drink powders and infant cereals containing banana and other fruits. Viteri et al.[71] reported that NaFeEDTA-fortified sugar is slightly yellow in color and, when added to tea, turned the tea black. Similarly, when added to corn starch puddings and gruels, it turned them a pinkish-violet color.

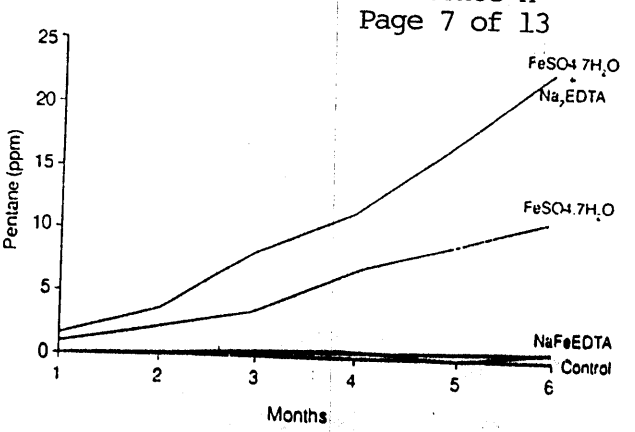

Figure 2. Pentane formation in stored wheat flour fortified with NaFeEDTA.

NaFeEDTA does have an advantage, however, when added to stored cereals, because unlike ferrous sulfate, it does not provoke the fat oxidation reactions that lead to rancid, oxidized products. We stored (unpublished results) dry white wheat flour mixed with NaFeEDTA, ferrous sulfate, or ferrous sulfate plus equimolar Na_2EDTA (15 mg Fe/100 g) in closed aluminum cans as described by Hurrell et al.[35] Fat oxidation was quantified by measuring the accumulation of pentane in the headspace. The results (Figure 2) show that stored wheat flour underwent little or no fat oxidation during 6 months storage at 37 °C when unfortified or fortified with NaFeEDTA. In contrast, when the flour was fortified with $FeSO_4\ 7H_2O$ (hepta hydrate), or $FeSO_4\ 7H_2O$ plus Na_2EDTA, lipids in the wheat flour were progressively oxidized during the storage periods and progressively more pentane accumulated in the headspace.

Regulatory Issues and the Current Use of EDTA in Foods. The Joint FAO/WHO Expert Committee on Food Additives (JEGFA)[73] permitted the use of $CaNa_2EDTA$ and Na_2EDTA up to 2.5 mg/kg body weight/day with a maximum acceptable daily intake (ADI) set at 150 mg/person/day. The ADI was extrapolated from the rodent study by Oser et al.[74] as the highest no-effect level (250 mg/kg), applying a safety factor of 100. Unfortunately, this study did not include higher levels of EDTA. These compounds are now permitted by local food and drug authorities for use in many countries in Asia, Africa, the Middle East, Europe, and America as a sequestering agent for metals to prevent flavor changes, rancidity, discoloration, turbidity, and texture loss. They are most often added to foods such as mayonnaise, canned vegetables (peas, beans, potatoes), canned fish and shell fish, carbonated beverages, beer, and margarine. In the United States, they are permitted in 34 different foods at levels varying from 33 to 800 mg/kg (Table 2), although the estimated daily intake is only 25

Table 2. Examples of Approved $CaNa_2EDTA$ Use in Foods in the United States

Food Products	Purpose	Amount Permitted (mg/kg)
Lima beans, canned	Retain color	310
Pinto beans, dried	Retain color	800
Cabbage, pickled cucumber	Retain color, flavor texture	200
Carbonated beverages	Retain flavor	33
Crabmeat, clams, shrimps	Retain color	250–340
Egg products	Preservative	200
Margarine	Retain color	75
Mayonnaise	Retain color	75
Mushrooms, canned	Retain color	200
Potatoes, canned	Retain color	110
Sandwich spread	Preservative	200

mg/person/day,[60] 10 times less than the ADI.

Although other regions, such as Malaysia and the Philippines, also allow EDTA in a wide range of foods, the European Union takes a more restrictive view and only allows addition to canned crab, canned shrimp, pickles, canned mushroom, glacé cherries, and sauces. EDTA compounds are currently not allowed in foods consumed by infants and young children.

Present Status of NaFeEDTA. Although NaFeEDTA would appear, at present, to be the most appropriate iron fortificant for use in developing countries, it is still about six times more expensive than ferrous sulfate. However, it is two- to threefold better absorbed than ferrous sulfate, and relatively expensive vitamin C does not need to be added as an absorption enhancer. Additional savings can be made in the packaging material, because less sophisticated packaging can be used for a NaFeEDTA-fortified food than for one fortified with ferrous sulfate (or other iron salts) and vitamin C. The better packaging material must be designed to protect vitamin C from degradation during storage.

However, before general use of NaFeEDTA can be recommended, more systematic studies are necessary to ascertain potential organoleptic problems in a variety of foods. Additionally, its influence on the absorption of the potentially toxic metals (Pb, Hg, Al, Mn) must be investigated and the physiologic importance of any demonstrated influence must be ascertained.

Food Vehicles for Iron Fortification

Cereal Products

Cereal flours are currently the most frequently used vehicles for iron fortification that reach the entire population. The amount of iron added is usually relatively low because it is added only to restore the iron level in milled flour to that of the whole grain. With true fortification, a higher amount than is usually present would be added. Wheat flour enrichment is mandatory in many countries, and the native level in 70% extraction flour (11–12 mg/kg) is enriched up to 44 mg/kg, which is the approximate content of whole-wheat grains. This is the situation in the United States. Other countries add even lower amounts of iron. In Denmark, the enrichment level is 30 mg/kg and in the United Kingdom it is 16.5 mg/kg, as the iron content in white flour is restored to that of 80% extraction flour.

In the United States, corn (maize) meal, corn grits, and pasta products also have federal standards for voluntary iron enrichment, and these commodities are mostly enriched by manufacturers similarly to other baked goods such as crackers, rolls, cookies, and doughnuts but to a lesser extent.[75] The contribution of fortified iron to iron intake is highest in the United States, where it accounts for 20–25% of total iron intake.[76,77] The contribution of fortified iron to iron intake in the United Kingdom is much lower, around 6%.[19]

Technology also exists for fortifying whole grains such as rice. This can be done by coating, infusing, or by using extruded grain analogues. The fortified grains are then mixed 1:100 or 1:200 with the normal grains. Hunnell et al.[78] described a sophisticated method of preparing fortified rice grains by first infusing B vitamins and then adding iron, calcium, and vitamin E in separate layers of coating material. The cost of these procedures together with the difficulty of completely masking the fortified grains is the main reason why no successful programs have been implemented in developing countries. Although iron fortification of rice is mandatory in the Philippines, it has never been enforced.[11]

Other commonly fortified foods are breakfast cereals and infant cereals. In industrialized countries, breakfast cereals can potentially provide a significant amount of iron, particularly to children and adolescents. In the United Kingdom, for instance, they can provide up to 15% of total iron intake in 11–12-year-olds.[79] The contribution of fortified iron from infant cereals is potentially much greater because they often provide the major source of iron at a critical time in a child's growth and brain development.

There are two major disadvantages to using cereal

products as vehicles for iron fortificati... First, they contain high levels of phytic acid, a potent... inhibitor of iron absorption[6]—up to 1% in whole grains ... about 100 mg/100 g in high-extraction flours. Second, ... are extremely sensitive to fat oxidation during stor... when highly bioavailable iron compounds such as ferrous sulfate are added.[35] For organoleptic reasons, cereal flours such as wheat and maize are usually fortified with poorly absorbed elemental iron powders, and rice with ferric orthophosphate or ferric pyrophosphate.[78] Only bread, wheat flour stored for less than 3 months, and pasta products, because of their low moisture content, can be fortified with the more highly available ferrous sulfate.[80] However, even with these foods, iron absorption will be inhibited by the presence of phytic acid unless an absorption enhancer is present. This is rarely the case, although NaFeEDTA would appear to be ideally suited to the fortification of cereal flours and perhaps even pasta products. The usefulness of the fortification of these cereal foods can therefore be questioned, because rather low levels of poorly absorbed iron compounds are added without absorption enhancers to products containing phytic acid.

Breakfast cereals are similarly fortified with reduced elemental iron,[80] and in the absence of vitamin C, the usefulness of this fortification is also doubtful. Infant cereals, by contrast, are fortified with much higher levels of iron (200–500 mg/kg) in the presence of large amounts of vitamin C. More bioavailable iron compounds such as ferrous fumarate are also often used,[35] and even with the electrolytic form of elemental iron, the efficiency of infant cereals to provide a nutritionally useful source of iron has been demonstrated.[30]

Salt

Iodine-fortified salt has successfully eradicated iodine deficiency in many countries,[81] so salt would also seem a highly suitable vehicle for iron fortification. However, iron fortification of salt poses many technical problems, and for developing countries, an efficient production and distribution system must also exist.

Almost all of the development work for the fortification of salt with iron has been conducted in India.[82-85] Color changes during storage have been the main problem, because salt in India is relatively crude and contains up to 4% moisture. All soluble iron compounds and vitamin C caused unacceptable color changes. Fortification was possible only with insoluble iron compounds, and ferric orthophosphate was recommended at 1 mg iron per gram salt so as to provide about 15 mg extra iron per day. When $NaHSO_4$ was added as an absorption promoter,[34] absorption was reported to be 80% that of ferrous sulfate. A small-scale fortification trial in which the fortified salt was included in school feeding program demonstrated an improvement in iron status.[84]

Salt that contains fewer impurities would undoubtedly be easier to ...tify, but the extra cost to the consumer is always a major ...nsideration in developing countries. In addition, there is always the possibility that the iron-fortified salt will cause unacceptable color reactions if added to vegetables in a meal. This was one of the explanations offered for the failure of a salt fortification program in the Seychelles and Mauritius in the early 1960s.[86] The other reasons were the relatively poor bioavailability of the ferric pyrophosphate used and the fact that it separated from the salt and sank to the bottom of the salt barrels.

Sugar

Sugar is an alternative vehicle for iron fortification in regions of the world where it is produced, such as the Caribbean and Central America, but in other developing countries refined sugar consumption is more common in the middle and upper socioeconomic segments of the population.[11] Iron from fortified sugar would be expected to be well absorbed if consumed with citrus drinks but poorly absorbed from coffee and tea owing to phenolic compounds or, if added to cereal products, owing to phytate.

As with salt, the main technical problem is to select a bioavailable iron compound that does not cause unwanted color changes in less pure sugar products. In Guatemala, this was overcome by adding NaFeEDTA.[71] Commercial white cane sugar would appear easier to fortify, and Disler et al.[32] reported the successful addition of several different ferric and ferrous compounds (100–200 mg iron/kg) together with vitamin C. There were, however, unacceptable color reactions when added to coffee and tea[32] or to certain maize products.[71] A successful fortification trial was reported in Guatemala, where NaFeEDTA added to sugar at 13 mg iron/kg to provide an extra 4 mg iron/day per person increased iron stores in all population groups receiving the fortified product.[71]

Milk

Infant formulas are usually milk based with added vegetable oils, minerals, and vitamins. Iron is almost always added as ferrous sulfate from 5 to 12 mg per liter,[87] and its absorption can be improved considerably by the addition of 100–200 mg vitamin C per liter.[49] The relatively low iron bioavailability from milk products can be assumed to be due to the presence of two inhibitory factors, calcium[88] and the milk protein casein.[89] In a series of fortification trials in Chile in which iron-fortified formulas were fed to infants, the improvement of iron status was only modest in the absence of vitamin C but improved considerably when it was added to formula.[20] The widespread consumption of iron-fortified (and vitamin C-fortified) formulas by infants in the United States is regarded as the reason for the dramatic fall in the prevalence of anemia over the last 30 years.[15]

Whole milk could also be considered as a vehicle for iron fortification, but because of the presence of calcium and casein, an absorption enhancer should be added to

improve absorption. Unfortunately, it is difficult to add vitamin C to fluid milk and it has been reported to degrade rapidly to diketogluconic acid leading to changes in flavor.[90] Many soluble iron compounds rapidly produce off-flavors when added to milk, owing to the promotion of lipolytic rancidity, oxidative rancidity by the oxidation of free fatty acids, and the partial or complete loss of vitamins A, C, and ß-carotene.[91]

After evaluation of a series of compounds, the addition of ferric ammonium citrate has been proposed for liquid milk[36,92] and for skim milk, skim milk concentrate, and dry milk powder.[93] The addition of NaFeEDTA would appear to be an interesting alternative, but it has not been evaluated extensively for organoleptic properties in milk. The usefulness of milk as a vehicle for iron fortification has been demonstrated in a Mexican school feeding program.[94] The hemoglobin level of children fed 200 mL milk containing 20 mg iron as ferrous chloride improved by 1 g/dL in 3 months. This study demonstrated that with high levels of added iron, the addition of vitamin C was not essential. As with iron-fortified sugar, when iron-fortified milk is added to tea, coffee, or cocoa, the beverages undergo unacceptable color changes.

Iron-fortified milk-based chocolate drinks are also food products that can be usefully targeted to children and adolescents. A variety of products are commercially available, although the phenolic compounds present in cocoa powder readily undergo color changes with soluble iron[33] and also bind iron in the gut and inhibit its absorption. Compounds such as ferrous fumarate, ferrous succinate, ferric saccharate, and ferric pyrophosphate have shown acceptable organoleptic properties,[39] with fumarate showing the highest absorption. The addition of vitamin C would presumably be necessary to overcome the inhibitory factors in the cocoa and milk.

Condiments

Condiments that are traditionally used in developing countries, such as monosodium glutamate, fish sauce, curry powder, and bouillon cubes, could be useful fortification vehicles. Monosodium glutamate is widely used as a flavor enhancer in Asia and has been successfully fortified with ferric orthophosphate and ferrous sulfate encapsulated in zinc stearate.[44] The latter compound had 70% of the relative bioavailability of ferrous sulfate in rodents and the capsule had a melting point of 122 °C. Pilot fortification trials with iron-fortified fish sauce[69] or curry powder,[72] both fortified with NaFeEDTA, resulted in significant improvement in iron status in the population consuming the fortified products. The success of fortified condiments presumably depends both on the absence of adverse color reactions and on the addition of an absorption enhancer, such as EDTA.

Coffee

In some populations coffee is consumed by most adults as well as some children, and it is technically and economically feasible to fortify coffee with iron. Johnson and Evans[95] reported the use of ferrous fumarate in roasted and ground coffee, in which one cup (200 mL) provided 1 mg added iron. The addition of iron to soluble coffee is also relatively easy; Klug et al.[96] reported that the addition of a range of soluble ferrous and ferric compounds was possible. Flavor and color changes, however, are a potential problem, and coffee, like tea and cocoa, contains phenolic compounds that strongly inhibit iron absorption.[97]

Conclusion

One strategy to overcome the high prevalence of iron deficiency anemia in developing countries is to fortify various food products with iron. There are several options with respect to the iron compound used and the food product to be fortified. Various factors, including cost effectiveness of the fortification in raising absorbable iron intake in the targeted population, the palatability of the fortified food, and the etiology of iron deficiency must be considered before initiating a fortification program. As most iron-fortified foods contain potential absorption inhibitors, it is essential to protect the fortification iron so as to ensure adequate absorption. This can be achieved easily in the food industry by adding vitamin C, although EDTA and, possibly, hemoglobin would seem better options for developing countries.

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MEDICAL TOXICOLOGY

DIAGNOSIS AND TREATMENT OF HUMAN POISONING

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who developed hemolytic anemia, renal failure, arrhythmias, and central nervous system depression during which an *E. coli* septicemia from intestinal wall invasion developed.[9]

TREATMENT

Vomiting usually makes emesis/lavage unnecessary. Activated charcoal/cathartic may be used but its role is unproven. Chelating agents are recommended in severe poisoning, but few pharmacokinetic data on humans exist to guide their use. Either intravenous $CaNa_2EDTA$ or intramuscular BAL is the agent of choice in severe ingestion. D-Penicillamine may be administered orally, if tolerated, to non-penicillin-allergic patients. Exchange transfusion has been used in a 2-year-old boy together with albumin-enriched peritoneal dialysis.[9]

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GOLD

In the form of gold sodium thiomalate, gold therapy is an acceptable treatment for rheumatoid arthritis. Adverse reactions occurring during therapy include interstitial pneumonitis,[1] dermatitis, stomatitis, bone marrow suppression (leukopenia, thrombocytopenia, anemia), nephrotic syndrome, nephritis, and hepatitis. An encephalopathy also has been associated with gold therapy.[2] Most overdoses to date involve the inadvertent administration of 500 mg gold salt as an intramuscular injection (10 times the therapeutic dose). Usually the patient remains asymptomatic but may develop mild elevations in serum hepatic transaminase levels[3] and thrombocytopenia.[4] A 32-year-old patient developed ventricular tachycardia 3 hours after the intramuscular injection of 500 mg of aurothiomalate.[5]

Studies in animals indicate that high gold concentrations produce acute renal failure.[6] The weekly administration of 50 mg of soluble gold salt produces steady-state serum gold concentrations of 400 to 800 μg/dL by the eighth week; toxicity, however, cannot be predicted by blood levels alone. Peak serum gold level was 5 mg/dL after an injection of 500 mg gold aurothiomalate.[4] Treatment includes the use of steroids for pneumonitis,[7] BAL chelation,[8] and supportive care. (A patient who received two 500-mg gold aurothioglucose injections within 1 week remained asymptomatic without chelation therapy.)[3]

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IRON

INTRODUCTION

Epidemiology

Approximately 5,000 cases of poisoning with iron preparations occur every year in the United States. In contrast to heavy-metal poisonings, which commonly are associated with work exposures, most iron toxicity results from the ingestion of iron-containing products by children. There has been a dramatic increase in iron poisonings over the last four decades. The introduction of the antidote deferoxamine has reduced the mortality in hospitalized patients from 50% to less than 2%. According to American Association of Poison Control Centers data, iron exposures are less frequent than exposures to calcium salts and fluoride, but fatalities have occurred after iron exposure.[1]

Product Formulations

The relative toxicity of iron results from the amount of elemental iron ingested. This in turn depends on the type of iron salt involved. The large majority of poisonings result from ferrous sulfate ingestion.

The percentages of elemental iron contained within specific salts are as follows:

Ferrous sulfate	
Anhydrous salt	36.8%
Crystalline salt	20.1%
Ferrous chloride	
Anhydrous salt	44.1%
Crystalline salt	28.1%
Ferrous gluconate	
Anhydrous salt	12.5%
Dihydrate salt	11.6%
Ferrous fumarate	33%
Ferric chloride	
Anhydrous salt	34.3%
Hexahydrous salt	20.7%
Ferric ammonium citrate	14%–18%

Estimation of Toxic Dosage

Remember that the reliability of estimating the number of tablets ingested is only as good as the history, which itself is often unreliable. Always treat symptoms rather than history. Based on the quantity ingested, the following amounts of elemental iron indicate the severity of toxicity:

Nontoxic Dose. <10 to 20 mg of elemental iron ingested per kilogram (e.g., 3 tablets of ferrous sulfate in a 10-kg child = 3 × (0.20) (325 mg)/10 kg = 19.5 mg/kg).

Toxic Range. >20 mg/kg (4 ferrous sulfate tablets in a 10-kg child). Decontamination is recommended at this level and referral to a physician above 60 mg/kg.

Lethal Range. 180 to 300 mg/kg (30–45 tablets in a 10-kg child). Death has been reported from the ingestion of 2.7 g (542 mg elemental iron) and survival from the ingestion of 19.5 g of ferrous sulfate (3.9 g elemental iron).

PHARMACOKINETICS

Absorption

Iron is absorbed through the mucosal barrier in the ferrous (2+) state where it oxidizes to the ferric (3+) state and attaches to the storage protein, ferritin. Control of iron stores depends on variation in absorption rather than excretion. A fatal case of iron toxicity developed in a worker who fell into a vat of ferrous chloride. Absorption has occurred through aspiration, ingestion, and burned skin.[2]

Distribution

Iron is released from the ferritin to the globulin transferrin in the plasma and then transported to the blood-forming sites.

Excretion

No good mechanism for iron excretion exists. Consequently, the natural elimination of iron by the body is extremely limited and occurs by blood loss or desquamation of gastrointestinal mucosa. Adults lose up to 2 mg of iron daily.

PATHOPHYSIOLOGY

Toxic doses of iron overwhelm the normal gastrointestinal regulatory mechanism (suggesting that saturable transport systems are not involved at high concentrations); this results in massive iron absorption.[3] Major toxicity occurs when serum iron levels exceed the iron-binding capacity of transferrin. Free circulating iron damages systemic blood vessels. The release of the potent vasodilator ferritin and, possibly, the release of serotonin and histamine potentiate the vascular damage caused by free serum iron. In severe iron overdose, the coagulative necrosis with platelet aggregation appears similar to the damage caused by corrosive agents.

Gastrointestinal Tract

The corrosive effect of iron results in stomach and intestinal erosions and ulceration (i.e., hemorrhagic gastritis and enteritis with blood loss); however, there is a lack of correlation between the severity of intestinal damage and death. Pyloric obstruction and intestinal scarring are rare, late complications.

Liver

Circulating free iron initially accumulates in the Kupffer cells and later the hepatocytes. The effects on the liver are highly variable and range from no abnormalities to cloudy swelling of the hepatocytes, portal iron disposition, fatty metamorphosis, and massive periportal necrosis.[4,5]

Hepatic damage may progress to hepatic failure with hypoprothrombinemia and hypoglycemia. Hepatorenal syndrome may occur. Free iron inhibits the thrombin-induced conversion of fibrinogen to fibrin and, therefore, directly affects coagulation.[6]

Cardiovascular System

Fatty degeneration of the myocardium occurs in iron intoxification. Iron acts on the vascular system to increase venous pooling (increased capillary permeability) and decrease cardiac output (reduced postarteriolar and venous tone) and, subsequently, produces hypotension. Proposed etiologies for postarteriolar dilation include a direct iron effect, ferritin release, and serotonin/histamine release.

Kidney

Masses of iron-containing granules accumulate in the capsular space and tubule lumen; however, tubular degeneration is rare.

Acidosis

Interference with oxidative enzymes, the release of hydrogen with formation of ferric hydroxides, and the accumulation of lactic acid from anaerobic metabolism may all result in severe metabolic acidosis.[7] Ferrous ions catalyze lipid peroxidation which can cause disruption of mitochondrial membranes and the Krebs cycle. Iron also shunts electrons from the electron transport system by acting as an electron sink.[8] The result is the production of a metabolic acidosis.

Brain

Iron can produce cerebral edema by an unknown mechanism.

CLINICAL PRESENTATION

Classically, severe iron toxicity presents in four distinct phases.[9] Symptoms in the first phase involve gastrointestinal tract irritation and metabolic abnormalities (e.g., acidosis).

Initial Period

A severe hemorrhagic gastritis characterizes the initial period (½–2 hours postingestion). Vomiting is the most sensitive indicator of serious ingestion, with a 94% sensitivity but only a 25% specificity.[10] Diarrhea is a less sensitive but more specific indicator of serious iron ingestions. Central nervous system (lethargy and coma) and cardiovascular (pallor, tachycardia, hypotension) symptoms may be manifested early in severe ingestions.

Quiescent Period

During this period (variable, up to 12 hours) a deceptive improvement and stabilization occur, which frequently result in premature discharge from health care facilities. Alternating periods of lethargy may appear during this stage. In severe overdoses this quiescent period may be brief.

Recurrent Period

Systemic symptoms that are life threatening predominate during this phase (12–48 hours).

Gastrointestinal Tract. Hematemesis, melena, gastrointestinal perforation.

Central Nervous System. Increasing lethargy, coma, convulsions.

Cardiovascular System. Vasomotor collapse, cyanosis, pulmonary edema.

Liver/Kidney. Hepatorenal failure with coagulation defects and hypoglycemia.[11] These effects developed toward the end of this phase. Some authors consider the hepatic necrosis a distinct phase separate from the recurrent phase.

Metabolic. Severe metabolic acidosis, hypoglycemia.

Late Period

Gastric scarring and pyloric obstruction appear during the late recovery phase (4–6 weeks).

LABORATORY

Serum Levels

Reliability

Although serum iron levels cannot always be correlated with the severity of intoxication, patients are at risk if free iron exists in the plasma (i.e., serum iron level exceeds the total iron-binding capacity [TIBC]). Peak serum iron levels occur 2 to 4 hours after ingestion and correlate best with potential toxicity. Serum iron levels drawn more than 4 to 6 hours postingestion may underestimate toxicity because of the binding of iron to ferritin and the distribution of iron into the tissues. The administration of deferoxamine interferes with chromogenic methods of iron determination but not with atomic absorption spectrophotometry.[12]

Indications

All symptomatic patients and those patients with a history of ingestion of more than 40 mg of elemental iron per kilogram should have blood drawn for serum iron and TIBC tests.

Interpretation

Heparinized samples of whole blood should be drawn 3 to 5 hours postingestion. Because of rapid iron clearance, low blood levels after this period may be misleading.

If TIBC levels are not available to determine the presence of free iron, serum iron levels may be used to predict toxicity. At high serum iron levels, high iron levels may falsely increase serum TIBC concentrations. Fewer than 10% of patients with serum iron levels below 500 μg/dL will develop cardiovascular collapse or coma. Between 500 and 700 μg/dL, the percentage increases to 25%. Above 700 μg/dL, approximately 50% of the patients have severe symptoms.[13] Correlation of serum iron levels (2–4 hours postingestion) with probable toxicity is as follows:

0–100 μg/dl	Normal range
100–350 μg/dl	Definite poisoning, questionable toxicity
350–500 μg/dl	Potentially serious toxicity
500–1000 μg/dl	Definite serious toxicity
Over 1000 μg/dl	Potentially fatal

Abnormalities

Abdominal X-Rays

Radio-opacity depends on several variables, including time since ingestion, content of elemental iron, and type of formulation (e.g., vitamins with iron and sugar-coated candy tablets are not radio-opaque). Negative radiographs, especially 2 hours after ingestion, do not exclude iron overdose.[14] Although chewable vitamins with iron are radio-opaque, visualization of these tablets clinically is unlikely (E. P. Krenzelok, personal communication). Within 2 hours the abdominal x-ray is useful as a measure of the efficiency of gastric emptying in all except minor ingestions.

Blood

Specific indicators of elevated serum iron levels include the white blood cell count and blood glucose levels. A leukocytosis over 15,000/mm^3 and a hyperglycemia exceeding 150 mg/dL correlated with elevated serum iron levels (over 300 μg/dL) in a retrospective study.[10] These measures are *not* sensitive and are *not* predictive if there are fewer than 15,000 WBC or the serum glucose is below 150 mg/dL. When serum iron levels are not immediately available, these levels may help predict potential toxicity *if* elevated.

Ancillary Tests

Supportive studies in patients with serious ingestions (serum iron levels over 350 μg/dL) include guaiac tests of the stool and gastric aspirate, serum hepatic transaminase levels, coagulation studies, complete blood count, hemoglobin, hematocrit, electrolytes, glucose, arterial blood gases, blood type, and antibody screen.

Rapid Screening Tests

Fischer developed a rapid serum detection method for iron using the chromogen 2,4,6-tripyridyl-*s*-triazine (TPTZ).[15] McGuigan et al described a qualitative deferoxamine color test for gastric aspirate as an adjunctive screening method for iron within 2 hours of ingestion.[16]

Two milligrams of gastric fluid and two drops of 30% H_2O_2 are placed in each of two plastic tubes. One-half milliliter of a deferoxamine solution (composed of one 500-mg ampule of deferoxamine and 4 mL of distilled water) is added to one tube. An immediate change of color (light orange to dark red) in that tube compared with the control indicates the presence of iron. Negative results more than 2 hours postingestion do not reliably exclude iron poisoning because of the possibility of absorption.

TREATMENT

Decontamination

Emesis

Emesis should be induced, unless there is a definite risk of aspiration, when the history indicates an iron ingestion exceeding 20 mg/kg or symptoms suggest significant iron ingestion.

Lavage

Gastric lavage is the alternative method of decontamination for obtunded patients who do not have a gag reflex. Mechanical removal may be difficult because of tablet size and cohesiveness. The type of lavage fluid used to complex iron is controversial. A 1% to 4% sodium bicarbonate solution (add 50-mEq ampule to 1 L D_5W/0.45% NaCl) complexes some of the free ferrous ion into the relatively nonsoluble ferrous carbonate form. The actual amount of ferrous carbonate formed has not been well studied in vivo and depends on gastric pH, contact time, and relative concentrations. The role of oral deferoxamine solution is unclear because of the controversy over whether or not the iron–deferoxamine complex is absorbed. This complex requires an alkaline solution and hence bicarbonate must be added. A major problem is the large amount (and high cost) of deferoxamine required to complex the iron (100 mg deferoxamine complexes 8.5 mg iron).

Oral Solutions

The standard bicarbonate solution (1 mL [1 mEq/mL]/kg administered after lavage or emesis) may be the only oral solution necessary in most cases. Whether this solution significantly decreases iron absorption remains controversial; conventional antacids may be an equally safe alternative.[17] However, in severe ingestions the addition of 5 to 10 g of deferoxamine may be theoretically helpful at the end of lavage. All potentially serious iron ingestions should receive an abdominal x-ray, and the decontamination procedures should be repeated if the upright abdominal film shows retained tablets. The use of undiluted sodium dihydrogen phosphate solution (Fleets Phosphasoda Enema) has caused severe hypernatremia and hypocalcemia.[18] This solution appears less efficacious in vitro than bicarbonate in complexing free iron. Even after lavage with either phosphate or bicarbonate, large amounts of iron remain free in solution based on in vitro studies.[19]

Bezoar Formation

Iron tablets may form concretions or adherent masses that are resistant to decontamination measures and endoscopic removal. Continuing release of iron from large bezoars may produce delayed elevation of iron levels, gastrointestinal inflammation, hemorrhage, and scarring.[20] In situations in which serum iron levels rose and the concretions failed to progress down the gastrointestinal tract, gastrotomy has reduced toxic effects and prevented perforations.[21,22]

Activated Charcoal

This compound does not effectively bind iron; however, the iron–deferoxamine complex does adsorb onto charcoal with an affinity similar to that of salicylates.[23]

hartics

Sodium sulfate or magnesium sulfate may be used unless the patient already has diarrhea.

Elimination Enhancement

Exchange transfusion offers the greatest potential for iron removal and in experiments in animals this procedure has removed more iron than intravenous deferoxamine. However, the clinical efficacy of such removal is uncertain, since deferoxamine chelates only the important toxic component (i.e., *free* iron), whereas exchange transfusion removes both free and bound iron. Hemodialysis removes the iron–deferoxamine complex but not the iron itself. Hence, its use is limited to those patients with impaired renal function. Methods to enhance elimination probably do not alter clinical outcome because only a small amount of absorbed iron is removed.

Antidotes (Deferoxamine [Desferal])[24]

Mechanism of Action

Deferoxamine is a specific chelator of ferric iron produced by the bacteria *Streptomyces pilosus*; it is currently the chelator of choice. Other chelating iron agents (e.g., ethylenediamine-*N*,*N*'-bis(2-hydroxyphenylacetic acid) ap- more effective in animals, but clinical testing has not t started.[25] Although 100 mg of deferoxamine will bind about 9 mg of free circulating elemental iron, deferoxamine does not remove iron from transferrin or hemoglobin. Deferoxamine may operate on the labile iron pool in the intracellular portion of hepatocytes where it preferentially removes ferritin iron over hemosiderin iron.[26]

Increasing the elimination of iron is not necessarily the main mechanism by which deferoxamine reduces iron toxicity.[27] Since the volume of distribution of the iron–deferoxamine (ferrioxamine) is relatively small, free iron is kept in the extracellular space. Furthermore, the binding of cytoplasmic free iron reduces the free iron–induced disruption of mitochondrial cell membranes and enzyme systems. The iron–deferoxamine complex, ferrioxamine, is highly stable at physiological pH.[28]

Pharmacokinetics

Deferoxamine is poorly absorbed from the gastrointestinal tract and, therefore, should be given parenterally for maximum effect. Deferoxamine has a volume of distribution of about 60% of body weight and a plasma half-life slightly over 1 hour. The liver detoxifies deferoxamine. Unlike elemental iron, the deferoxamine iron–complex is excreted from the kidney.

Adverse Effects

ssemia patients have received deferoxamine, 425 mg/kg intravenously over 24 hours (i.e., 16 g), without complications.[29] Intravenous doses of 125 mg/kg each day for a number of days caused night blindness and visual field defects which improved on withdrawal.[30] Long-term deferoxamine therapy may cause cataracts, cone and rod dysfunction, and dyschromatopsia, particularly in patients with renal dysfunction.[31] Rheumatoid arthritis patients treated with deferoxamine doses as low as 15 g over a week have developed retinal damage.[32] Flushing, urticaria, and rarely cases of anaphylactic reactions may occur possibly because of histamine release. The most common toxic reactions include gastrointestinal distress and hypotension. Doses of 0.75 mg/kg/min produce hypotension which usually responds to reduced infusion rates and fluid challenges. Vasopressors may be necessary. Rapid desensitization protocols have been developed for sensitized patients with serious iron toxicity.[33] Since the ferrioxamine complex is renally excreted, deferoxamine should be used cautiously in patients with compromised renal function. Hemodialysis may be considered when high deferoxamine doses are needed. Deferoxamine has been administered to pregnant women without adverse effects to the developing child,[34] and, conversely, a pregnant mother died of iron poisoning (serum iron, 1700 mg/dL) after deferoxamine was withheld.[35]

Indications

Therapy can be based on the severity of symptoms and serum iron levels (Fig. 37-1).

Peak Serum Iron Levels below 350 μg/dl. The value of deferoxamine at this level is minimal, if any, since significant toxicity usually does not occur. However, should the TIBC fall significantly below serum iron levels, a deferoxamine intramuscular challenge may be used to detect elevated free iron levels.

Peak Serum Iron Levels between 350 and 500 μg/dl. Any symptomatic patient with these levels should be given deferoxamine. No clear, well-documented guidelines exist to decide which asymptomatic patients in this range will develop subsequent toxicity. Hence, the use of deferoxamine in this range requires clinical judgment. Again, a deferoxamine challenge can be used to identify those patients with free serum iron who may need further chelation therapy.

Peak Serum Iron Levels above 500 μg/dl. All patients should have prompt intravenous deferoxamine therapy.

Significantly Symptomatic Patients. All patients with altered mental status (be sure to check glucose level and give intravenous glucose), hypotension, bleeding, or protracted vomiting should receive prompt intravenous deferoxamine therapy. Do not wait for serum iron levels to return from laboratory.

Dose Recommendations

Deferoxamine Challenge. This procedure helps identify those patients with free, circulating iron who may need

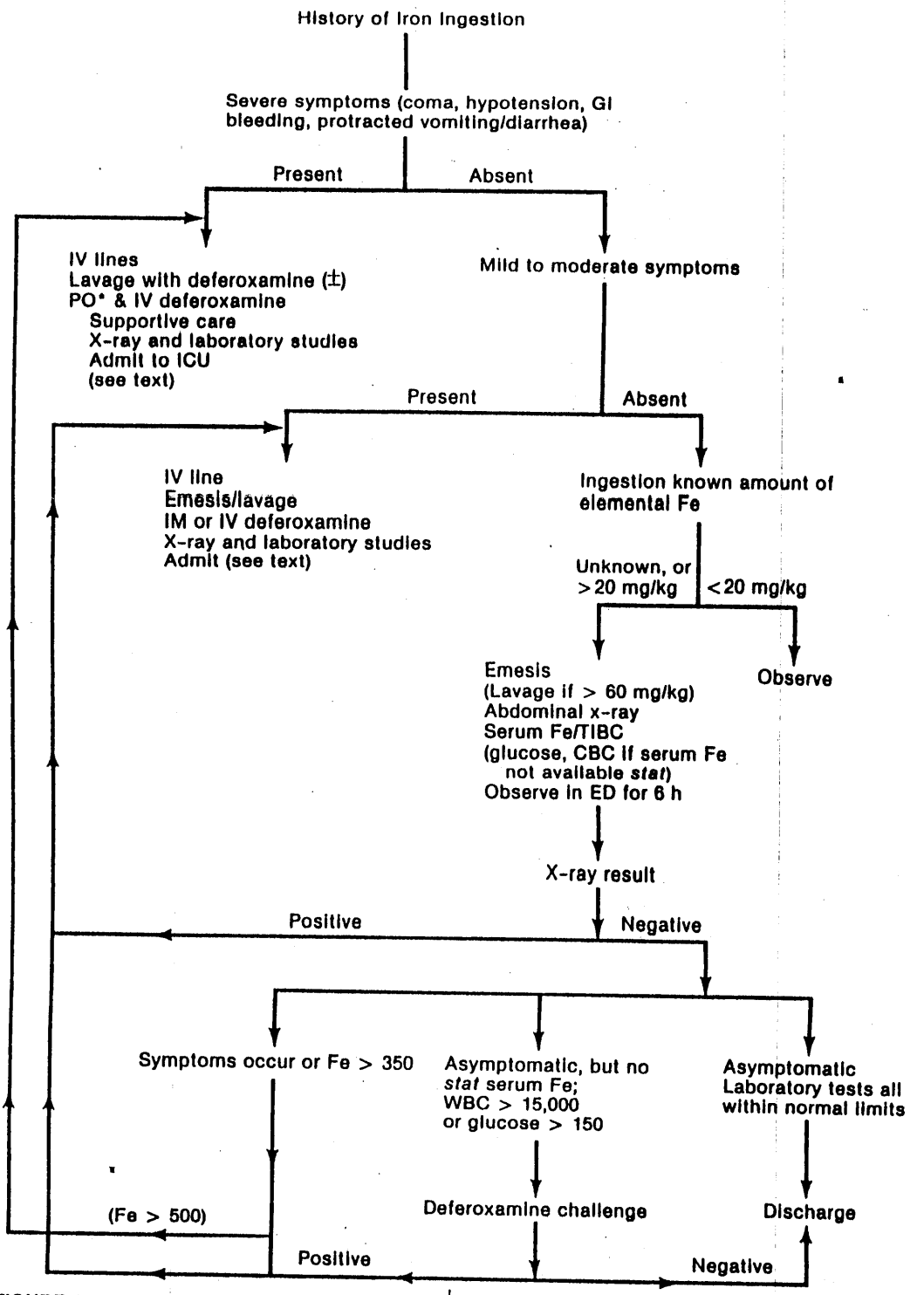

FIGURE 37-1. This algorithm outlines the initial approach to iron ingestion. *Oral use of deferoxamine is controversial; see text for discussion. Adapted from Henretig FM, Temple AR: Acute iron poisoning in children. Emerg Med Clin North Am 1984;2:127. Used with permission from W. B. Saunders Co.

further chelation therapy when serum iron is unavailable or the history suggests a toxic ingestion. The appearance of the iron–deferoxamine complex turns the urine a vin-rose color. Since chelation occurs optimally at a urine pH of 7 to 8, check urine pH periodically. Rarely, high iron levels occur in the absence of colored urine. Dosage of deferoxamine is 40 mg/kg as a deep intramuscular injection (may dilute 500 mg deferoxamine in 2 mL sterile water).

Parenteral Deferoxamine. Intramuscular deferoxamine may be used for patients not showing signs of hypotension. The intravenous route is probably more effective because of the short half-life of deferoxamine (about 1 hour) and the constant exposure to free circulating iron during the redistribution phase.[26] The intramuscular dose is 40 to 90 mg/kg as a deep intramuscular injection, up to a maximum of 2 g per injection. Daily doses should not exceed 6 g.

Intravenous deferoxamine is preferred for any serious iron ingestion and probably is more efficacious for all other patients requiring iron chelation. Although the minimal effective dose has not been calculated, a dose of 15 mg/kg/h usually does not produce hypotension and probably chelates all free circulating iron.[28]

Duration of Treatment

Subsequent doses of intravenous deferoxamine can be reduced when the serum iron level falls below the TIBC. Remember that ferrioxamine interferes with the colorimetric assay of iron. Some authors recommend that deferoxamine treatment continue 24 hours after the urine returns to normal color.[24] However, the exact length of therapy of iron required awaits the clarification of mitochondrial toxicity of iron and the effects of deferoxamine at these sites.[20]

Supportive Care

1. Watch vital signs carefully for signs of hypovolemia.
2. Replace fluid loss aggressively.
3. Watch for signs of blood loss (guaiac-positive stool) and type and cross-match blood.
4. Follow creatinine and prothrombin time/transaminase levels as measures of renal and hepatic function, respectively.

Admission Criteria

1. All patients who require chelation.
2. All positive provocative chelation tests.
3. Patients who remain asymptomatic 6 hours after ingestion (e.g., no vomiting/diarrhea/epigastric pain/lethargy) and who have no leukocytosis (less than 15,000), hyperglycemia (< 150 mg/dL), or positive upright abdomen film for pills may be discharged.[7] Questionable cases should receive a provocative chelation test. Symptomatic cases should receive chelation.

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LEAD

INTRODUCTION

Epidemiology

Lead has been smelted, ingested as a homeopathic medicine, applied as a cosmetic, painted on buildings, and glazed on ceramic pots since the earliest recorded times. By the time of the fall of the Roman Empire, an estimated 40 million tons of lead were produced, primarily as a by-product of silver mining.[1] Lead may also be the oldest recognized chemical toxin.[2] A Greek poet–physician first described occupational lead poisoning in the 2nd century BC. Lead use and environmental pollution have increased dramatically over the last 50 years, as demonstrated in sequential layers of ice in Greenland. At the beginning of the Industrial Revolution in 1780, 1 g of ice contained 10 pg of lead. Two hundred years later, the lead concentration of 1 g reached a level 20 times greater (200 pg), with the greatest increases occurring since 1940.[3] Each year, the United States consumes 1.3 million tons of lead and releases an estimated 100,000 tons into the air and water.[4]

Lead serves no known useful purpose in the body. Throughout life, humans accumulate lead in their bodies based on their exposure. Urban residents have the highest blood lead levels (20–25 μg/dL); suburban (15–20 μg/dL) and rural populations (10–14 μg/dL) have lower levels.[5] These levels correlate with air lead levels and *perhaps* leaded gasoline use. The average US blood lead level declined 37% from 1976 to 1980 as leaded gasoline consumption declined 55%.[6] In the women of Wales, blood lead levels dropped 30% between 1972 and 1982 despite little change in the total amount of lead used in gasoline.[7] Vehicle exhaust contributes up to 24% to 27% of total blood lead.[8]

Recent research work on the clinical effects of lead has focused on the subtle neuropsychiatric, reproductive, and renal effects of chronic low-dose lead exposure. Children are particularly susceptible to lead-induced impairment of neuropsychological development because of their reduced ability to excrete lead and their enhanced absorption of lead compared with adults. Death in children from undetected lead poisoning may be greater than heretofore suspected.[9]

The effect of low-level lead exposure on adults is less clear. Because the body stores over 90% of the total lead body burden in bones, the blood lead concentration reflects recent rather than cumulative absorption.[10] This inability to detect directly the extent of exposure confounds epidemiological studies. To date, studies correlating elevated blood lead levels to hypertension are conflicting.[11] Concern exists over the possibility that soft acid water increases the solubility of lead and that elevated lead levels account for the increased incidence of hypertension and cardiovascular mortality in areas with soft-water supplies. The contribution of increased lead absorption to gout, hypertension, nephropathy, and neurotoxicity remains to be determined.

TABLE 37-3
MAJOR OCCUPATIONS ASSOCIATED WITH RISK OF LEAD POISONING

Battery makers	Metal grinders/burners/refiners
Brass worker	Painters
Bronzers	Pigment makers
Cable makers/splicers	Pipe cutters
Chemical operators	Pottery workers
Foundrymen	Printers (linotype/electrotype)
Glass makers/polishers	Solderers
Gunshot/gun barrel makers	Stained glass makers
Jewelers	Welders
Lead burners/smelters	

Adapted from Cullen MR, Robins JM, Eskenazi B: Adult inorganic lead intoxication: Presentation of 31 new cases and a review of recent advances in the literature. Medicine 1983;62:231. Copyright 1983 Williams & Wilkins. Used with permission.

Sources[12]

Adults

Lead toxicity in adults results primarily from workplace exposure via inhalation. Lead exposure can occur by ingestion as a result of the lack of proper hygiene in lead-contaminated environments (e.g., eating or smoking in areas of lead work).[13] Table 37-3 lists some occupations at risk. Over 92% of all elevated adult blood levels in one series resulted from occupational exposure.[14] Lead toxicity has resulted from the subdermal injection of lead paint.[15] Nonoccupational sources of exposure include hobbies, lead-lined containers, lead bullets near joints,[16] and home-distilled whiskey (Table 37-4). Acid foods such as fruit and vegetable juice can release lead from improperly fired ceramic glazes leading to increased lead consumption.

TABLE 37-4
NONOCCUPATIONAL SOURCES OF LEAD POISONING

Battery burning	Home abortifacients
Bullet retention	Target shooting
Ceramic making	Ingestion of lead-containing herbal medicines
Eating from unfired pottery	Use of lead-containing cosmetics
Cooking in leaden pots	Soldering
Home-distilled wine/whiskey	

Adapted from Cullen MR, Robins JM, Eskenazi B: Adult inorganic lead intoxication: Presentation of 31 new cases and a review of recent advances in the literature. Medicine 1983;62:231. Copyright 1983 Williams & Wilkins. Used with permission.

CHAPTER TWENTY-NINE

The Metals

HERBERT E. STOKINGER, Ph.D.

1 ALUMINUM, Al

1.1 Source and Production (1)

Primary Al production in the United States in 1973 amounted to 4529 thousand short tons, representing an increase of 10 percent over that in 1972. Recovery of secondary Al was 1038 thousand short tons, also a 10 percent increase over that in 1972. Increased recovery of secondary Al and Al alloys (alloy zinc and steel) was projected by several Al smelting companies for the mid 1970s, including added tonnage of recycling of Al beer and soft-drink cans.

Aluminum is produced by the electrolysis of bauxite ($Al_2O_3 \cdot 2H_2O$) in a bath of molten cryolite ($3NaF \cdot AlF_3$), now mostly made synthetically from fluorspar (CaF_2) or fluosilicic acid (H_2SiF_6), which is a by-product of fluoride-containing gases evolved during the processing of phosphates in fertilizer production. Two types of electrolytic reduction cells are used and are related to the anode type. In the "prebake" pot or cell, the carbon anode is prebaked, whereas in the Soderberg process, the carbon paste is delivered directly to the cell and baked as the anode is consumed. For a detailed description of Al production, see Reference 2.

1.2 Uses and Industrial Exposures

The major use of Al is structural in the building industry; it is also used in consumer durables, in containers and packaging. In recent years increasing amounts have been used in the automotive industry to reduce weight, and the canning industry is a growing consumer. Another large user is highway products such as signs, fencing, lighting, and signal supports. Smaller quantities of Al as powder and flake are used in the paint

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the dose, during which time it is accumulating in the liver and kidneys. The phagocytized In is retained by the spleen and liver; next in diminishing order of retention are the kidneys, femoral bone, muscle, and lung.

Although both In compounds followed the usual excretion pattern with a fast and slow component, the fast component of In^{3+} accounted for about 50 percent of the dose in 1.9 to 2.1 days, whereas only half the amount was excreted during this time by the colloidal oxide. The slower component was similar for each, requiring 69 to 74.5 and 62 to 74 days for In^{3+} and the oxide, respectively. As could be expected, the partition between urine and feces favored the former for In^{3+} (52 vs. 35 percent) versus 9.7 and 53 percent for the colloid.

15.5.3 Mode of Action and Toxicity Prevention

Only one piece of indirect evidence for the manner by which In exerts its toxicity has been found; $InCl_3$ has been found to be a "direct calcifier," causing topical calcification at the site of injection when introduced into connective tissue, and acute, fatal, hepatic necrosis (639). Ferric dextran, prophylactically administered, not only prevented the calcifying action of In, but protected the liver against hepatic necrosis. Rats that had received a 2 mg dose $InCl_3$ intravenously on the sixth day after pretreatment on the first day with an intraperitoneal dose of ferric dextran (Imposil®) equivalent to 50 mg Fe showed no obvious sign of toxic injury at any time (11 days) and the hepatic lesions seen in the untreated rats were absent. The mechanism suggested by the authors was that Fe dextran interferes with the capacity of the liver to metabolize normally the PAS-positive organic matrix of soft tissue calcinosis under pathological calcification processes induced by In.

15.5.4 Industrial Experience

No industrial experience has been reported of exposures to In or its compounds.

15.6 Hygienic Standards of Exposure

A TLV of 0.1 mg/m³ for In, and for its compounds as In, was adopted by the American Conference of Governmental Industrial Hygienists in 1969 as a time-weighted average value for an 8-hr workday (640). A STEL (Short-Term Exposure Limit) of 0.3 mg/m³ was tentatively set by the TLV Committee in 1976. The TLV is based on the severity of effects on the lung from respiratory exposure to In salts.

Finland (1972) and Italy (1974) followed the precedent set by the TLV Committee and adopted the 0.1 mg/m³ limit.

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16 IRON, Fe

16.1 Source and Production (1, 2)

Domestic (U.S.) production of crude Fe ore, mainly taconite; a low grade ore composed chiefly of hematite ($FeO(OH)\cdot xH_2O$) and silica from the Great Lakes region, totaled 217.2 million long tons in 1974. Open pit mines produced 96 percent of the total, and nearly 98 percent of the crude ore that went to beneficiation plants. The average Fe content of crude ore mined was 33.7 percent. The Lake Superior district accounted for about 84 percent of the ore, Minnesota produced 69 percent usable ore, Michigan produced 13 percent, and the remaining 18 percent was produced by 19 other states. Taconite and natural ore pits were mined with rotary drills for blast holes, large-capacity shovels, and haulage trucks. Beneficiation of Fe ore varies from simple screening operations and washing to complex grinding, roasting, magnetic separation, or flotation. The metallurgy of Fe consists essentially of the passage of the ore, coke, and limestone through a blast furnace. As the mixture passes downward, C combines with O_2 of the ore, freeing Fe, which is tapped as a liquid from the furnace. The worldwide trend continues (10 countries) in the production of iron ore pellets for blast furnace operation, although large tonnages of direct-shipping ore containing 52 to 60 percent Fe will be available for at least several decades. Pellet plant operations in the United States, in the forefront of this trend, has a scheduled capacity for 1978 of 89 million tons. World production of Fe ore, concentrates, and agglomerates in 1974 had a total gross weight of 879,414 million long tons with a metal content of 503,677 million long tons, produced by almost every industrialized country in the world.

Steel production in the United States in 1974 amounted to 145.7 million short tons (raw steel, ingots and castings); 56 percent was produced by the basic O_2 process, 24 percent by open hearth, and 20 percent by electric furnaces. USSR production exceeded

that of the United States, by a few million tons. World production of raw steel totaled 779 million tons and of pig iron, 567 million tons.

16.2 Industrial Exposures

Mining and handling of Fe ores provide exposure to dusts of SiO_2 and Fe oxides. Carbon monoxide is a hazard in the operation of blast furnaces for the production of pig iron. The use of fluorspar (CaF_2) in steelmaking gives rise to gases containing SiF_4 and other F-containing substances, and the manufacture of alloy steels introduces hazards attendant on the use of metals such as Cr, Mn, Ni, V, W, Mo, and Cu. "Pickling" of Fe containing As and P liberates arsine (AsH_3) and phosphine (PH_3). Certain grades of ferrosilicon used in steelmaking decompose with explosive violence on contact with moist air, evolving various toxic gases such as acetylene, H_2S, SiH_4, AsH_3, and PH_3. Fatal intoxications have occurred from such accidents during transportation, particularly at sea (641) (see also Section 16.5.5).

16.3 Physical and Chemical Properties

The physical and chemical properties of Fe and a few of its many compounds are given in Table 29.16.1.

The *Handbook of Chemistry and Physics* for 1974–1975 (583) gives the physical properties of 102 inorganic compounds of Fe and 62 organometallic derivatives; the Toxic Substances List for 1976 (171) supplies acute animal toxicity data for 29 inorganic and organic derivatives.

Fe is the fourth most abundant element on the face of the earth (5 percent), existing as hematite, Fe_2O_3; limonite, $Fe_2O_3 \cdot 3H_2O$; magnetite, Fe_3O_4; taconite and siderite, $FeCO_3$; pyrites, FeS_2; and chromite, $Fe(CrO_2)_2$.

The physical properties of Fe, the metal, are profoundly affected by impurities and by changes in temperature and treatment. Iron is superior to all other elements in magnetic properties. Iron, in almost pure state, loses its magnetism when removed from an electric field; when Fe contains small amounts of C, Co, or Ni, the retention of magnetism is increased. When heated to 770°C, Fe loses its magnetism; on cooling, it retains this property. Iron undergoes a variety of structural changes (transformations) on heating that form the basis of the heat treatment of ferrous metals.

The principal compounds of Fe are ferrous (Fe^{2+}) and ferric (Fe^{3+}). In general, ferrous and ferric forms are mutually interconvertible. The oxidation potential against the normal hydrogen electrode for the ferrous form is −0.43 V, for the ferric form +0.77 V. ...ompounds are more stable than ferric when ionized, less stable when covalent. ...arge proportion of Fe salts are water-soluble; exceptions are carbonates, oxides, hydroxides, phosphates, sulfides, and ferrous fluoride. Iron of both valences tends to form complexes in which the commonest coordination number is 6. Iron has a strong tendency to combine with O, as in the form of OH groups, with resultant stable compounds, especially as chelates. Iron compounds exhibit marked catalytic activity in the

Table 29.16.1. Physical and Chemical Properties of Iron and Some of Its Compounds

Form of Fe	At. or Mol. Wt.	Sp. Gr.	M.P. (°C)	B.P. (°C)	Solubility
Iron (Fe)	55.85	7.86	1535	2750	Insol. hot or cold H_2O; alkalies, alcohol, ether; sol. acids
Ferrous oxide, black (FeO)	71.85	5.7	1420	—	Insol. hot or cold H_2O; sol. acid; insol. alcohol, alkalies
Ferric oxide, red-brown ($Fe_2O_3 \cdot xH_2O$)	159.69	5.24	1565	—	Insol. cold, hot H_2O; sol. HCl, H_2SO_4
Iron oxide magnetiic, red (Fe_3O_4)	231.54	5.18	Dec. 1538	—	Insol. cold, hot H_2O; sol. conc. acid; insol. alcohol, ether
Ferric chloride ($FeCl_3$)	162.21	2.898 (25°C)	306	Dec. 315	744 g/liter (0°C); 5.35 kg/liter (100°C); v. sol. EtOH; MeOH, ether
Ferric nitrate hexahydrate $[Fe(NO_3)_3 \cdot 6H_2O]$	349.95	—	35	Dec.	1.5 kg/liter (0°C); inf. sol. hot H_2O
Ferric orthophosphate $[FePO_4 \cdot 2H_2O]$	186.85	2.74	Dec.	—	V. sl. sol. cold H_2O; 6.7 g/liter (100°C); sol. HCl, H_2SO_4; insol. HNO_3
Ferric sulfate $[Fe_2(SO_4)_3]$	399.87	3.097 (18°C)	Dec. 480	—	Sl. sol. cold H_2O; dec. hot H_2O; insol. H_2SO_4, NH_3
Ferrous sulfate $[FeSO_4 \cdot H_2O]$	169.96	2.970 (25°C)	—	—	Sl. sol. cold H_2O; sol. hot H_2O
Ferrocene, dicyclopentadienyl-Fe $(C_5H_5FeC_5H_5)$	186.04	—	172.5–173	Subl.	Insol. cold, hot H_2O; sol. EtOH, ether, C_6H_6, MeOH

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promotion of synthesis, both of chemical and biologic importance. Iron forms several carbonyls, [illegible] that were also discussed.

An interesting section of the chemistry of the array of compounds with bonds to carbon. Cementite, Fe_3C, is a component of steel. The cyanide complexes of both ferrous and ferric iron are very stable and are not strongly magnetic in contradistinction to most Fe coordination compounds. The cyanide complexes form colored salts, including Prussian blue, $KFe[Fe(CN)_6]$, made from ferric ion and potassium ferrocyanide, $K_4Fe(CN)_6$. The compound [illegible] blue, made from ferrous ion and potassium ferricyanide, $K_3Fe(CN)_6$, is known as the chemical to Prussian blue. There are many compounds containing [illegible] groups and some other group (such as NO, CO, SO_3^{2-}, NO_2^-, NH_3, and H_2O) [illegible] Fe. The compound $Na_2Fe(NO)(CN)_5 \cdot 2H_2O$ is one such compound [illegible] test for sulfide ion.

Iron [illegible] group of materials known as ferroalloys that are important as additions [illegible] iron, as they [illegible] as also a major constituent of many special-purpose alloys developed for their [illegible] characteristics with respect to magnetic properties, electrical resistance, [illegible] resistance, corrosion resistance, and thermal expansion.

Among the ferrous alloys, the type of Fe alloys is that with C, the principal ones of which are wrought Fe, steel, Fe, and cast Fe. Good wrought Fe contains no more than 0.035 percent C, but contains also 0.075 to 0.15 percent Si, 0.1 to 0.25 percent P, less than 0.02 percent S, and 0.06 to 0.1 percent Mn, not all of which are alloyed with the Fe.

Cast Fe contains 2 to 4 percent C and varying amounts of Si, P, S, and Mn, to obtain a wide range of physical and chemical properties. Alloying elements such as Si, Ni, Cr, Mo, Cu, and Ti may be added in amounts varying from a few tenths to 30 percent or more.

Steel is a generic name for a large group of Fe–C alloys in which the C content is about 2 percent. To this basic steel, other alloying elements may be added, the more common types of which are Al, Cr, Co, Cr–Ni, Cr–Al, Mn, Ni, Si, and W, each of which has particular uses arising from its special properties.

The several Fe oxide forms find use as paint pigments, polishing compounds, magnetic inks, and coatings for magnetic tapes. The soluble salts (Table 29.16.1) are variously used as dyeing [illegible], catalysts, pigments, fertilizer, feeds, disinfectants, and in tanning, soil conditioning, and treatment of sewage and industrial wastes. Ferrocene is used as an additive to fuel oils to improve combustion efficiency and eliminate smoke; [illegible] catalyst, high temperature lubricant, and UV absorber. For uses of other Fe compounds see [illegible] Table 29.16.1, see Reference 642.

16.4 Analytic Determination

[illegible] of the [illegible] spectrophotometric methods for Fe have used 1,10-phenanthroline. The [illegible] procedure introduced by Collins and Diehl (643a) and Reynolds and Mosbaugh (643b) [illegible] increased the sensitivity and lessened the interference of the method [illegible] applicable to air, dust fall, and biologic samples. Keenan and Minderman (644), using the 2,2-dipyridyl derivative, had previously determined the

conditions necessary for accurate analysis of welding-fume samples containing high concentrations of Fe. With the phenanthroline method, 0.5 μg Fe can be determined on a standard linear curve that follows Beer's law from 0.0 to 12.5 μg Fe. However, separation of small amounts of Fe is often desirable; this is best done by means of cupferron (ammonium salt of nitrosophenylhydroxylamine) (645). Spectrographic determination of Fe is not particularly well suited for quantitative estimation of Fe in biologic specimens.

Neutron activation analysis using oxidizing air–acetylene as gases and at a wavelength of 2483 Å is now available. It has a sensitivity of 0.1 μg/ml and a range of 0.1 to 10 μg/ml (63).

16.5 Physiologic Response

16.5.1 Acute Toxicity

Orally, Fe salts of both valence forms are not strikingly toxic; on the other hand, when introduced directly into the bloodstream Fe salts are highly and instantaneously toxic, particularly ferric salts. For example, the intraperitoneal LD_{50} of anhydrous ferric chloride for the mouse is 68 mg/kg and orally it is 400 mg/kg; the corresponding intraperitoneal LD_{50} of the hexahydrate, $FeCl_3 \cdot 6H_2O$, is 260 mg/kg, from reports published in the 1960s and 1970s (171). The data in the older literature (*Heffter's Handbuch*, 1930) indicated considerably greater toxicity; for example, the intravenous LD_{50} for $FeCl_3$ for the rabbit is given as 7 mg/kg. The oral mouse and rat LD_{50} of anhydrous $FeCl_3$ is reported to be 440 and 900 mg/kg, respectively (171).

The oral rat LD_{50} for $Fe(NO_3)_3 \cdot 9H_2O$ is given as 3250 mg/kg, and the corresponding LD_{50} for $FeSO_4$ is 1480 mg/kg; the lowest toxic dose, TD_{Lo}, by mouth is given for $FeSO_4$ as 600 mg/kg with effects on the gastrointestinal tract. For the adult female the value is 60 mg/kg, with effects primarily on the central nervous system (647). The acute toxicity of reduced Fe powder, by comparison, was very low as determined orally in the rat; the LD_{50} was found to be 98.6 g/kg or about 1/100 that of $FeSO_4$ determined under the same conditions (648).

The immediate cause of death from these inorganic compounds of Fe in animals is respiratory failure. Clinical signs preceding death are anorexia, oligodipsia, oliguria, alkalosis, diarrhea, loss of body weight, hypothermia, and alternating irritability and depression. At autopsy there is loss of weight in most organs, accompanied by dehydration when death occurred early, and edema when death was delayed. Vascular congestion of the gastrointestinal tract, liver, kidneys, heart, lungs, brain, spleen, adrenals, and thymus gland is the dominant histopathological sign. Toxic signs began to disappear in survivors toward the end of 1 week, and had completely disappeared at 2 to 4 weeks (648). In human poisonings, symptoms of iron intoxication include vomiting, hematemesis, diarrhea, lethargy, coma, irritability, seizures, and abdominal pain. Signs may include an increased cardiac and respiratory rate, while a marked increase in total peripheral vascular resistance may maintain arterial blood pressure for variable periods

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before manifestations of low output shock ensue. Biochemical consequences of acute iron intoxication include metabolic acidosis, due in part to the accumulation of lactic and citric acids, and hypoglycemia (649).

The lowest toxic dose (TD_{LO}) or the LD_{50}, determined on seven Fe substances of industrial or pharmaceutical interest relative to their screening for their neoplastic potential (Table 29.16.3) are listed in Table 29.16.2. To be noted is the wide difference between the TD_{LO}s when response was measured as neoplasia (compounds 3, 5–7) when dosages were small and repetitive at weekly intervals, and when response was measured as granulomata (compounds 1, 2) or as a lethal response (compounds 4, 7b) resulting from a single dose. The orders of magnitude difference is indicative of the body's capacity to metabolize small, widely spaced, repetitive doses, and its inability to handle a single large and overwhelming dose.

16.5.2 Chronic Toxicity

Apart from the tumor-screening work on Fe and its inorganic and organic derivatives, the bulk of the toxicologic information on Fe compounds is the result of long-term exposures, and has been determined largely in man (see Sections 16.5.5, 16.5.6).

Neoplastic Activity in Animals. Following the observation by Richmond in 1957 (653) on the tumorigenicity of an Fe–dextran, this complex, as well as other Fe derivatives, was further explored by Haddow and Horning (650) (Table 29.16.3). In the screening of Fe and its inorganic compounds by subcutaneous injection, it is noted that with the exception of one fibroma from ferrous sulfate, neither Fe nor any of its inorganic compounds, including hematite, was productive of any tumors; moreover, ferric

Table 29.16.2. Toxic Doses for the Mouse of Some Inorganic and Organic Compounds of Iron of Industrial and Medical Interest

Compound	TD_{LO} or LD_{50}	Route	Ref.
1. Magnetite (black Fe_3O_4)	400 mg/kg (TD)	Intrapleur.	651
2. Olivine ($Fe_2Mg_2OSiO_2$)	400 mg/kg (TD)	Intrapleur.	651
3. Fe–dextran	104 g/(kg)(13 weeks) (TD)	S.c.	650
4. Ferrocene	335 mg/kg (LD)	I.p.	652
	1550 mg/kg (LD)	Oral	
5. Ferrous gluconate	2600 mg/(kg)(13 weeks) (TD)	S.c.	650
6. Ferrous lactate	4200 mg/(kg)(21 weeks) (TD)	S.c.	650
7. Ferrous sulfate	(a) 1600 mg/(kg)(16 weeks) (TD)	S.c.	650
	(b) 100 mg/kg (LD)	I.p.	171

oxide given by inhalation or by intratracheal route (not shown in Table 29.16.3) was not found tumorigenic in the mouse, hamster, or guinea pig (654a, 655). Similarly, among the organic derivatives, ferrocene, ferritin, ferric citrate and salicylate, and Fe ascorbate were nonproductive of tumors. However, Fe–dextran, a complex with a molecular weight 180,000, introduced into clinical and veterinary medicine in the 1950s, did result in several types of tumors at the injection site, but only at massive doses; other results from administration of low doses of short duration, not shown in Table 29.16.3, gave no evidence of sarcoma development, indicating a threshold dose (656). Iron lactate and gluconate yielded a small number of tumors, but thymomas and thecomas are evidence that Fe derivatives can result in tumors distant from the site of injection. For carcinogenic response in humans, see Sections 16.5.5 and 16.5.6.

Apart from tumor screening, much of the long-term exposure effects, or lack of them, have been evaluated in humans (see Sections 16.5.5, 16.5.6). The radiographic stippling seen in the lungs of rouge polishers, however, has been reproduced by Harding in rats (657) following intratracheal injection of rouge. Highly significant was the finding by Gardner and McCrum (658) showing that even severe pulmonary irritation from welding fumes (and gases) does not favor infection with tubercle bacilli nor occasion progressive tuberculosis. The daily administration of from 0.2 to 0.8 g $FeCl_2$ to dogs produced no noteworthy physiological changes (659). For the toxicity of iron carbonyls see Section 23 on metal carbonyls.

16.5.3 Metabolism

An excellent review of the absorption and metabolism of Fe has been made by Gubler (660). The amount of Fe used daily by an adult for hemoglobin synthesis is 26 to 27 mg. Owing to extensive Fe reuse, this is far in excess of the daily dietary Fe requirement, which is about 1.2 mg of Fe/day, or the amount of Fe excretion barring blood loss. Allowing a factor of 10 for low absorption of food Fe, 10 mg/day is considered a normal daily allowance for a man and 12 mg for a woman. Ferrous Fe is generally absorbed from the gastrointestinal tract more readily than ferric Fe, presumably because of greater solubility of ferrous compounds. The amount of Fe absorbed is inversely proportional to the intake. A number of factors influence absorption; among them are acidity of the gastric juice, composition of diet (high phosphate and phytic acid reduce absorption), vitamin B_6, Ca, Cu, and others. Regulation of intestinal Fe absorption is not completely understood but it appears to depend on body stores and requirements. An intestinal "acceptor" is postulated, because a single, large dose of Fe can block absorption for several days. The protein apoferritin is believed to be the Fe acceptor and is synthesized as need occurs. The steps in Fe absorption and storage are pictured by Granick (661) in the following way. Iron passes as ferrous Fe into the intestinal mucosal cell. In the cell Fe^{2+} is converted to Fe^{3+} in ferritin. No Fe absorption as ferritin occurs until the cell is physiologically "depleted." However, Fe is withdrawn from ferritin as Fe^{2+} as need arises. Iron released directly into the bloodstream is quickly oxidized by dissolved O_2 to Fe^{3+} which complexes with the specific Fe-transport β_1-globulin (transferrin). Iron in the plasma in excess of the

Table 29.16.3. Neoplastic Potential of Iron and Compounds Determined in Animals

Substance	Incidence Tumors	Types of Tumors	Species (No.)	No. Weekly Injections	Dose	Months on Study	Ref.
Metallic sponge Fe	0/20		Mouse (20)	16	20 mg	15	650
Dialyzed Fe (Fe_2O_3, 5%)	0/20		Mouse (20)	16	0.2 ml	15	650
Fe_2O_3, "hematite" (synthetic)	0/20		Hamster (20)	15	3 mg	>12	654
Ferrous sulfate	1/20	Fibroma	Mouse (20)	16	2.5 mg	14	650
Fe-dextran (Inferon)	70/95	41 Sarcomas, 6 histocytomas, 1 epithelioma	Mouse	11–30	0.2 or 0.3 ml	6–18	650
Ferrocene	0/20		Mouse	28	5 mg	7	650, 652
Ferritin	0/20		Rat	15	5 mg	7	650
Ferric cetrate	0/20		Mouse	33	5 mg	9	650
Ferric salicylate	0/20		Mouse	36	5 mg	12	650
Iron ascorbate	0/20		Mouse	43	0.3 mg Fe	12	650
Ferrous lactate	1/20	Sarcoma	Mouse	21	5 mg	12	650
Ferrous gluconate	3/20	Fibroma, thymoma, thecoma	Mouse	13	5 mg	12	650

binding capacity of this β_1-globulin is loosely combined in a nonspecific way with plasma proteins. It is this fraction that causes toxic reactions, and is rapidly removed from the plasma. Mean, normal, human plasma Fe levels are 129 μg/100 ml for men, and 110 μg for women. This means that the β_1-globulin is normally about one-third saturated with Fe on the basis of its constituting 3 percent of the serum proteins, its molecular weight of 90,000, and its two atoms/molecule Fe-binding capacity. It is a very important fraction, however, although it comprises only 0.1 percent of total circulating Fe and serves as a sensitive index of Fe metabolism. Possibly more use should be made of plasma-bound Fe as an index of exposure in workers exposed to excessive amounts of Fe dust (see Section 16.5.6).

In addition to the above metabolic aspects, Fe functions in the transport of O_2 in hemoglobin in the blood, in myoglobin in the muscle, where it delivers its O_2 to the cytochrome system of the cells (a 4:1 complex of ferroporphyrin with cytochrome oxidase, and the cytochromes a, b, c). Catalase and peroxidase are two other ferroporphyrin enzymes present in nearly all tissues for the decomposition of peroxide oxygen.

Storage of Fe is divided into four main compartments. The normal human body contains 4.5 g Fe; of this, hemoglobin, which is almost entirely in the blood, comprises 72.9 percent of total Fe; myoglobin, 3.3 percent; parenchymal Fe (oxidative enzymes) 0.2 percent; and storage Fe (ferritin, hemosiderin, and unaccounted Fe) 23.5 percent. Most of the storage Fe is found in the liver, bone marrow, and spleen.

Because the erythrocytes are undergoing continual disintegration, mostly in the spleen, but to some extent in the bone marrow and other reticuloendothelial tissues capable of phagocytic action, the breakdown of hemoglobin in this process leads to the release of Fe and the formation of bile pigments. The average life-span of erythrocytes is about 120 days for humans, 100 days for dogs, and 32 days for chickens. The excretion of Fe in the urine is normally inconsiderable. Its excretion from the skin is continuous, and may be important in the daily economy of the body. Iron released from transferrin in the blood of the subcutaneous capillaries combines with the proteins in the dermis, and is carried slowly to the surface of the skin as the cells of the epidermis desquamate.

Because Fe is a critical element in the body's metabolism, it is understandable that its state (valence) and amount can be influenced as a result of exposure to many kinds of industrial substances. von Oettingen (662) lists 30 industrial substances with the potential to produce methemoglobinemia, in which normal, reduced hemoglobin with Fe^{++} of valence 2 is oxidized to Fe^{+++} of methemoglobin; 20 substances in industrial use, capable of eliciting Heinz bodies in the red blood cells, which are believed to be particles of denatured protein freed of Fe; and at least 60 substances capable of causing hemolytic anemia, a condition brought on from relatively trivial exposures in those individuals who have glucose-6-phosphate dehydrogenase deficiency (663).

16.5.4 Mode of Toxic Action

It has been only recently, in the early 1970s, that the mode and site of toxic action of Fe have been hypothesized (649) with supporting evidence (664, 665); the second edition of

this book contained no section on mechanism. On the basis of electron microscopic observations of electron-dense deposits, believed to be Fe, between the inner and outer membranes of the mitochondria, as well as in the intracristae lumen and the matrix of the hepatocytes, the primary and initial site of injury, poisoning of the mitochondria was noted as early as 3 hr after ingestion of a toxic dose of Fe (664). The mechanism believed to explain these observations (649) is the uptake by the exogenous, excess Fe of electrons donated by ferric reductase in the mitochondrial membrane that normally catalyzes endogenous Fe^{3+} to Fe^{2+}, resulting in immediate cessation of aerobic synthesis of adenosine triphosphate, initiating a cellular energy crisis and cell death (665). This mechanistic explanation can be correlated with the elevated lactic and citric acid levels and the depletion of glycogen stores observed in Fe poisoning. The ferric reductase mechanism need not be restricted to the liver mitochondria, but can be equally applicable to the cardiovascular, neurological, and gastrointestinal manifestations associated with Fe intoxication.

16.5.5 Clinical Experience with Fe Therapy

Carbohydrate complexes of Fe have been in use for two decades for the correction of iron-deficiency anemia in humans and baby pigs. The Fe–dextran complex, the one chiefly used for parenteral administration, consists of 5 percent wt./vol. Fe and 20 percent wt./vol. dextran. The therapeutic dose is 1 to 5 ml (50 to 250 mg Fe) daily by deep intramuscular injection. Investigations of the metabolism of Fe–dextran showed that it disappeared from the injection site in man rather rapidly; 60 percent in 24 hr and 95 percent in 5 days, with a peak plasma level in 24 hr and with very little Fe excreted in the urine. Following reports of sarcoma development in rodents, Fe–dextran was temporarily withdrawn from the market in 1960, only to be reintroduced in 1962, when the risk of malignancy in man was considered to be very low. Although no epidemiologic or long-term studies have been reported, a single case of undifferentiated soft tissue sarcoma at the injection site is all that has been recorded. The sarcoma appeared 3 years after six inoculations of Fe–dextran of 100 mg each for blood loss anemia. Histological examination of injection sites following usual therapeutic doses of Fe–dextran have shown little or no change. In two cases, massive doses produced some fibrosis and heavy accumulations of Fe in macrophages, but no fibroblastic proliferation indicative of neoplasia or preneoplasia. By 1967, it was estimated that the Fe–dextran market in the United States amounted to $3.2 million.

16.5.6 Industrial Experience

The hygienic significance of mottling of the lungs, siderosis or, as preferred by Sander (666), "iron pigmentation," is now considered that of a benign pneumoconiosis because it does not lead to fibrous proliferation, is of low order of severity, and usually requires 6 to 10 years of exposure before diagnosable roentgenographic changes occur (667). The condition commonly occurs in electric-arc welders after years of exposure, but may occur

in silver polishers or rouge users, according to McLaughlin et al. (668). Buckell et al. (669) X-rayed the lungs of 171 iron turners and found reticulation from Fe oxide present in 15 men. In five cases, workers had been at the trade for 20 years. The lung changes were moderate, symptoms were few, and only one man complained of shortness of breath, although six noted a tendency to cough. Healing of tuberculous lesions despite continuous exposure to Fe oxide fumes, first noted by Sander (666), has been repeatedly confirmed in humans (670) and animals (659). Physical examinations and tests of work capacity of welders with Fe pigmentation show that it causes little or no disability (670). Gardner (671) regarded Fe oxide as a retardant of the development of conglomerate silicotic fibrosis. (See, however, discussion of lung fibrosis of steel foundrymen and hematite miners below.) Chemical data on the Fe content of the lungs of workers in the dusty trades are given by Gerstel (672).

There is accumulating evidence, however, that Fe oxides may not act to prevent silicosis and tuberculosis in all types of exposure. Iron and steel foundrymen (England) subjected to high temperature Fe oxide fume along with silica were reported by McLaughlin and Harding (673) to develop "siderosis, silicosis, and mixed dust fibrosis." Moreover, a high incidence of bronchiogenic carcinoma was noted among the foundrymen. It would seem, in the face of apparent experimental evidence to the contrary (674), that Fe oxides freshly formed at high temperatures may act much the same way that Al_2O_3 and SiO_2 fumes act to produce Shaver's disease, a fibrotic condition of the lung.

The subject of hematite pneumoconiosis in Cumberland Fe ore miners has been reopened with a report by Faulds (675). It is a progressive, massive fibrosis, appearing as a modified form of infective pneumoconiosis; it was considered to be tuberculosis when first described, but may not be so invariably. However, tuberculosis is the terminal event in most cases, probably because of a relative increase in the degree of silica exposure. An increased incidence of lung tumors in the Fe ore miners was noted; of 238 necropsies, there were 24 cases of carcinoma, compared with less than one-third this number in nonminers.

A statistical-epidemiologic follow-up study of these miners concluded that although the miners suffered a lung cancer mortality of about 70 percent higher than "normal" for the area, it could not be concluded whether the risk was due to radioactivity of the mines (av. radon concentration 10 pCi/liter) or to a carcinogenic effect of Fe oxide, or both (676). In a similar vein, a report on the causes of death in a small number of nonfoundry Fe and steel workers in England revealed that silicosis was more prevalent than fibrosis from mixed, Fe-containing dust (677).

A definite correlation between serum Fe levels and radiographic findings in Fe workers in Bavaria has been reported (678); serum Fe levels are considered as a reflection of partial release of Fe in the lungs. Serum Fe levels of 47 pneumoconiotic workers averaged 160 μg percent compared with a normal of 127 μg percent in healthy nonexposed workers. The increase was proportional to the degree of exposure to the ore dust and the lung changes.

Phosphine liberation was reported (679) in the ambient air about the machining of

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spheroidal graphite Fe; 6 ppm PH_3 was measured near the tool point, and 0.8 ppm at 20 cm. No coolant was used in machining.

16.5.7 Treatment of Acute Intoxication

Iron salts which ulcerate in excessive amounts can be fatal. A review of the literature in 1958 revealed an overall mortality of 50 percent of the reported cases of Fe intoxication. Although fatal doses of $FeSO_4$ range from 3 to 18 g, a young child survived who had swallowed 20 g but had been treated within a few hours with 13.5 g desferrioxamine mesilate sulfonate (*Merck Index*, 9th ed., 1976, p. 374), a potent Fe chelator, by gastric tube and 500 mg intramuscularly. Intramuscular injections of 250 mg were continued at intervals of 8 hr, or as oral administration of the same dose for 5 days, with a complete recovery in 1 week. Of the 20 g $FeSO_4$ ingested (6 g Fe) about 1 g was recovered unabsorbed. The calculated therapeutic dose of 6 g desferrioxamine was not administered because of possible side effects [illegible] urine discoloration and quantitative estimation of urinary Fe are considered the best indicators of Fe overload (680).

16.6 Hygienic Standards of Exposure

The TLV of Fe oxide fume of 15 mg/m³ has been successively reduced since its first adoption in 1957 by the Threshold Limits Committee of the American Conference of Governmental Industrial Hygienists. At that time, 15 mg/m³ was the accepted limit for "inert" or nuisance particulates. In 1967, the TLV was revised downward to 10 mg/m³; not for health reasons, but to improve visibility in the workplace. In 1975, the TLV was still further reduced to 5 mg/m³, and in 1977 a 10 mg/m³ limit was instituted as a tentative short-term exposure limit (STEL), with the stipulations stated in the preface to the TLV booklet of 1976. Again, the reduction was not for health reasons but to prevent development of X-ray changes in the lungs on long-term exposure, changes not associated with any physical disability but that may present difficulties in differential diagnosis.

A TLV of 1 mg/m³ for soluble Fe salts was adopted in 1969, and in 1976, the first year of listing STELs, a tentative STEL of 2 mg/m³ as Fe was proposed, these values intended to reduce the likelihood of respiratory tract irritation and skin effects from contact with aerosols.

Hygienic standards in other countries follow: Germany, Fe oxide fume, 8 mg/m³ (1974); Sweden, Fe oxide fume, 5 mg/m³ (1974); Soviet Union, Fe oxide, 1 mg/m³ (1973). The OSHA standard is 10 mg/m³ (1978).

16.7 Flammability Limits

From the data that appear in Volume I of this book (3rd ed., 1978, p. 1432), minimum ignition temperatures for iron dust clouds range from 470 to 780°C; for layered dust, the range is 220 to 320°C.

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17 THE LANTHANIDES (RARE EARTH METALS)

The lanthanides (or lanthanons) are a group of 15 elements of atomic numbers from 57 through 71 in which yttrium (at. no. 39) is usually included (see Table 29.17.1).

Considerably more toxicologic information on this group of metals has become available since the publication of the second edition of this book in 1962, because of the development of methods of separating and purifying these chemically similar elements on a commercial scale and at greatly reduced cost. Nevertheless, their similar chemical and toxicologic properties warrant their being considered as a group.

17.1 Source and Production (563)

The only commercially useful ores are massive monazite and monazite sand, a phosphate of the Ce group metals; bastnasite and related fluocarbonate minerals of the Ce group; and minerals of the Y group—gadolinite, a silicate of Y, Ce, Cr, Be, and Fe; euxenite, a mineral containing Y, Ce, Er, Nb, Ti and U; and xenotime, mainly a YPO_4 mineral, which may contain Th and some of the Ce subgroup metals.

The most important sources of monazite sand are Florida (U.S.), Australia, the states of Rio de Janeiro, Espirito Santo, and Bahia (Brazil), and Travancore, India. Stream placer deposits of bastnasite are in commercial production in Idaho and North and South Carolina, and deposits in San Bernadino County, California are capable of supplying the industry for many years. Production of Y-group ores is considerably less than that of monazite or bastnasite; euxenite is recovered from a placer deposit near Bear Valley, Idaho, and some xenotime from some monazite placer deposits.

The relative abundance of certain of the lanthanides is quite high; the oxides of Ce,

Table 29.17.1. The Lanthanides

Cerium Subgroup, "Light" Lanthanides	Yttrium Subgroup, "Heavy" Lanthanides	
Lanthanum, La	Samarium, Sm	Holmium, Ho
Cerium, Ce	Europium, Eu	Erbium, Er
Praseodymium, Pr	Gadolinium, Gd	Thulium, Tm
Neodymium, Nd	Terbium, Tb	Ytterbium, Yb
Prometheum (illinium), Pm	Dysprosium, Dy	Lutetium, Lu
	(Yttrium, Y)	

Table 29.17.2. Compositions of Commercial Rare Earth Metals

Metal	Percent Composition				
	Ce	Nd	Pr	Sm	La and Other Rare Earths
Lanthanum	<0.1	<0.1	<0.1	<0.1	99.9
Neodymium-praseodymium	1	78	15	2	4
Cerium	97	0.9	0.5	0.1	1.5
Misch metal[a]	52	18	5	1	24
La-enriched misch metal[a]	47	19	6	1	27

[a] Obtained from monazite, and often sold or referred to as "cerium metal."

La, and Nd occur as 29.9, 17, and 11 percent, respectively, in Idaho monazite; in California bastnasite concentrate, the values are 47.1, 24.6, and 12.6 percent. The lanthanides are formed in the fission of U and Pu; indeed, Pm is derived solely from atomic reactors.

In the extraction and separation of the lanthanides, monazite and bastnasite ores are generally "opened" by heating with sulfuric acid and the resulting sulfates separated from the reaction products with water. Thorium, from monazite sources, is removed from the lanthanide sulfate solution most commonly by precipitation as the pyrophosphate. The lanthanides, in turn, are recovered by precipitation as the oxalates or Na double sulfates. Oxalate precipitation is complete, but the double sulfate precipitate leaves some of the Ce earths and most of the Y earths in the liquor. If hydrated oxides are desired the precipitates are boiled with NaOH which yields granular hydroxides. Drying the hydroxides gives hydrated oxides. If oxides are desired, the oxalates or hydroxides are calcined. Separation of Ce, one of the lanthanides of greatest industrial use, depends on oxidation of Ce to the tetravalent state; this form has solubility properties that differ from nearly all the lanthanides, because it is the only lanthanide that exists as a quadrivalent ion in aqueous solution. Purification is done by precipitation as the basic salt.

Most commercial lanthanide salts are mixtures containing the lanthanides in much the same ratio as they occur in the ore. Separation of the remaining lanthanides is difficult because of great similarity of chemical properties. For separation of the Ce group, fractional crystallization of salts such as the double NH_4 or Mg lanthanide nitrates are used. For the heavy lanthanides, ion exchange methods are used for separation and purification (purities varying from 90 to 99.99 percent) of the remaining lanthanides and Y. The method consists of absorbing the mixed lanthanides on the top of a cation ion exchange resin column in the copper cycle, and then eluting the lanthanides selectively from the resin column with ammonium ethylenediaminetetraacetate solution. The various commercial and laboratory methods used for the preparation of lanthanon metals and salts are given in Reference 563. The composition of commercial lanthanide is given in Table 29.17.2.

TISSUE CHANGES IN RATS' LUNGS CAUSED BY HYDROXIDES, OXIDES AND PHOSPHATES OF ALUMINIUM AND IRON

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(Plates LXXXVI-LXXXIX)

It has been shown (King *et al.*, 1955 and 1958) that aluminium and certain relatively insoluble aluminium compounds, the hydroxide γ-AlOOH and the phosphate berlinite ($AlPO_4$ with a crystal structure similar to quartz), behave as fibrogenic materials when injected into the lungs of rats.

A sample of γ-AlOOH (particle-size a few hundred A.U.) given in a single dose of 100 mg. produced fibrosis of grade 3 (lesions somewhat cellular but made up mostly of collagen) after 4 months and of grade 5 (confluent lesions) after one year. Aluminium powder at 100 mg./rat had given fibrosis of grade 3 after 4 months and of grade 4 after 7 months and up to one year. The fibrosis induced by aluminium phosphate of average particle-size 3 μ, injected in amounts of 50 mg. per rat, had not exceeded grade 3 after 14 months. There had been strong evidence, from aurine-stained sections, that free alumina was lost from the lungs in the course of time and aluminium-protein complexes were suggested as having something to do with causing the fibrosis. These observations had come as a surprise, because previously silica was believed to be unique in having specific fibrogenic properties. It was therefore considered advisable to extend the range of observations.

In parallel studies in experimental silicosis it had been found that size and crystal structure of silica had an effect on fibrogenic activity in rats' lungs. In particular, tridymite had acted more strongly than quartz. As aluminium phosphate exists in the same modifications as silica it was decided to test this compound in its quartz-like and tridymite-like modifications, to test a number of aluminium oxides or hydroxides and to extend the study also to the phosphate and hydroxides of iron.

Materials

Table I lists the samples used, together with relevant details. Figs. 1 and 2 show X-ray diffraction patterns and electron micrographs.

The aluminium hydroxide (γ-AlOOH, Gardiner's HX1010) was a poorly crystalline, commercially prepared sample, identical with that used to produce fibrosis grade 5 in our previous experiment (King *et al.*, 1955). To contrast with it, a well-crystallised sample of γ-AlOOH of average size 2 μ was used

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(trade name Cera hydrate). γ-Al_2O_3 was prepared by heating the aluminium hydroxide (HX1010) at 850°C. for 5 hr; there was little evidence of sintering in the sample according to the electron micrographs (fig. 2). α-Al_2O_3 (corundum) was prepared by heating the aluminium hydroxide (HX1010) at 1200° C. for 5 hr; the sample appeared coarser than the original HX1010 and was re-ground in a mortar of sintered alumina.

The crystalline iron hydroxides goethite (α-FeOOH) and lepidocrocite (γ-FeOOH) were synthetic materials obtained from paint manufacturers. Their degree of crystallinity was intermediate between that of the aluminium hydroxide HX1010 and that of Cera hydrate. They consisted of aggregates of lath-like particles, well below 2 μ in size.

TABLE 1

Characteristics of aluminium and iron hydroxides, oxides and phosphates used for injections

Material	X-ray.	Degree of crystallinity	Mean particle diameter (μ) *	Dosage (mg./kit)	No. of rats
Aluminium hydroxides and oxides					
γ-AlOOH, HX1010	1046	poor	c. 0·02	70†	12
				14	12
γ-AlOOH, Cera hydrate	823	good	3	60†	12
γ-Al_2O_3, HX1010 at 850° C.	1342	poor	c. 0·02	50	12
α-Al_2O_3, HX1010 at 1200° C.	1838	good	<1	50	12
Iron hydroxides					
α-FeOOH	1418	medium	<1	100	15
γ-FeOOH	1870	medium	<1	100	15
Aluminium phosphates					
$AlPO_4$, quartz structure	2515	good	2	50	15
$AlPO_4$, tridymite structure	2507	good	2	50	15
Iron phosphate					
$FePO_4$, quartz structure	2257	good	2	100	15

* assessed from electron photomicrographs.
† equivalent to 50 mg. Al_2O_3.

Aluminium phosphate of quartz structure was prepared from alumina and phosphoric acid. Pure hydrated alumina was ignited at 850° C. in a platinum dish. After cooling, an equivalent amount of phosphoric acid was added, the mixture was slowly heated and stirred with a platinum rod, and finally heated for 4 hr in an electric muffle furnace at 600° C. The material was ground in a mortar of sintered alumina, suspended in water, and a fraction below 2 μ in particle diameter prepared by repeated sedimentation and centrifuging. The sample gave an X-ray diffraction-pattern very similar to that of quartz (see fig. 1) but it may have been slightly contaminated by the cristobalite modification.

Aluminium phosphate of tridymite structure was prepared by heating phosphoric acid with a 10 per cent. excess of aluminium chloride ($AlCl_3 . 6H_2O$). The mixture was finally heated at 600° C. for 4 hr. It was powdered and a fine fraction separated by sedimentation. X-ray diffraction showed mainly a structure resembling tridymite (fig. 1) but there was a little of the quartz modification present. Table II gives chemical analyses of these samples.

Iron phosphate, which exists only in the quartz structure, was prepared by heating iron chloride with excess phosphoric acid, and finally keeping the temperature at 650° C. for 4 hr. The sample was ground and sedimented, and showed an X-ray pattern resembling that of quartz (fig. 1).

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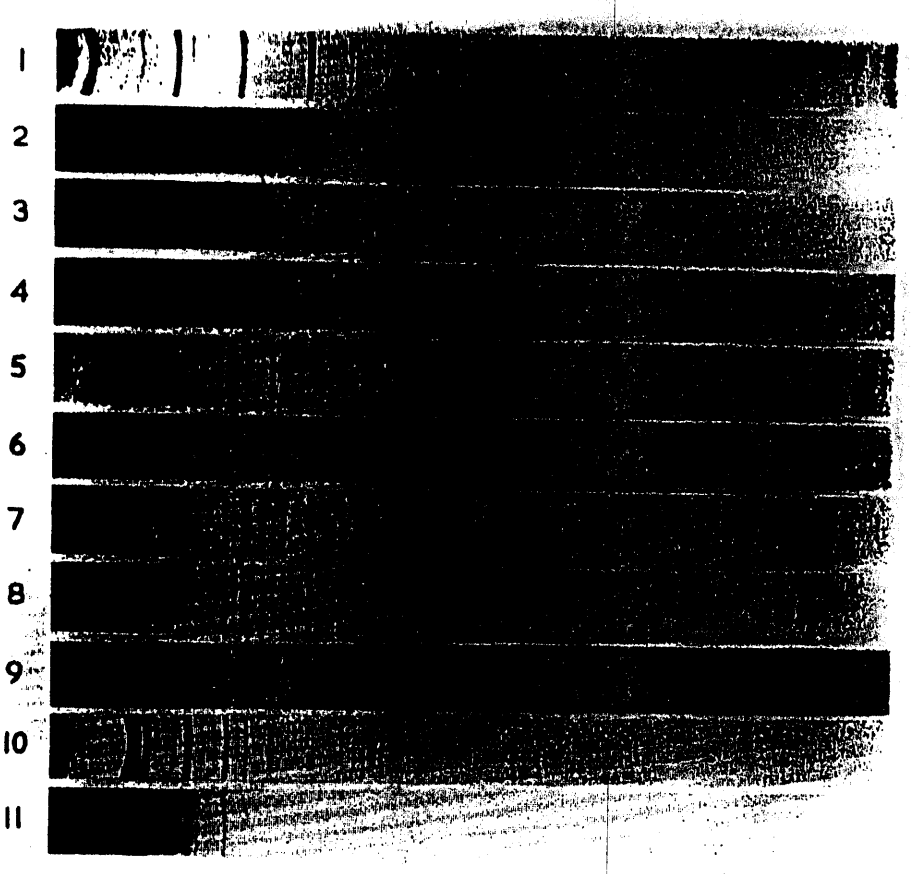

FIG. 1.—X-ray diffraction patterns of minerals used in animal experiments (see table I). 1, γ-AlOOH, Corn hydrate; 2, γ-AlOOH, HX1010; 3, γ-FeOOH; 4, γ-Al_2O_3; 5, α-Al_2O_3; 6, α-FeOOH; 7, quartz; 8, $AlPO_4$, quartz structure; 9, $FePO_4$, quartz structure; 10, tridymite; 11, $AlPO_4$, tridymite structure.

Alumina solubilities

Solubilities of the aluminium compounds were determined at room temperature in sodium acetate buffer of pH 4·1 at a concentration of 5 g. sample per 100 ml. buffer. The samples were shaken continuously in plastic tubes for 3, 6, 22, 38, and 73 days. At the end of each period the tubes were centrifuged, the clear supernatant siphoned off, and fresh buffer added. Two samples of each

TABLE II

Chemical analyses of aluminium phosphates

Constituent	Percentage content of constituent in $AlPO_4$		
	according to theory	by chemical analysis of	
		quartz modification	tridymite modification
Al_2O_3	41·8	41·2	42·7
P_2O_5	58·2	62·3	56·8

material were used, and duplicate colorimetric determinations of dissolved aluminium made on each sample. The *p*H of the extracts varied somewhat but did not fall outside the range 4·1-4·7. The dissolved aluminium was complexed with aluminon reagent at *p*H 4·1, and the colour compared with a set of standards prepared from analar $KAl(SO_4)_2 12H_2O$. The results of the solubility determinations are shown in table III.

TABLE III

Cumulative alumina solubilities of different aluminium compounds after repeated extractions with phosphate buffer pH 4·1 *at room temperature*

Period of extraction (days)	Percentage of total Al_2O_3 originally present in sample dissolved from					
	Corn hydrate	$AlPO_4$ modifications		BX1010		
		X2518 (quartz)	X2507 (tridymite)	heated to 1200° C.	original	heated to 920° C.
3	0·0035	0·34	0·57	1·42	2·1	5·09
6	0·014	0·54	0·91	1·95	3·7	7·95
22	0·05	0·84	1·4	2·57	7·6	11·22
38	0·12	1·0	1·7	3·14	12·2	15·4
73	0·18	1·2	1·0	3·6	15·9	19·1

EXPERIMENTAL

Samples of the different powders were weighed and transferred to all-glass tissue-grinders containing normal saline in amounts sufficient to give the final concentration of each powder indicated in table I, the dose administered being contained in 1 ml. of the final suspension. The mixtures were well ground until fine suspensions were obtained. They were then transferred to screw-capped glass bottles and sterilised by autoclaving. Each dust suspension was prepared in this way immediately before injection, before which it was kept continuously shaken in a mechanical shaker.

The dust suspensions were injected intratracheally by the method of Kettle and Hilton as modified by King *et al.* (1958), the dust being introduced into the lung from a syringe through a long blunt needle inserted via the mouth into the trachea. For each animal injected, the dose indicated in table I was given in 1 ml. of saline, an extra 0·1 ml. of suspension being injected (total 1·1 ml.) in order to allow for the small amount lost on the walls of the syringe and needle. There was no regurgitation of the administered suspensions. No post-operative deaths occurred.

The necropsies, removal of the lungs, fixation, embedding, sectioning and staining were according to the descriptions in our previous communications (King *et al.*, 1955, 1958).

The histological grading of fibrosis was according to Belt and King (1945): grade 1, loose reticulin and no collagen; grade 2, compact reticulin with or without a little collagen; grade 3, somewhat cellular but made up mostly of collagen; grade 4, wholly composed of collagen fibres and virtually acellular; grade 5, acellular, collagenous, confluent.

The animals used were rats of the black-and-white hooded variety of the Medical Research Council strain. Their average weight was 200 g. The number of animals in each group was either 13 or 15. The experiments lasted for one year, and animals were killed at monthly intervals.

Results

Pathological findings

Some congestion and discrete collections of dust were found in the lungs of rats that died or were killed soon after receiving 70 mg. γ-aluminium hydroxide (HX1010). Firm, confluent, fibrotic patches were present in the lungs of animals killed at 150 days and after.

Rats receiving 14 mg. γ-aluminium hydroxide (HX1010), i.e. one-fifth of the previous dose, showed the expected smaller number of smaller focal accumulations of dust, which did not exceed 2-5 mm. in diameter. The collections were most numerous dorsally. The lesions were firm, discrete and only rarely confluent.

With Cera hydrate γ-aluminium hydroxide (60 mg.) small white lesions were found scattered over the lung surface of the rat killed at 30 days. They were larger at 150 days, but the dust collections remained discrete until the end of the experiment.

With γ-alumina (HX1010 heated to 850° C., 50 mg.) numerous small white patches (2-4 mm.), sometimes confluent, were found in the dorsal aspects of both lungs. As early as 60 days there were large white patches, and at 180 days there were firm fibrotic areas. The white, firm, consolidated areas appeared to increase in size as the experiment progressed.

With α-alumina (HX1010 heated to 1200° C., 50 mg.) there was a marked contrast with the previous sample. Only a few small (1-2 mm.) white areas were seen in the animal killed at 30 days. Although the areas were larger in animals killed later, no massive fibrosis was associated with the dust collections at any period.

The two iron hydroxides (α-FeOOH and γ-FeOOH) produced results indistinguishable from each other. Subpleural collections of the yellow-brown dusts were seen at 30 days. They were larger and

FIG. 2.—Electron micrographs of minerals used in animal experiments (see table I). Numbers as in fig. 1.

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The aluminium phosphates ($AlPO_4$, quartz and tridymite structures) produced similar gross appearances in the lungs. At 90 days small white lesions, concentrated dorsally, were dotted over the lungs. By 180 days, greyish-white patches of fibrous tissue were visible, and the patchy mottled appearance persisted until the end of the experiment. At one year the patches were firm and on the whole discrete. With these two dusts, the tracheobronchial lymph glands were greyish-white, firm and considerably enlarged.

The iron phosphate ($FePO_4$, quartz structure) produced little change other than scattered brown patches of dust dorsally in both lungs; these patches persisted until the end of the experiment.

Histology

With 70 mg. of γ-AlOOH (HX1010) there is a rapid development of fibrous nodules. By 30 days there are compact nodules of reticulin. During the remaining 11 months there is a steady maturation of fibrous tissue; grade 3 fibrosis, collagenous and still somewhat cellular, was not exceeded. The lesions were not as numerous and there did not appear to be as much dust in the lungs of the rat killed at one year as in those killed earlier (fig. 3).

With 14 mg. of γ-AlOOH (HX1010) there are numerous, small, irregularly-shaped aggregates of dust. At 30 days silver impregnation shows the presence of fine reticulin-fibrils within the nodule. Later the reticulin forms a loose meshwork within the lesion and the fibrils become thicker, with some collagen. Late in the experiment the nodules are composed largely of collagen, and grade 3 fibrosis is reached. The lesions are finally as advanced with the 14 mg. as with the 70 mg. dose, but they are much less numerous.

Cera hydrate, the well-crystallised variety of γ-AlOOH, shows only a slight macrophage response at 30 days. Dust lies loosely in the alveoli, some particles engulfed in phagocytes. At first there is no focal accumulation of dust cells, but by 150 and 180 days there are small collections, associated with a mild fibrous reaction (loose reticulin, grade 1 fibrosis), which show no further progress up to one year after injection (fig. 4).

The pathological action of γ-Al_2O_3 (HX1010 heated to 850° C.) is much greater. At 30 days large discoloured discrete collections of dust are found, containing compact fibrils of reticulin and some collagen (grade 2 fibrosis, maximum). At 90 and 150 days the lesions are less cellular and more collagenous (grade 3 fibrosis). Almost the whole of one lung in the animal killed at 210 days is a dense mass of fibrous tissue (grade 4 fibrosis). Later, fibrous nodules coalesce, and the resulting mass of confluent collagenous tissue largely fills the

lung (grade 5 fibrosis, fig. 5). In the last animal of this group, as in that of the 70 mg. aluminium hydroxide group, there appears to be less dust than had been seen earlier in the experiment.

By contrast with γ-Al_2O_3, α-Al_2O_3 (HX1010 heated to 1200° C.) appeared to be less pathogenic, the most advanced lesions consisting of compact nodules of reticulin (grade 2 fibrosis). There are numerous small compact aggregates of dust cells at 60 and 90 days, and at all stages most of the dust is concentrated in the focal accumulations (fig. 6).

The results obtained with α-FeOOH and γ-FeOOH in the various stages of the experiment were so similar that they are described together. At 30 days the particles are engulfed in macrophages, and focal accumulations of dust cells are found. The smaller collections consist of macrophages, laden with the brown particles, lying free in the alveoli. The larger collections are compact accumulations of many macrophages. The cellular nature of the foci is difficult to discern, because the brown dust in the macrophages obscures the nuclei. In some cases there is swelling of the alveolar septa. At 90 and 150 days the foci are more compact, but there is little increase of reticulin; at 300 and 365 days most of the dust is in the focal accumulations. A slight reticulinosis (grade 1 fibrosis, minimum) is the only evidence of reaction to the dust (fig. 7).

$AlPO_4$, quartz structure, and $AlPO_4$, tridymite structure, gave very similar results. Both were fibrogenic, though perhaps less so than γ-Al_2O_3. By 30 days both materials have provoked an active dust-cell reaction, and most particles are in macrophages. Cellular nodules are formed by the focal accumulation of macrophages, the larger ones obliterating the structure of the lung. Silver impregnation shows that the nodules were enmeshed and interwoven with reticulin fibrils with a little collagen (grade 2 fibrosis). The $AlPO_4$ particles are doubly refractile, and are confined to and concentrated within the nodules. The fibrous response to the tridymite-like $AlPO_4$ is a little less advanced at this stage than the response to the quartz-like $AlPO_4$. At 60 and 90 days the dust collections are compact, and the surrounding tissue almost free from dust in both groups. The lesions are larger and more fibrous, and collagen formation was prominent. By 120 and 150 days the lesions are noticeably less cellular and the coarse strands of collagen more numerous. Coalescence of nodules has occurred in some areas at 180 days. The lesions are mainly collagenous, but still contain some reticulin (grade 3 fibrosis, maximum). Fully collagenous and completely acellular nodules of grade 4 fibrosis are seen at 300 days. At 330 and 363 days there are areas in the lung sections consisting of compact, confluent masses of acellular collagenous connective tissue (grade 5 fibrosis). This is a somewhat more prominent feature with the quartz-like than with the tridymite-like $AlPO_4$. There appears to be less doubly-refractive dust in the lungs at the end of the experiment than at the beginning (figs. 8 and 9).

$FePO_4$, quartz structure, like the iron hydroxides, produced very little fibrous response. There is a macrophage reaction at 30 days and most of the particles are engulfed by cells, but there is little tendency for the dust to be aggregated into foci. Much of the dust lies loosely in the alveoli, and at 90 days there are still only a few focal accumulations. The appearance of the lungs is very similar at 180 days and later. Very little reticulin is formed, and until the end of the experiment most of the injected material remains dispersed in loosely associated dust cells in all areas of the lung (fig. 10). Neither

TABLE IV

Fibrosis produced in rats' lungs by aluminium and iron hydroxides and phosphates

Days	Aluminium hydroxides			Aluminium oxides		Iron hydroxides		Aluminium phosphates		Iron phosphate
	γ-AlOOH (HX1010) (70 mg.)*	γ-AlOOH (HX1010) (14 mg.)	γ-AlOOH (Cera hydrate) (60 mg.)*	γ-Al_2O_3 (850°) (60 mg.)	α-Al_2O_3 (1200°) (50 mg.)	α-FeOOH (100 mg.)	γ-FeOOH (100 mg.)	$AlPO_4$ (quartz structure) (50 mg.)	$AlPO_4$ (tridymite structure) (50 mg.)	$FePO_4$ (quartz structure) (100 mg.)
30	(4) D (1) K2+	(2) K1	(1) K0	(1) D (1) K2+	(1) K0	(2) D0 (1) K0	(1) D0 (1) K0	(1) K2	(1) K1 (1) D	(1) D0 (1) K0
60	(1) K2	(1) K1	(1) K0	(1) D	(1) K1	(1) K0	(1) K0	(1) K2+	(1) K2−	(1) K0
90	(1) K2	(1) K1	(2) K0	(1) K3	(1) K1	(1) K0	(1) K0	(1) K3	(1) K2+	(1) K0
120	(1) K3	(1) K1+	(1) K0	(1) K3	(1) K1	(1) K0	(1) K0	(1) K3	(1) K3	(1) K0
150	(1) K3	(1) K1	(1) K0	(1) K1	(1) K1	(1) K0	(1) K0	(1) K3+	(1) K3	(1) K0
180	...	(1) K2	(1) K0	(2) K3	(1) K1	(1) K0	(1) K0	(2) K3	(1) K3+	(1) K0
210	...	(1) K1	(1) K0	(3) K4	(1) K1	(1) K0	(1) K0	(1) K3	(1) K3+	(1) K0
240	(2) D	(1) K1	...	...	(1) K1	(1) K0	(1) K0	(1) K3+	(1) K3	(1) K0
270	...	...	(1) K0	...	(1) K1	(1) K0	(2) K0	(1) K4	(1) K3+	(2) K0
300	...	(1) K1+ (1) K2−	(1) K0	(1) K5	(1) K1	(1) K1−	(1) K0	(2) K4	(2) K5	(2) K0
330	...	(1) K3	...	(3) K4	(1) K1	(1) K1−	(2) K1−	(2) K5	(2) K4	(1) K0
365	(1) K3		(2) K1	(1) K4						

* 70 mg. HX1010 and 60 mg. Cera hydrate = 50 mg. Al_2O_3.

Numbers in brackets = numbers killed (K) or dead (D), and the following numbers = grade of fibrosis, e.g., (2) K1 = 2 killed animals with grade 1 fibrosis in the lungs.
\+ = Maximum within the grade of fibrosis. − = Minimum within the grade of fibrosis.

iron hydroxide nor iron phosphate appears to diminish noticeably in the lungs with progress of time, but the amount of dust in the peribronchial and perivascular lymphatics visibly increases with time.

The assessment of the fibrosis, and the times of death or killing for all nine samples are set out in table IV.

COMMENT

The lesions produced by aluminium compounds after injection into rats' lungs showed the same type of development as do silicotic lesions; the grading given in table IV and in the previous paper is therefore valid and was used.

The grade of fibrosis reached depended on dosage and type of material. Fibrosis due to γ-Al_2O_3 was found to be the most severe in the present series. It reached grade 3 after three months and grades 4 or 5 after seven months. At the same level of 50 mg. Al_2O_3 per rat,

fibrosis due to Gardner's HX1010 reached grade 3 after four months and did not progress further. At one-fifth of this dosage it only reached grade 3 fibrosis after one year. Previously (King *et al.*, 1955) Gardner's HX1010 at 100 mg. per rat had also given grade 3 after four months; this had ultimately reached grade 5 in one animal after one year. α-Al_2O_3 was almost completely inert (grade 1 fibrosis) and the coarsely crystalline γ-AlOOH (Cora hydrate) was nearly inert up

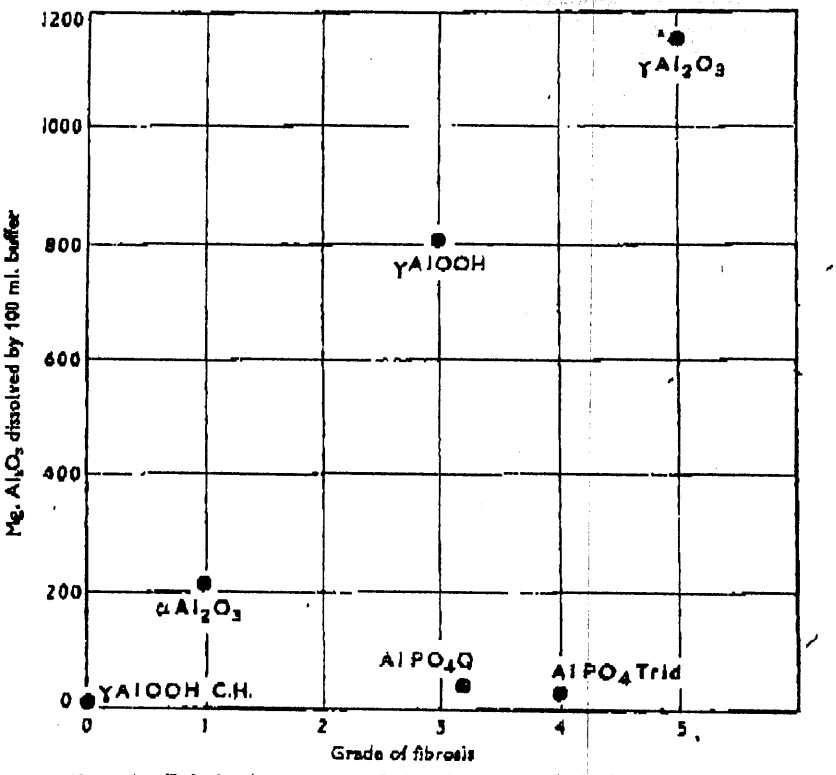

FIG. 11.—Relation between cumulative alumina solubility in 73 days and degree of fibrosis produced.

to one year. For these four samples there appeared to be a direct relation between alumina solubility and fibrogenic activity. This is shown in fig. 11 where the cumulative solubility after 73 days is plotted against the grade of fibrosis reached after 300 days. Fig. 11 also shows that the two forms of $AlPO_4$ did not follow this trend.

In animal experiments with silica, tridymite had been found to be more fibrogenic than quartz, and a similar effect has appeared likely with the closely similar crystal structures of the two $AlPO_4$ modifications. Both, however, produced lesions at about the same rate; these developed further than would have been expected from the alumina solubilities. At present we cannot explain this, especially

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PLATE LXXXIX

ALUMINIUM AND IRON EFFECTS IN RAT LUNG

FIG. 7.—Ferric hydroxide, 50 mg., 365 days. Compact accumulations of dust causing minimal reticulinosis. Hæmatoxylin and eosin. ×45.

FIG. 8.—Aluminium phosphate, quartz structure, 50 mg., 330 days. Confluent lesions composed entirely of collagen, grade 5 fibrosis. Silver impregnation. ×50.

FIG. 9.—Aluminium phosphate, tridymite structure, 50 mg., 330 days. Confluent lesions composed entirely of collagen, grade 5 fibrosis. Silver impregnation. ×50.

FIG. 10.—Ferric phosphate, quartz structure, 365 days. Remarkably loose distribution of dust in the alveoli, no fibrosis. H. and E. ×45.

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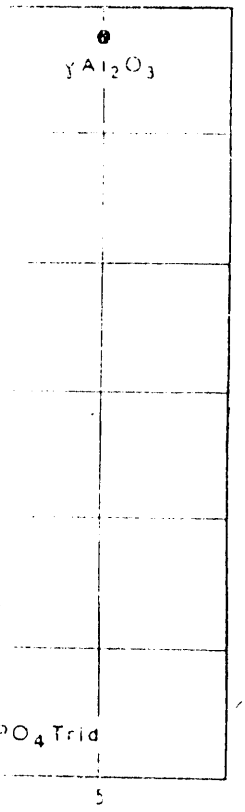

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FIG. 3.—Rat lung. γ-aluminium hydroxide (HX1010), 70 mg., 365 days. Lesion composed of gross collagen fibres, grade 3 fibrosis. Silver impregnation. ×45.

FIG. 4.—Gora hydrate (highly crystalline γ-aluminium hydroxide), 60 mg., 365 days. Lesion with loose formation of reticulin fibres, grade 1 fibrosis. Silver impregnation. ×95.

FIG. 5. γ-alumina (aluminium hydroxide HX1010 heated to 850° C.), 50 mg., 365 days. Acellular lesions composed of dense collagen fibres, grade 5 fibrosis. Silver impregnation. ×45.

FIG. 6.—α-alumina (aluminium hydroxide HX1010 heated to 1200° C.), 50 mg., 320 days. Lesions composed of gross reticulin with some collagen fibres, grade 2 fibrosis. Silver impregnation. ×90.

as $AlPO_4$ with quartz structure had been found to be fairly inert by van Marwyck (1954) and Rüttner *et al.* (1956) in mice, and Pratt *et al.* (1953) in guinea-pigs.

The large range in alumina solubilities found was not necessarily due to the differences in crystal structure, but may have been mainly due to the very wide range of specific surface of the different samples. This could not be measured but only assessed roughly from the electron micrographs of the original HX1010 and the samples of γ-Al_2O_3 and α-Al_2O_3 derived from it. It is therefore not possible to give accurate figures for solubility per unit-surface or to separate the effects of crystal structure and size. But it appears significant that the histological sections showed evidence of loss of dust with the progress of time. Although the form of the lesions resembled that of silicotic lesions, their mode of formation may have been different insofar as it was caused by the products of dissolution of the aluminium compounds.

The iron compounds tested, including $FePO_4$ with quartz structure, were all equally inert and the iron dust deposits did not appear to diminish with time. This seems to be in conformity with experience in man, where iron-oxide deposits, in welders for instance, may give X-ray shadows but do not appear to cause a significant fibrosis if quartz is absent (benign siderosis).

The above experiments show certain aluminium compounds to be fibrogenic when injected into the lungs of rats. Although the lesions appeared similar to those seen in experimental silicosis, they may have been caused by a different mechanism. The fibrosis was probably due to dissolved aluminium ions reacting with proteins (see King *et al.*, 1955), and consequently the tridymite modification of $AlPO_4$ did not act more strongly than the quartz modification.

Summary

The fibrogenic activity of several hydroxides, oxides and phosphates of aluminium and iron was tested by intratracheal injection into rats, with histological observation up to one year after injection.

γ-Al_2O_3 was found to be the most fibrogenic material; this was followed by the quartz-like and tridymite-like modification of $AlPO_4$, which acted equally—in contrast to the differing fibrogenicity of the corresponding silica forms. A poorly crystallised sample of γ-AlOOH of very small size was fairly fibrogenic, but a well-crystallised sample of γ-AlOOH was inert. α-Al_2O_3 was almost inert, and all iron compounds tested were completely so.

There was a positive correlation for the aluminium oxides and hydroxides between alumina solubility and fibrogenic activity, but the alumina phosphates were more fibrogenic than their solubility suggested.

We are grateful to the Medical Research Council and the National Coal Board for grants covering part of the expenses of this investigation, to Mr J. Cartwright for the electron micrographs, and to Mr B. S. C. Hollands for skilled

technical assistance. This paper is published by permission of the Ministry of Power, and Crown Copyright is reserved for figs. 1, 2 and 11.

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Volume II, Part C
Toxicology

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Volume II of this series is dedicated to Paul D. Halley, past president of the American Industrial Hygiene Association, former Director of Environmental Health Services for AMOCO, (Industrial Hygiene, Safety and Toxicology), and Editor-in-Chief for eight years of the *AIHA Journal*, who, after retirement from the latter position, initiated contacts for the fourth revision of this volume, but was forced to relinquish its editorship because of illness.

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16 IRON, Fe

16.1 Sources, Uses, and Industrial Exposures (1, 3)

Iron [CAS # 1309-97-1] is a silver white solid metal of Group VIII, the transition elements of the periodic table. The chemical symbol, Fe, is from *ferrum*, the Latin word for iron. Elemental iron has been known since prehistoric times. Around 1200 BC, iron was obtained from its ores; this achievement marks the beginning of the Iron Age. Even with the development of other materials, iron and its alloys remain crucial in the economies of modern countries. Iron is also critical to life. It is an essential element and a component of hemoglobin.

Iron is the fourth most abundant element (5.1 percent) in the earth's crust. The molten core of the earth is primarily elemental iron. Iron occasionally occurs in its pure form; however, it is abundant in combination with other elements as oxides, sulfides, carbonates, and silicates. Iron ore reserves are found worldwide. Areas with more than 1 billion metric tons of reserves include Australia, Brazil, Canada, the United States, Venezuela, South Africa, India, the former Soviet Union, Gabon, France, Spain, Sweden, and Algeria. The ore exists in varying grades, ranging from 20 to 70 percent iron content. North America has been fortunate in its ore deposits. There are commercially usable quantities in 22 U.S. states and in six Canadian provinces. In the United States the most abundant supplies, discovered in the early 1890s, are located in the Lake Superior region around the Mesabi Range. Other large deposits are found in Alabama, Utah, Texas, California, Pennsylvania, and New York. These deposits, particularly the Mesabi Range reserves, seemed inexhaustible in the 1930s when an average of 30 million tons of ore was produced annually from that one range. The tremendous demand for iron ore during World War II virtually tripled the output of the Mesabi Range and severely depleted its deposits of high-grade ore. The major domestic (U.S.) production is now from crude iron ore, mainly taconite, a low-grade ore composed chiefly of hematite ($FeO(OH)\cdot H_2O$) and silica found in the Great Lakes region.

After the war an intensive search revealed large quantities of rich ore, acceptable for blast-furnace use, in newly discovered deposits. Most of these discoveries involved reserves located close to the surface, allowing the use of open-pit mining

rather than the more costly underground mining that had been necessary to reach many of the older reserves. In addition, new ore upgrading techniques were developed to exploit the large reserves of low-grade ores such as taconites and jaspers.

These techniques include sintering and pelletizing. Sintering is used when ore and other iron-bearing materials are too fine to be charged directly into the furnace. These materials are agglomerated with a mixture of coal and coke fines, or powders, which, when ignited, provide the heat for the sinter process. The result is a porous, clinker-like mass that enhances the upward flow of hot gases through the blast furnace burden.

Pelletizing is used to increase the iron content of low-grade (20 to 30 percent iron) ores. After being crushed, screened, and concentrated, the ore fines are formed into small balls or pellets with an iron content of 60 percent or more. The pellets are then hardened by heating to increase their strength and durability for subsequent processing. Thus ores that were once considered unsuitable now supply a substantial portion of the industry's requirements.

Perhaps the most important alloy of iron is steel, which contains up to approximately 2 percent carbon. Steels that contain about 0.25 percent carbon are called mild steels; those with about 0.45 percent carbon are medium steels; and those with 0.60 percent to 2 percent carbon are high-carbon steels. Within this range, the greater the carbon content, the greater the tensile strength of the steel. The hardness of steel may be substantially increased by heating the metal until it is red hot and then quickly cooling it, a process known as quench hardening. An important component of many steels is cementite, a carbon–iron compound. Mild steels are ductile and are fabricated into sheets, wire, or pipe. The harder medium steels are used to make structural steel. High-carbon steels, which are extremely hard and brittle, are used in tools and cutting instruments.

Wrought iron, which is nearly pure iron, has a lower carbon content than steel. Because of its low carbon content (usually below 0.035 percent), it is forgeable and nonbrittle. Iron of high carbon content (3 to 4 percent), obtained when pig iron is remelted and cooled, is called cast iron. If cast iron is cooled quickly, hard but brittle white cast iron is formed; if it is cooled slowly, soft but tough gray cast iron is formed. Because it expands while cooling, cast iron is used in molds.

The addition of other materials in alloys—for example, manganese or silicon—also increases the hardness of steel. The inclusion of tungsten permits high-speed drills and cutting tools to remain hard even when used at high temperatures. The inclusion of chromium and nickel improves the corrosion resistance of the steel and, within certain limits of composition, is called stainless steel. A common stainless steel contains 0.15 percent C, 18 percent Cr, and 8 percent Ni. It is used in cooking utensils and food-processing equipment. The inclusion of silicon, ranging from 1 to 5 percent, results in an alloy that is hard and highly magnetic. An alloy with cobalt is used for permanent magnets.

In the United States, steel ranks among the 10 largest industries. Steel producers fall into two major categories. Integrated steel makers convert iron ore into steel through a lengthy process that employs a blast furnace to produce iron from iron ore, and a basic oxygen or open hearth furnace to transform the iron into steel.

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Nonintegrated steelmakers melt steel scrap in electric arc furnaces to produce liquid steel in facilities that are sometimes referred to as minimills. Given the very large size of many nonintegrated steel facilities, however, the term "scrap-based mill" is also used to describe a steel plant that does not convert iron ore to iron; and "ore-based mill" has become another term to describe an integrated steelmaker.

The rapid expansion of foreign steel industries created unprecedented competition for the U.S. industry, which must increase its investment in new technologies to reduce costs, improve steel quality, and meet more demanding performance specifications. However, foreign steel, much cheaper than domestic steel, resulted in many older mills closing. The reduction of demand for domestic steel and the reduction of man-hours required to produce steel in modernized plants have reduced the number of workers exposed in this industry.

Mining and handling of iron ores provide exposure to dusts of SiO_2 and iron oxides. Carbon monoxide is a hazard in the operation of blast furnaces for the production of pig iron. The use of fluorspar (CaF_2) in steelmaking gives rise to gases containing SiF_4 and other fluorine-containing substances. The manufacture of alloy steels introduces hazards attendant on the use of metals such as chromium, manganese, nickel, vanadium, tungsten, molybdenum, and copper. "Pickling" of iron containing arsenic and phosphorus liberates arsine and phosphine. Certain grades of ferrosilicon used in steelmaking decompose with explosive violence on contact with moist air, evolving various toxic gases such as acetylene, H_2S, SiH_4, AsH_3, and PH_3. Fatal intoxications have occurred from such accidents during transportation, particularly at sea (546).

Because iron is essential to health, iron supplements are frequently used in the treatment of iron deficiency or iron malabsorption syndromes. Iron dextran is a complex of ferric hydroxide with dextran. It is injected to treat iron deficiency anemia in humans and in baby pigs. Exposure occurs in manufacturing and repacking, and use is limited. Slightly more than 1000 workers may be so exposed; about half are women (113). A great many more workers are exposed in the manufacture of oral iron preparations.

Iron in its various oxidation states readily combines with many carbon compounds to form organometallic compounds. Finely divided iron reacts with carbon monoxide under pressure to form the yellow liquid iron pentacarbonyl, $Fe(CO)_5$. This transition-metal carbonyl, like many others, contains the metal in a zero oxidation state. The compound is the starting material for iron compounds in unusually low oxidation states. On decomposition, iron pentacarbonyl yields pure iron. Iron pentacarbonyl is used as a gasoline additive (0.2 percent) in Europe, similar to the use of tetraalkyl lead in the United States.

A new type of organometallic compound was discovered in 1951. If ferrous chloride is reacted with cyclopentadiene in the presence of a strong organic base, the orange crystalline compound ferrocene (CAS # 102-54-5) is the product. This compound, which has a highly stable structure, is called a "sandwich" compound because the iron atom is strongly held between the two flat C_5H_5 rings. In this case, it is not useful to attempt to assign an oxidation state to iron. The characterization of this compound has led to extensive transition metal organometallic

Table 27.21. Chemical and Physical Characteristics of Iron and Some of Its Salts

Form	At. or Mol. Wt.	Sp. Gr.	M.P. (°C)	B.P. (°C)	Solubility
Iron, Fe	55.85	7.86	1535	2750	Insol. water; sol. acids
Ferrous oxide, black, FeO	71.85	5.7	1420	—	Insol. water; sol. acid; insol. alcohol, alkalies
Iron oxide, magnetite, red, F_3O_4	231.54	5.19	Dec. 1538	—	Insol. water; sol. conc. acid; insol. alcohol, ether
Ferric chloride, $FeCl_3$	162.21	2.898 (25°C)	306	Dec. 315	5.25 kg/l (100°C); v. sol. EtOH, MeOH, ether
Ferric sulfate, $Fe_2(SO_4)_3$	399.87	3.097 (18°C)	—	—	Sl. sol. cold water; dec. hot water; insol. H_2SO_4
Ferrous sulfate, $FeSO_4 \cdot H_2O$	169.96	2.97 (25°C)	—	—	Sl. sol. cold water
Ferrocene, $C_5H_5FeC_5H_5$	186.04	—	172.5	Subl.	Insol. water; sol. EtOH, ether, MeOH
Iron carbonyl, $Fe(CO_5)$	195.9	1.46	−20	103	Insol. water, dilute acids; sol. most organic acids

chemistry. Ferrocene (dicyclopentadienyl iron) is a relatively volatile, organometallic compound used as a chemical intermediate, a catalyst, and as an antiknock additive in gasoline.

16.2 Physical and Chemical Characteristics

The chemical and physical characteristics of iron and some of its compounds have been listed in Table 27.21.

The physical properties of iron, the metal, are profoundly affected by impurities and by changes in temperature and treatment. Iron is superior to all other elements in magnetic properties. Iron, in an almost pure state, loses its magnetism when removed from an electric field; when iron contains small amounts of carbon, cobalt, or nickel, the retention of magnetism is increased. When heated to 770°C, iron

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loses its magnetism; on cooling, it retains this property. Iron undergoes a variety of structural changes (transformations) on heating that form the basis of the heat treatment of ferrous metals.

The principal compounds of iron are ferrous (Fe^{2+}) and ferric (Fe^{3+}). In general, ferrous and ferric forms are mutually interconvertible. The oxidation potential against the normal hydrogen electrode for the ferrous form is -0.43 V, and for the ferric form, $+0.77$ V. Ferrous compounds are more stable than ferric when ionized, less stable when covalent.

A large proportion of iron salts are water soluble; exceptions are carbonates, oxides, hydroxides, phosphates, sulfides, and ferrous fluoride. Iron of both valences tends to form complexes in which the most common coordination number is 6. Iron has a strong tendency to combine with oxygen, as in the form of hydroxyl groups, with resultant stable compounds, especially as chelates. Iron compounds exhibit marked catalytic activity in the promotion of oxidations, which are of both chemical and biologic importance. Iron forms several carbonyls; their properties and uses are discussed.

An interesting aspect of iron chemistry is the array of compounds that bond to carbon. Cementite, Fe_3C, is a component of steel. The cyanide complexes of both ferrous and ferric iron are very stable and are not strongly magnetic in contrast to most iron coordination complexes. The cyanide complexes form colored salts, including Prussian blue, $KFe_2(CN)_6$, made from ferric iron and potassium ferrocyanide. The compound Turnbull's blue, made from ferrous iron and potassium ferricyanide, is considered identical to Prussian blue.

Iron forms a large group of materials known as ferroalloys that are important as addition agents in steelmaking. Iron is also a major constituent of many special-purpose alloys developed for characteristics related to magnetic properties, electrical resistance, heat resistance, corrosion resistance, and thermal expansion.

Among the better-known types of Fe alloys are those with carbon, of which the principal ones are wrought iron, cast iron, and steel. Good wrought iron contains no more than 0.035 percent C, but also contains 0.075 to 0.15 percent Si, 0.1 to 0.25 percent P, less than 0.02 percent S, and 0.06 to 0.1 percent Mn, not all of which are alloyed with the iron.

Cast iron contains 2 to 4 percent C and varying amounts of silicon, phosphorus, sulfur, and manganese, to obtain a wide range of physical and chemical properties. Alloying elements such as silicon, nickel, chromium, molybdenum, copper, and titanium may be added in amounts varying from a few tenths to 30 percent or more.

Steel is a generic name for a large group of Fe–C alloys in which the carbon content is about 2 percent. To this basic steel, other alloying elements may be added, the more common types of which are aluminum, chromium, cobalt, Cr–Ni, Cr–Al, manganese, nickel, silicon, and tungsten, each of which has particular uses arising from its special properties.

The several iron oxide forms are used as paint pigments, polishing compounds, magnetic inks, and coatings for magnetic tapes. The soluble salts are variously used

as dyeing mordants, catalysts, pigments, fertilizer, feeds, and disinfectants, and in tanning, soil conditioning, and treatment of sewage and industrial wastes.

The minimum ignition temperatures for iron dust clouds range from 470 to 780°C; for layered dust, the range is 220 to 520°C (1).

Iron pentacarbonyl, $Fe(CO)_5$, like nickel carbonyl, is insoluble in water and unreactive in dilute acids. It may ignite spontaneously in air. Concentrated reducing acids yield ferrous salts, as do gaseous halogens. Iron pentacarbonyl is a strong reducing agent changing ketones to alcohols, benzil to benzoin, and nitrobenzene to aniline.

Iron pentacarbonyl has an ignition temperature of 320°C; the minimal explosive concentration is 105 oz/ft^3; 10 percent oxygen is the limiting concentration to prevent ignition (547).

Although information on storage and handling has been given specifically for $Fe(CO)_5$ (548), it can be assumed that the information applies in like manner to all industrial metal carbonyls. Because the vapors of $Fe(CO)_5$ form explosive mixtures with air, this chemical should be stored under CO, CO_2, or N_2; and because of its high toxicity, handling of this substance should be done in well-ventilated hoods. The danger of spontaneous ignition can be reduced by the addition of hydrocarbons, their halogen derivatives, or alcohol. Workrooms should be provided with good general ventilation, and only persons trained in handling extrahazardous materials should be employed for this work.

16.3 Monitoring

Collection of a particulate filter and analysis by X-ray fluorescence spectrophotometry is the NIOSH method for iron oxide fume (111).

16.4 Physiological Response

The oral absorption of iron is largely limited by physiological homeostatic mechanisms that regulate the intake based on the need. The intestinal mucosa is the major site at which the absorption is limited, but hepatic and pancreatic secretions may influence the absorption. However, in cases of acute iron poisoning the gastric mucosa is often disrupted. The iron transport system is overloaded, and this results in circulating free iron. In the normal homeostatic mode the divalent iron is absorbed into the gastric mucosa where it is converted to the trivalent form. The toxicokinetics of injectable iron and organo-iron compounds, like ferrocene, are not affected by the homeostatic gastrointestinal control of iron absorption. The trivalent iron attached to ferritin passes into the bloodstream and is converted into transferrin. Transferrin is transported to the spleen or liver where it is stored as ferritin or hemosiderin. Under normal conditions the body burden of iron is about 4 g. Hemoglobin contains the greatest amounts of body iron (67 percent), and this largely in the red blood cells. Twenty-seven percent of the total body iron is in the liver as ferritin or in pathological conditions as hemosiderin. Because iron is so important in physiological function, the body tends to conserve iron. The major

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mechanisms for the excretion of iron are desquamation of the gastrointestinal tract and blood loss. However, the iron-deferoxamine formed as the result of administering the specific iron chelator, deferoxamine, is excreted in the urine (71).

Ingestion of iron-containing tablets by children is a frequent occurrence. The estimated toxic dose for a 10-kg child is 20 mg Fe/kg. According to Ellenhorn and Barceloux (112), 5000 cases of iron poisoning occur in the United States each year. One case of acute industrial iron poisoning has been reported. In this case a worker fell into a vat of $FeCl_3$ (549).

The first phase of acute oral iron intoxication is gastrointestinal irritation and damage. Vomiting may occur at this phase. Central nervous system depression, as well as cardiovascular symptoms, such as pallor, tachycardia, and hypotension, may occur. Following the initial phase, the patients may appear to recover. However, in 12 to 48 hr after the ingestion, life-threatening symptoms can appear. These include gastrointestinal perforation, coma, convulsions, vasomotor collapse, cyanosis, and pulmonary edema. Hepatorenal failure may develop. Most deaths occur during this phase. In the prolonged recovery, pyloric constriction and gastric fibrosis may occur (71).

Chronic oral iron intoxication is relatively rare, but can lead to hemosiderosis or hemochromatosis. Hemosiderosis is a condition in which there is a generalized increase in the iron content in the body tissues, particularly the liver and spleen. Hemochromatosis is marked by the accumulation of iron, as in the Kupffer cells of the liver and in the reticuloendothelial cells of the spleen and bone marrow. This is accompanied by fibrotic changes in the affected organ, most often the liver.

Hemosiderosis has been reported in the Bantu of Africa. This may be due to the use of iron pots for cooking, the nature of the diet, and the use of beer brewed in ironware. "Bantu siderosis" occurs more frequently in men than in women and may be a geographic cluster of primary hemochromatosis (71).

Primary hemochromatosis is a genetically determined autosomal recessive disorder occurring most often in men, characterized by the excessive accumulation of body iron (550). The disorder is determined by a locus closely linked to the HLA loci on the short arm of chromosome 6. There is a recessive mode of transmission. The gene frequency may be as high as 0.05 in some parts of the world. HLA typing makes it possible to identify family members who are homozygous for idiopathic hemochromatosis, and measurement of transferrin saturation and serum ferritin concentration will identify those with iron overload (551). Hypogonadism of either testicular or central origin is a frequent complication (552).

Pulmonary siderosis results from inhalation of iron dust or fumes. It falls into the group of pneumoconioses in which the pulmonary reaction is minimal, despite a heavy dust load. Because fibrosis is not caused by inhalation of iron dust, the clinical course is benign; and pulmonary function tests and blood gases are within normal limits (553).

Marazzini et al. (554) showed an increase of bronchial obstruction due to exposure in an iron foundry. In a 100-subject sample, all working in the iron foundry were affected only by small airway obstruction. Thirty months later, 99 of these subjects were reexamined and the present airway condition determined. In 43

subjects there were abnormal results of the tests, indicating total airway obstruction after 30 months. Even in the subsample of nonsmokers, a deterioration had occurred.

A retrospective cohort mortality study was conducted by Andjelkovich et al. (555) among 8147 men and 627 women employed in a gray iron foundry for at least 6 months between 1950 and 1979. More than 1700 deaths occurred during a 35-year period of observation. Standardized mortality ratios (SMRs) for all causes were close to expected values, based on the U.S. general population as the standard. The mortality of nonwhite men was significantly increased for lung cancer (SMR 132) and ischemic heart disease (SMR 126). Other moderate, but nonsignificant, excesses were noted among nonwhite men for cancers of the stomach, pancreas, and prostate, for diabetes mellitus, and for pulmonary emphysema, and among white men for cancers of the lung and stomach, gastric and duodenal ulcers, pulmonary emphysema, and suicide. Small mortality increases were observed in both racial groups for cerebrovascular disease. The lack of a trend with time since hire and duration of foundry employment suggests that lung cancer mortality may not be associated with exposure to the foundry environment. Utilizing indirect measures of smoking, it appears that virtually all excess lung cancer deaths among whites, and at least some of the excess among nonwhites, could be explained by smoking habits. Similarly, smoking may have been responsible for the mortality excesses from emphysema, cerebrovascular diseases, and ischemic heart disease.

Underground hematite mining has been associated by IARC (152) with cancer among workers. It has been suggested that this may be due to excessive exposure to radon. In a retrospective cohort mortality study of 10,403 Minnesota iron-ore (hematite) miners no excesses of lung cancer mortality were present among either underground (SMR = 100) or aboveground (SMR = 88) miners. Yugoslav-born miners incurred a twofold significant excess mortality for lung cancer that did not appear to be associated with their mining exposures. Significant excesses in mortality due to stomach cancer were found for both underground (SMR = 167) and aboveground (SMR = 181) miners as compared with U.S. white males. However, except among Finnish-born miners, these excesses disappeared when comparisons were made with the appropriate country rate. The authors (556) concluded that the apparent absence of significant radon exposure, a strict smoking prohibition underground, an aggressive silicosis control program, and the absence of underground diesel fuel use may explain why these underground miners did not appear to incur the lung cancer risk reported in other studies.

In contrast, a cohort mortality study was conducted with regard to a pyrite mine located in central Italy, where there was exposure to radon. The concentration of free silica in the dust was less than 2 percent. The cohort was determined from company files and included 1899 subjects. Mortality was studied for the years 1965 to 1983. The loss to follow-up was less than 2 percent. The SMR for all causes and all neoplasms was 97 and 107, respectively. That for lung cancer and for nonmalignant respiratory diseases was 131 and 173, respectively. The investigators (557) estimated that the extra cases of lung cancer attributable to radon daughters numbered 13 per 10^6 person-years and working level month in the whole cohort. The

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extra cases of lung cancer were 21.3 per 10^6 person-years in the subcohort with 10 to 25 years of exposure.

Mortality during the years 1947 to 1983 was studied by Cooper et al. (558) in 3444 men employed during the years 1947 to 1958 for at least 3 months in Minnesota taconite mining operations. Taconite is a low-grade iron ore consisting of iron, quartz, and numerous silicates. Taconite from the eastern part of the Mesabi Iron Range contains the amphibole silicate cummingtonite–grunerite, which is a mineral relative of amosite asbestos. During 86,307 person-years of observation, there were 801 deaths for a standardized mortality ratio (SMR) of 88 (U.S. white male rates) or 98 (Minnesota rates). The 41 deaths from respiratory cancer were fewer than expected, the SMR being 61 (U.S. rates) and 85 (Minnesota rates). There were 25 respiratory cancers 20 or more years after first taconite employment, for an SMR of 57 (U.S. rates). SMRs for colon cancer, kidney cancer, and lymphopoietic cancer were elevated, but below the level of statistical significance. There was one death from pleural mesothelioma 11 years after first taconite employment in a man with a long prior employment as a locomotive operator. The pattern of deaths did not suggest asbestos-related disease in taconite miners and millers.

In 1967, 240 workers in the Kiruna, Sweden iron mine were examined with regard to lung function and respiratory symptoms. Seventeen years later, 167 of these workers were reexamined using a structured interview which covered respiratory symptoms, smoking habits, and workplace conditions; lung function tests, including dynamic spirometry and closing volume, were also analyzed. The prevalence of chronic bronchitis in the latter study was 9.6 percent. There was a strong relationship between chronic bronchitis and smoking, but no relationship between chronic bronchitis and working underground in the mine. Only three persons had chronic obstructive lung disease. In the still active mine workers, dynamic spirometry results showed no difference between smokers and nonsmokers or between underground and surface workers. Thus the authors reported no excess of chronic obstructive lung disease or lung function disturbances in the mine workers studied. This may reflect a self-selection process whereby the workers with airway obstruction due to smoking or underground exposure have left underground work and, also, the company. Underground workers with chronic mucous hypersecretion, on the other hand, have not felt motivated to leave underground work because of this. Some, however, may have stopped smoking, but not necessarily because of the hypersecretion (559).

Both NTP and IARC have determined that iron dextran may reasonably be anticipated to cause cancer in humans. This determination is based on the finding of injection site tumors, particularly in rats after subcutaneous injections of iron dextran. Additionally, a few human cases of injection site tumors arising after treatment with iron dextran have been reported (152). The nature of these reported tumors suggests that they may not have been due to iron dextran. However, the finding of injection site tumors in experimental animals alone cannot be considered indicative of an occupational cancer hazard; there is virtually no information to suggest that exposure to iron or iron compounds by any route except intramuscular or subcutaneous injection poses a cancer hazard. However, further studies with

injectable iron compounds have indicated that high doses given intravenously to pregnant rats may result in teratogenic changes (hydrocephalus, anophthalmia). These teratogenic effects can be reduced by deferoxamine (71).

Signs and symptoms of overexposure to $Fe(CO)_5$ resemble those of $Ni(CO)_4$—immediately upon exposure, giddiness and headache, occasionally accompanied by dyspnea and vomiting. Removal from exposure reverses the symptoms, but dyspnea returns in 12 to 36 hr, accompanied by fever, cyanosis, and cough. Death usually occurs in 4 to 11 days from exposure to lethal concentrations. Pathological changes consist of pulmonary hepatization, vascular injury, and degeneration of the central nervous system (1).

Ferrocene has been suggested as a therapeutic agent for anemia related to malabsorption of iron, as well as a gasoline additive. There are no published data with regard to adverse effects resulting from occupational exposure. However, F344/N rats and B6C3F1 mice were exposed to 0, 2.5, 5.0, 10, 20, and 40 mg ferrocene vapor/m^3, 6 hr/day for 2 weeks. During these exposures, there were no mortalities and no observable clinical signs of ferrocene-related toxicity in any of the animals. At the end of the exposures, male rats exposed to the highest level of ferrocene had decreased body-weight gains relative to the weight gained by control rats. The body-weight gains for all groups of both ferrocene and control female rats were similar. Male mice exposed to the highest level of ferrocene also had decreased body-weight gains, relative to controls. The female mice had relative decreases in body-weight gains at the three highest exposure levels. Male rats had a slight decrease in relative liver weights at the highest level of exposure, whereas no relative differences in organ weights were seen in female rats. Male mice had exposure-related decreases in liver and spleen weights, and an increase in thymus weights, relative to controls. For female mice, decreases in organ weights occurred in the brain, liver, and spleen. No exposure-related gross lesions were seen in any of the rats or mice at necropsy (560).

16.5 Health Standards

Although iron dextran is classified as "reasonably expected to be carcinogenic" by NTP and a B2 carcinogen by IARC, its harmful exposure in workers is limited. The TLV for iron oxide fume (Fe_2O_3) is 5 mg/m^3, and the TLV committee also classifies it as a B2 carcinogen. The OSHA PEL for iron oxide is 10 mg/m^3 as total particulate. The TLV and the PEL for iron salts are both 1 mg Fe/m^3 (69). The TLV was selected to prevent the development of X-ray changes following long-term exposure to iron oxide dust and fume, whereas the TLV for the iron salts was recommended to reduce the likelihood of respiratory irritation and skin irritation (105).

The TLV for iron $Fe(CO)_5$, as Fe, is 0.23 mg/m^3 as an 8-hr TWA with a short-term exposure limit (STEL) of 0.45 mg Fe/m^3, whereas the OSHA PEL is 0.1 mg/m^3 as Fe with a STEL of 0.2 mg Fe/m^3 (69). The TLV is believed to be "more than adequate to protect against acute and chronic systemic effects." A previous

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TLV of 0.01 mg/m³ was recommended because of acute toxicity and suspected carcinogenic potential (105).

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17 THE LANTHANIDES (RARE EARTH METALS)

17.1 Sources, Uses, and Industrial Exposures (1, 3)

The lanthanides (or lanthanons) are a group of 15 elements of atomic numbers from 57 through 71 in which yttrium (atomic number 39) and scandium (atomic number 21) are sometimes included. The lanthanide series is the group of chemical elements that follow lanthanum in Group IIIB of the periodic table. Their distinguishing atomic feature is that they fill the *4f* electronic subshell. Actually, only those elements with atomic numbers 58 through 71 are lanthanides. Most chemists also include lanthanum itself in the series because, although it does not fill the *4f* subshell, its properties are very like those of the lanthanides. The IIIB elements, including scandium and yttrium as well, are also known as the rare earths because they were originally discovered together in rare minerals and isolated as oxides, or "earths." In comparison with many other elements, however, the rare earths are not really rare, except for promethium, which has only radioactive isotopes. The relative abundance and atomic numbers are tabulated in Table 27.22.

Scandium is a silvery white metallic chemical element, the first member of the first transition series. The name is derived from Scandinavia, where the element was discovered in the minerals euxenite and gadolinite. In 1876, L. F. Nilson prepared about 2 g of high-purity scandium oxide. It was subsequently established

Table 27.22. Atomic Numbers, Weights, and Concentration of the Rare Earths (Lanthanide Series)

Element	Atomic No.	Atomic Weight	Earth's Crust (ppm)
Scandium (Sc)	21	44.9559	5–6
Yttrium (Y)	39	88.9059	28–70
Lanthanum (La)	57	138.9055	5–18
Cerium (Ce)	58	140.12	46
Praseodymium (Pr)	59	140.9077	6
Neodymium (Nd)	60	144.24	24
Promethium (Pm)	61	145	4.5×10^{-20}
Samarium (Sm)	62	150.4	6
Europium (Eu)	63	151.96	1
Gadolinium (Gd)	64	157.3	6
Terbium (Tb)	65	158.9254	0.9
Dysprosium (Dy)	66	162.50	4
Holmium (Ho)	67	164.9304	1
Erbium (Er)	68	167.26	2
Thulium (Tm)	69	168.9342	0.2
Ytterbium (Yb)	70	173.04	3
Lutetium (Lu)	71	174.97	0.8

that scandium corresponds to the element "ekaboron," predicted by Mendeleyev on the basis of a gap in the periodic table. Scandium occurs in small quantities in more than 800 minerals and causes the blue color of aquamarine beryl. The chemical properties of scandium resemble those of yttrium and the rare earth metals. It has 11 known isotopes, only one of which occurs in nature. Scandium exhibits an oxidation state of exclusively 3+. Because it is difficult to process, scandium has few commercial uses, but shows promise in electronics and high-intensity lighting.

Yttrium is one of four chemical elements (the others being erbium, terbium, and ytterbium) named after Ytterby, a village in Sweden which is rich in unusual minerals and rare earths. Yttrium is a metal with a silvery luster and properties closely resembling those of rare earth metals. Its principal use is as the matrix of europium-activated red phosphors that give the red hue in color television tubes.

Lanthanum is a chemical element, a white, malleable metal, and the first of the rare earths. Lanthanum is found with other lanthanides in monazite, bastnaesite, and other minerals. It was discovered in 1839 by the Swedish chemist Carl G. Mosander. Scientists have created many radioactive isotopes of lanthanum. Because lanthanum increases the refractive index of glass, it is used in manufacturing high-quality lenses. Lanthanum is largely used as a catalyst for cracking crude petroleum. It is also used as a reagent and as a phosphor in fluorescent lamps.

The lanthanides are in many minerals, principally monazite. The only commercially useful ores are massive monazite and monazite sand, a phosphate of the cerium group metals: bastnasite and related fluocarbonate minerals of the cerium group; minerals of the yttrium group—gadolinite, a silicate of yttrium, cerium,

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1

IRON BIOCHEMISTRY

1.1 FUNCTION AND CHEMISTRY

Iron (atomic weight 55.85, atomic number 26), the second most abundant metal in the earth's crust, exists in two valency states: ferrous (FeII) and ferric (FeIII). Over 500 million years ago large amounts of reduced iron (FeII) would have been present in the low-oxygen environment, but now iron exists almost exclusively in the less soluble oxidized state (FeIII). This has greatly reduced its accessibility to many forms of life, including humans, and this is suggested to be one of the main contributory factors in the aetiology of iron deficiency anaemia, one of the most common nutritional deficiency disorders in the world (FAO/WHO, 1988).

The chemistry of iron is complex, primarily because of its dual valency and reactivity with oxygen. Ionic iron is an active promoter of free-radical reactions, and is toxic to living cells. Biological systems have therefore developed several ways of limiting the entry of iron into the body and converting any absorbed iron into a bound 'safe' form. In mammals serum iron is bound to transferrin, and most body iron is present as iron porphyrin complexes (haemoglobin, myoglobin and haem-containing enzymes). Iron is stored as ferritin and haemosiderin. The distribution of iron in the body is illustrated in Figure 1.1.

The nutritional need for iron in living organisms is derived from the central role that it plays in the energy metabolism of living cells. Iron is a transition metal and can take part in redox processes by undergoing reversible valency changes, such as reduction by an organic substrate and re-oxidation by oxygen. It can also bind oxygen either on its own or as part of a complex.

1.2 IRON COMPOUNDS IN THE BODY

Proteins of iron transport (transferrin) and storage (ferritin and haemosiderin) are discussed in Chapter 4. Functionally important forms of iron in the body are haemoglobin, myoglobin, cytochromes, iron–sulphur proteins, iron enzymes and lactoferrin.

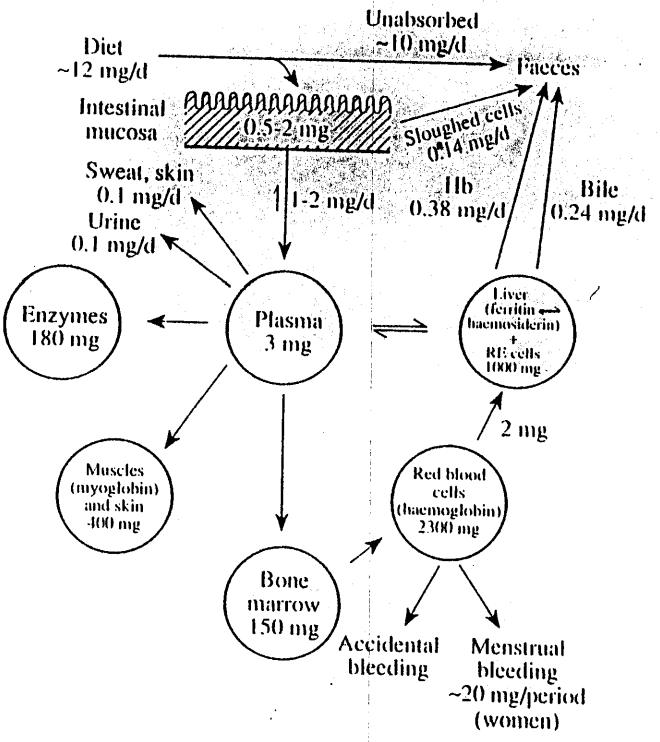

Figure 1.1 Iron distribution (mg) and metabolism within the body. RE: Reticuloendothelial cells

1.2.1 Haemoglobin (Hb)

About two thirds of body iron is present in haemoglobin in red blood cells, where it is essential in the transport of oxygen. The haemoglobin molecule consists of four subunits, each of them a polypeptide chain bound to a haem molecule, and has a molecular weight of 65 000 and an iron content of 0.34%. Iron is stabilized in the ferrous state which allows it to be reversibly bound to oxygen. The synthesis of haem and its attachment to globin take place in the bone marrow in the late stages of the development of the red blood cell. Iron is carried to the bone marrow as ferric iron bound to transferrin: it is released within the red cell precursors, reduced to the ferrous form and transferred to protoporphyrin (Chapter 7).

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1.2.2 Myoglobin

Myoglobin, the red pigment of muscle, is a single peptide homologue of haemoglobin with a molecular weight of 17 000. Its function is to store oxygen delivered to the tissues by haemoglobin for utilization during muscle contraction. This protein accounts for 5–10% of total body iron.

1.2.3 Cytochromes

Cytochromes, the electron-transport enzymes, are located in the mitochondria as well as in other cellular membranes. They are able to undergo reversible oxidation by way of changes in the oxidation state of iron. Cytochromes a, b and c are present in all aerobic cells, within the cristae of mitochondria, and are essential for the oxidative production of cellular energy in the form of ATP. Cytochrome c has a molecular weight of 13 000 and, like myoglobin, is made up of a single peptide chain and one haem group, containing an atom of iron. Extra-mitochondrial cytochromes include cytochrome P-450, located within microsomal membranes of the liver, which is involved in oxidative degradation of drugs and endogenous substrates, e.g. steroids.

1.2.4 Iron–sulphur proteins

The iron–sulphur proteins contain iron and acid-labile sulphur in equimolar amounts, and are involved in electron transport by undergoing reversible Fe(II)–Fe(III) transitions. They include flavoproteins found in the mitochondria, such as NADH dehydrogenase and succinic dehydrogenase, and aconitase.

1.2.5 Iron enzymes

The haem enzymes catalase and peroxidase contain four haem groups, each with one iron atom; they are widely distributed in the body but are particularly abundant in red blood cells and the liver. They function in the reduction of hydrogen peroxide produced in the body. Other non-haem iron enzymes include aconitase and the flavoprotein, xanthine oxidase.

1.2.6 Lactoferrin

The glycoprotein lactoferrin (molecular weight 80 000) is a cationic iron carrier, very similar to transferrin, that is present in high concentrations in human breast milk (1 mg/ml). It binds two atoms of ferric iron per molecule and is found in neutrophilic granulocytes and on mucosal surfaces as part of their protective coat. Lactoferrin is believed to participate in the defence of the breast-fed infant against infection by depriving bacteria of the iron needed for growth, and by donating iron to generate reactive oxygen radicals to enhance the microbicidal mechanisms of phagocytes.

1.3 INTERACTIONS BETWEEN IRON AND OTHER MICRONUTRIENTS

There are a number of micronutrients that affect iron metabolism either before or after absorption from the gut (Table 1.1). Uptake of iron may be modified by other minerals, such as calcium and nickel. Interactions occur in the gastrointestinal tract, primarily with calcium, zinc, manganese and vitamin C (Chapter 2). Subsequent physiological utilization of the element may be impaired with riboflavin, vitamin A or copper deficiencies.

Table 1.1 Interactions between iron and other micronutrients

Site of interaction	Nutrients involved
Food chain (soil–water–plant–animal)	Calcium, nickel
Lumen of gastrointestinal tract (uptake across brush border)	Calcium, zinc, manganese, copper, cobalt
Serosal transport (transport from mucosal cell to the circulation)	Riboflavin, calcium
Erythropoiesis	Vitamin A, riboflavin, copper

2

IRON ABSORPTION

2.1 INTRODUCTION

The capacity of the body to excrete iron is extremely limited (McCance and Widdowson, 1937), therefore the absorptive process plays the major role in the maintenance of iron homeostasis In general, only a small proportion of dietary iron is absorbed, and the amount is quite variable both between and within individuals (Kuhn *et al.*, 1968). It is significantly influenced by a number of factors, both diet- and host-related.

Measurements of iron intake are of limited value in assessing the nutritional value of a diet without some indication of iron bioavailability. This is defined as the proportion of the total intake that is potentially available for absorption and normal metabolic functions, as discussed in the Report of the Panel on Dietary Reference Values (DH, 1991). Most absorbed iron is incorporated into red blood cells. The amount depends on the iron status and erythropoietic activity of the individual, and values of 80–95% have been reported.

2.2 MEASUREMENTS OF IRON AVAILABILITY FROM FOODS

The various techniques that have been developed to assess the availability of iron from foods can be broadly subdivided into *in vitro* and *in vivo* techniques (Table 2.1). The method adopted for any study must consider:

- resources available (e.g. financial, skill-base, and equipment);
- question(s) to be answered (e.g. iron bioavailability from specific foods, whole diets, or effects of processing techniques);
- ethical considerations (e.g. use of radioisotopes in subjects under investigation).

Table 2.1 Techniques used to study iron bioavailability (source: Fairweather-Tait, 1992a)

In vitro methods	*In vivo* methods
Measurement of soluble/dialysable iron	Perfusion experiments with ligated loops
Intestinal vesicle preparations	Rate of repletion following depletion
Everted small intestinal rings/sacs	Chemical balance
	Plasma appearance
	Whole body counting (^{59}Fe)
	Radio- or stable isotopic balance
	Haemoglobin incorporation of isotopes

In vitro methods

One approach is to measure iron that is 'available for absorption' using *in vitro* methods, by determining ionizable iron (Narasinga Rao and Prabhavathi, 1978), or dialysable iron using equilibrium dialysis (Miller *et al.*, 1981) or continuous flow dialysis (Minihane *et al.*, 1993). These methods avoid the need to understand and control all the physiological factors that affect the efficiency with which iron is absorbed and should, in theory, provide a consistent and reproducible means of assessing the effect of dietary variables on absorbable iron. Clearly it is not possible to simulate the physiological factors that account for major variations in the absorption of iron. Thus the objective of the *in vitro* methods is to rank individual foods in order of available iron content and to predict correctly the relative effects of enhancers and inhibitors of absorption. *In vitro* methods are less expensive and generally require fewer resources than *in vivo* techniques, and are thus worthy of further development. However, caution must be applied in the interpretation of results from such studies (Valdez *et al.*, 1992; Miller and Berner, 1989).

2.2.2 *In vivo* methods

(a) Isotopic iron incorporation into haemoglobin

Incorporation of iron into haemoglobin is probably the only true method of determining bioavailability since it is a direct measure of iron utilization. Iron

repletion studies are useful when considering the value of different iron sources in treating iron deficiency anaemia, but they are lengthy and require strict dietary control. Furthermore, they are not necessarily appropriate for the study of iron replete individuals, whose efficiency of absorption is much lower than that of iron deficient subjects. The method of choice is to use radioisotopes (^{55}Fe and ^{59}Fe) to label extrinsically iron in individual foods or in meals, and to determine the incorporation of the dose into haemoglobin 14 days post-dosing (described by Bothwell *et al.*, 1979).

The marked effect of body iron stores on absorption requires a method for correcting individual absorption values to a common reference point. The most widely applied technique is to use one isotope to label the food iron and a different one to label a reference dose (3 mg of iron as ferrous ascorbate). Absorption/haemoglobin incorporation of both isotopes is measured, and food absorption corrected to a mean reference value of 40% in each subject by multiplying by 40/R, where R is the reference dose absorption. The value of 40% is taken to represent the amount of iron that is absorbed by someone with virtually zero iron stores but with a 'normal' haemoglobin concentration (Magnusson *et al.*, 1981). An alternative approach, suggested by Cook *et al.* (1991), is based on the inverse relationship between serum ferritin concentrations and iron absorption (Cook *et al.*, 1974; Walters *et al.*, 1975; Magnusson *et al.*, 1981). Dietary absorption is corrected to a value corresponding to a serum ferritin of 40 μg/l (the overall mean of all the volunteers in the study) from the following equation:

$$\text{Log } A_c = \text{Log } A_o + \text{Log } F_o - \text{Log } 40$$

where A_c is corrected dietary absorption, A_o is observed absorption and F_o is observed serum ferritin. Absorption can be predicted in groups of subjects with different levels of body stores (i.e. different serum ferritin values) but if this technique is to be employed the determination of serum ferritin must be carried out very carefully, and preferably more than once during the course of a study.

When determining isotopic incorporation into haemoglobin to measure iron absorption, an assumption has to be made as to the percentage of absorbed iron that is incorporated into the red blood cells. This is usually taken to be 80% (Bothwell *et al.*, 1979) but it is possible to measure it accurately by injecting a known (small) dose of radiolabelled iron into the blood at the same time as giving the oral dose of iron labelled with a different isotope (Brise and Hallberg, 1962).

In studies of iron absorption multiple dose design is preferred, if possible, since it overcomes to some extent the problem of intra-subject variability in efficiency of absorption (Kuhn *et al.*, 1968).

Where there are ethical constraints regarding the use of radioisotopes, alternative methods have been developed using stable isotopes (Janghorbani *et al.*, 1986). These are more appropriate for work with infants (Fairweather-Tait *et al.*, 1995; Fomon *et al.*, 1989) where the doses needed to achieve a measurable enrichment in the blood are much lower than with adults (Barrett *et al.*, 1992). However, a very important consideration when employing stable isotopes of iron for bioavailability studies is the validity of extrinsic labels, and the effects of adding non-negligible quantities of iron to produce labelled foods/meals (discussed by Sandstrom *et al.*, 1993).

(b) Whole body counting/faecal monitoring

Other *in vivo* techniques involve the measurement of iron absorption and/or retention in the body. The method of choice is to administer a meal labelled with the radioisotope ^{59}Fe and then measure retention in the body by means of whole body counting. Where there is no access to a suitable counter, isotopic retention can be determined from faecal monitoring, which, unlike whole body counting, is also suitable for use with other isotopes of iron, both radio- and stable. As with the haemoglobin incorporation technique, the use of stable isotopes to label food (endogenous) iron requires further critical evaluation.

(c) Plasma appearance

Plasma appearance of an oral isotope (radio- or stable) can be used to quantify iron absorption (Whittaker *et al.*, 1991). An intravenous (iv) dose of a different iron isotope is given at the same time as the oral dose and the area under the curve (AUC) of the plasma enrichment of both isotopes is measured for at least 6 hours post-administration. For practical reasons blood sampling is usually discontinued before isotopic enrichment has returned to baseline values; therefore an extrapolation area is calculated from the enrichment of the last sample time and an estimate of the elimination rate constant. The smaller the contribution of the extrapolation area to the total area, the more accurate the estimation of total area. Absorption from the oral dose is calculated as:

$$\% \text{ absorption} = \frac{\text{AUC (oral)}}{\text{AUC (iv)}} \times \frac{\text{dose (iv)}}{\text{dose (oral)}} \times 100$$

2.3 SINGLE MEALS *VS* WHOLE DIET

A very important aspect of iron bioavailability studies that should be considered is the extent to which the single meal approach (i.e. the measurement of

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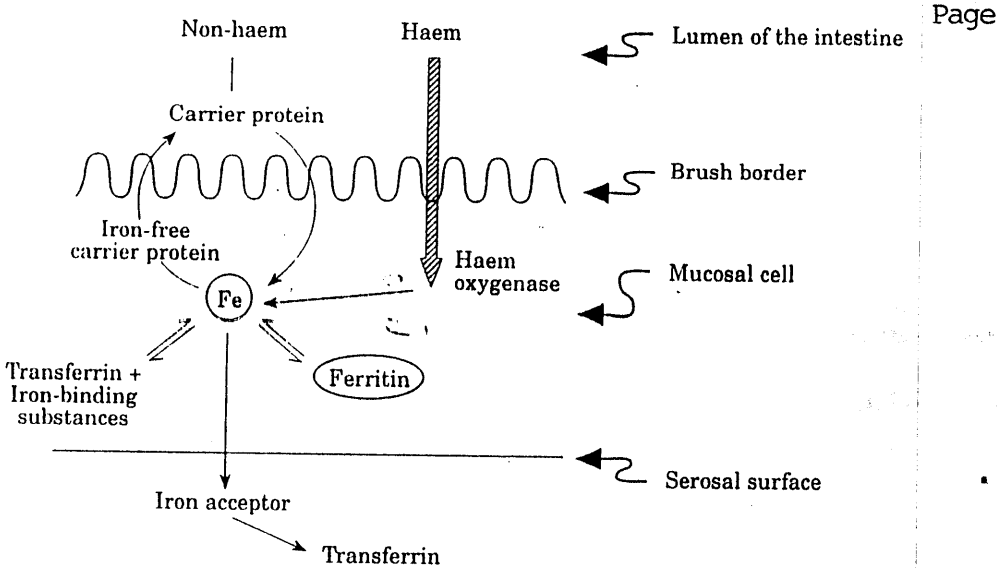

Figure 2.1 Mechanism of iron absorption.

iron absorption from a labelled single meal in a previously fasted subject) represents absorption from the diet as a whole. Cook *et al.* (1991) found that when subjects consumed their normal diets, there was good agreement between dietary absorption (6.4%) and representative single meals fed in the laboratory (6.1%). When the diet was modified to note iron absorption, dietary absorption eased only slightly (8.0%) and remained significantly lower than it was from single meals (13.5%). With a diet selected to inhibit iron absorption, the decrease from single meals was similarly exaggerated. These results indicate the presence of short-term compensatory adaptive mechanisms whereby bioavailability data obtained from single test meals may be an over- or under-estimate for the same meals when taken in the context of the whole diet.

2.4 DIETARY FACTORS AFFECTING IRON BIOAVAILABILITY

2.4.1 Physico-chemical form

Iron in foods exists in two main forms:

- haem iron – in meat as part of haemoglobin and myoglobin;
- non-haem iron – in cereals, vegetables, meat and other foods.

n compounds can be added deliberately to fortify ls, or adventitiously via contamination from metal objects or soil. Iron supplements are another source of dietary iron but, as with the fortification of foods, the efficiency with which the iron is absorbed depends to a great extent on the physico-chemical form of the iron. The homeostatic control of iron absorption mediated via the intestinal mucosal cells is of special importance when considering the efficiency of absorption of high intakes of iron, such as from supplements.

Haem and non-haem iron are absorbed by different pathways (Figure 2.1) with different degrees of efficiency depending upon the chemical form, other dietary constituents and the level of iron stores in the individual (Hallberg, 1981).

It is generally agreed that 20–30% of haem iron is absorbed and that this is a constant figure, being relatively unaffected by other dietary or physiological variables (FAO/WHO, 1988). On the other hand, a large number of dietary variables that enhance (Table 2.2) or inhibit (Table 2.3) non-haem iron absorption have been identified (see reviews by Fairweather-Tait, 1992b; Hallberg, 1981). The various mechanisms whereby dietary substances affect iron absorption include:

- chemical reactions in the chyme such as chelation or changes in iron valency;
- effects on intestinal or mucosal function;
- competition with other minerals for transport protein.

2.4.2 Other dietary constituents

- Ligands, such as citric and ascorbic acid, fructose and amino acids, form soluble monomeric complexes with iron thus preventing precipitation and polymerization, and thereby promoting absorption.
- Other chelating compounds, including polyphenols (containing alkyl groups), phosphates,

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Table 2.2 Dietary constituents that enhance the absorption of non-haem iron

Enhancing food	Degree of effect	Active substance(s)	Reference
Guava, paw paw	+++	Ascorbic and citric acids	Ballot *et al.* (1987)
Beef, lamb, pork, liver, chicken, fish	+++	Cysteine-containing peptides	Cook and Monsen (1976b) Taylor *et al.* (1986)
Orange, pear, apple, pineapple juices	+++/++	Ascorbic and citric acids	Rossander *et al.* (1979) Hallberg *et al.* (1986) Ballot *et al.* (1987)
Cauliflower	++	Ascorbic acid	Hallberg *et al.* (1986)
Beer	++	Ethanol, lactic acid	Derman *et al.* (1980)
Sauerkraut	++	Lactic acid	Gillooly *et al.* (1983)
Plum, rhubarb, banana, mango, pear, cantaloup	++/+	Ascorbic and citric acids	Ballot *et al.* (1987)
Carrot, potato, beetroot, pumpkin, broccoli, cauliflower, tomato, cabbage, turnip	++/+	Citric, malic and tartaric acids	Gillooly *et al.* (1983)
Salad (lettuce, tomato, green pepper, cucumber)	+	Ascorbic acid	Hallberg *et al.* (1986)
Wine	+	Ethanol	Hallberg and Rossander (1982)
Rice miso	+		Macfarlane *et al.* (1990)
Soy sauce	+	Fermentation products	Baynes *et al.* (1990)
	+	Cysteine	Martinez-Torres *et al.* (1981)
	+	Glutathione	Layrisse *et al.* (1984)

carbonates and oxalates have an adverse effect on bioavailability. Their inhibitory effect is usually due to the formation of large polymers.

- Meat, fish and poultry promote non-haem iron absorption. The mechanism is not yet known, but probably the formation of iron complexes with amino acids such as cysteine or peptides counteract luminal factors that inhibit absorption.
- Reducing agents such as ascorbic acid change the valency of iron from Fe(III) to Fe(II), which increases absorption. Fe(II) is more soluble than Fe(III) at pH values greater than 3, as found in the duodenum.
- Associated anions affect iron absorption; for example, ferric chloride is more soluble than ferric phosphate (an important constituent of vegetables), even at low pH.
- Competition between similar cations for uptake into the intestinal mucosal cells has been described between copper, zinc, manganese and cobalt. The mechanisms for these interactions have not yet been established.
- Dietary constituents that alter gut secretions and transit time affect the bioavailability of iron. For example, alcohol and meat promote gastric acid production, lowering the pH of the proximal small intestine and increasing the solubilization of iron.
- Calcium reduces iron absorption. Hallberg *et al.* (1991) reported a marked inhibition of iron absorption from wheat rolls in the presence of calcium, but Turnlund *et al.* (1990) found that milk had no effect on iron absorption from cereal-based diets. In view of the high prevalence of iron deficiency in young women, Hallberg *et al.* (1992) recommended a reduction in the intake of dairy products with principal iron-providing meals, but the further implications of such a recommendation, in particular the effects on calcium nutrition, warrant careful consideration. Sokoll and Dawson-Hughes (1992)

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Table 2.3 Dietary constituents that inhibit the absorption of non-haem iron

Inhibitory food	Degree of effect	Active substance(s)	Reference
W bran	+++	Phytate	Bjorn-Rassmussen (1974);
Tea	+++	Polyphenols	Disler *et al.* (1975) Hallberg and Rossander (1982)
Nuts	+++	Phytate, polyphenols	Macfarlane *et al.* (1988)
Legumes	+++	Phytate, polyphenols	Lynch *et al.* (1984)
Soya protein	+++	Phytate	Cook *et al.* (1981) Lynch *et al.* (1985, 1994)
Oats	+++	Phytate	Rossander-Hulthen *et al.* (1990) Brune *et al* (1989)
Oregano	+++	Polyphenols	Brune *et al.* (1989)
Leafy vegetable (*Leucaema glauca*)	+++	Polyphenols	Tuntawiroon *et al.* (1991)
Coffee	+++/++	Polyphenols	Hallberg and Rossander (1982) Morck *et al.* (1983)
Maize (tortilla, corn meal, bran)	+++/++	Phytate	Acosta *et al.* (1984) Hurrell *et al.* (1988) Siegenberg *et al.* (1991)
M hocolate	++	Phytate, calcium, polyphenols	Rossander *et al.* (1979)
Milk, cheese	++	Calcium plus phosphate	Deehr *et al.* (1990) Gleerup *et al.* (1995) Monsen and Cook (1976)
Rice	++/+	Phytate	Tuntawiroon *et al.* (1990)
Eggs	+	Phosphoprotein, albumin	Rossander *et al.* (1979) Monsen and Cook (1979) Hurrell *et al.* (1988)
Spinach	+	Polyphenols, oxalic acid	Brune *et al.* (1989)
	+	Oxalic acid	Gillooly *et al.* (1983)
	+	EDTA	Cook and Monsen (1976a)

showed that calcium supplements (1000 mg/day for 12 weeks) did not reduce iron stores in premenopausal women, but further studies are needed to investigate the longer-term effects of high calcium intakes on iron status.

2. Iron dose

Not only does the form of iron affect its bioavailability, but also the quantity of iron has an effect. There is a negative relationship between iron dose and percentage absorption but, provided that the iron is in an assimilable form, there is a progressive rise in the actual amount absorbed; the upper limit to iron absorption is determined by host factors such as iron 'status'. Acute iron poisoning can occur, but usually only when the physiological intestinal mucosal homeostasis is overwhelmed by a massive iron overload. A high oral intake over a prolonged period may contribute to chronic iron overload, but usually only if

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Table 2.4 Host-related factors that affect non-haem iron absorption

Variable	Effect on absorption	Reference
Size of body iron stores • Low • Normal, high	 Marked effect (inverse) Minor effect (inverse)	Baynes *et al.* (1987)
Rate of erythropoiesis	Positive correlation	Skikne and Cook (1992)
Physiological state	Increased absorption in pregnancy	Whittaker *et al.* (1991) Barrett *et al.* (1994)
Iron content of mucosal cells	Exposure to iron reduces subsequent absorption	O'Neil-Cutting and Crosby (1987) Fairweather-Tait and Minski (1986)
High altitude, hypoxia	Increased absorption	Skikne and Baynes (1994)
Secretion of gastric juice	Positive correlation	Bezwoda *et al.* (1978)
GI secretions (bile, pancreatic secretions, mucus)	Increased absorption in presence of amino acids, peptides, ascorbic acid and mucoproteins	Bothwell *et al.* (1979)

there is some underlying disturbance of iron metabolism or erythropoiesis (Chapter 8). The classic example of such iron overload, resulting in 'bronze diabetes', was first observed in South Africa and associated with the consumption of large quantities of local beer, brewed in iron pots, although this is now thought to be, in part, secondary to a genetic abnormality (Chapter 8). There are other documented cases of iron overload in subjects taking medicinal iron over many years but it is not known whether the subjects also carried the gene for haemochromatosis.

2.5 PHYSIOLOGICAL FACTORS AFFECTING ABSORPTION

2.5.1 Systemic factors

The amount of iron that is absorbed is markedly influenced by the iron content in the body. However, the efficiency of absorption is affected by a number of factors (Table 2.4):

- the level of iron to which the intestinal mucosal cells have been previously exposed (short-term control) (Fairweather-Tait, 1986; O'Neil-Cutting and Crosby, 1987);
- body iron stores, as measured by serum ferritin concentrations (long-term control) (Cook *et al.*, 1974);
- rate of erythropoiesis (Bothwell *et al.*, 1979);
- tissue hypoxia.

2.5.2 Physiological state

The absorption of iron is known to increase under conditions in which tissue iron is reduced, such as during growth and pregnancy. During the latter half of pregnancy the efficiency of iron absorption is increased from both the diet (Apte and Iyengar, 1970) and from inorganic iron (Whittaker *et al.*, 1991). Reports concerning the size of the increase vary, depending upon several factors including quantity and form of iron administered, iron status of the individual, method of measuring absorption, and stage of pregnancy. Recently Whittaker *et al.* (1991) used stable isotopes of iron to measure absorption in pregnant women from 5 mg iron as ferrous sulphate. They observed increases between 12, 24 and 36 weeks gestation from a mean of 7.6% to 21.1% and 37.4% respectively. Absorption was still elevated (26.3%) 12 weeks post-delivery.

2.5.3 Other physiological factors

Other physiological factors that affect iron absorption and utilization include:

- Gastric juice. Hydrochloric acid plays a key role in the release of iron from food during peptic digestion. Achlorhydria results in a reduced absorption of non-haem iron, although haem iron is unaffected. Gastric acid output is affect-

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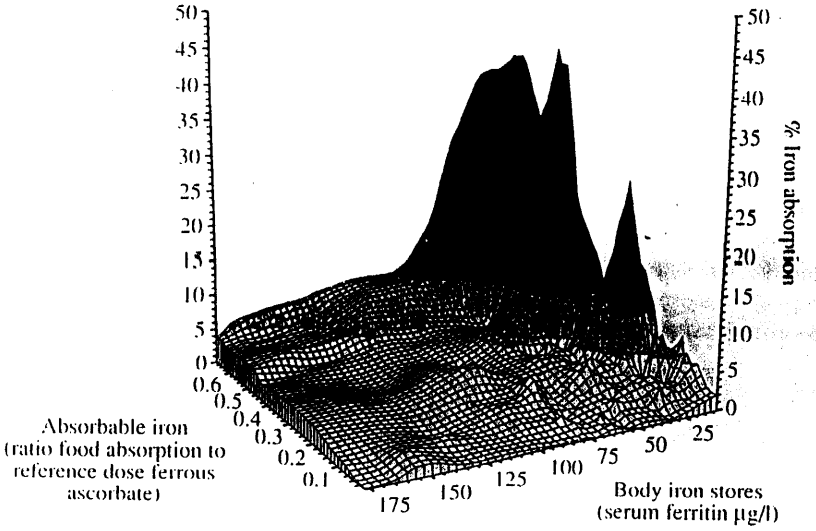

Figure 2.2 Effect of dietary and physiological factors on iron absorption.

ed by dietary constituents as well as factors unrelated to diet such as genetic predisposition and stress.

- Stomach emptying. The longer the food stays in the acidic environment of the stomach, the greater the proportion of iron that will be solubilized. Patients who have undergone partial gastrectomy have impaired iron absorption; this may be due to the partial loss of the reservoir function of the stomach and consequent accelerated progress of the food bolus through the upper gastrointestinal tract. As yet there is no evidence that small intestinal transit time has any effect on the efficiency of iron absorption (Fairweather-Tait and Wright, 1991).
- Pancreatic secretions. Pancreatin *per se* has no effect on iron absorption, but bicarbonate will promote the formation of unavailable iron hydroxide polymers. However, the overall effect of pancreatic juice may be to enhance iron absorption by releasing amino acids and polypeptides from foods which can then act as absorption promoting ligands.
- Biliary and other intestinal secretions. Animal studies indicate an enhancing effect of bile on iron absorption (Wheby *et al.*, 1962). It has been suggested that this is due to the ascorbic acid in bile, but *in vitro* studies have demonstrated the formation of mucoprotein ligands rather than iron–ascorbic acid complexes (Jacobs and Miles, 1970). Studies in rats have shown that fasting increases the quantity and iron-binding properties of the mucus layer (via a change in sialic acid content), which results in increased iron transport (Quarterman, 1987).

2.6 RELATIONSHIP BETWEEN DIETARY FACTORS AND PHYSIOLOGICAL FACTORS

Although the variations in non-haem iron absorption between (and within) individuals are very wide, depending on the dietary source of iron and accompanying dietary constituents, figures have been agreed for the purposes of deriving dietary reference values/recommended allowances. In diets containing generous levels of meat, poultry, fish and/or high in foods containing high amounts of ascorbic acid (promoters of iron absorption), as found for example in the UK, mean absorption from the whole diet (haem and non-haem iron) by individuals with low iron stores is taken to be 15% (DH, 1991; FAO/WHO, 1988).

Recently, Cook *et al.* (1991) examined the nutritional relevance of absorption studies investigating dietary factors believed to modify iron absorption. Iron absorption was found to be generally higher from test meals than the diet as a whole because of the experimental conditions used (e.g. fasting of subjects). The conclusion from the study was that for mixed Western diets, the bioavailability of non-haem iron is less important than absorption studies with single meals would suggest.

The relationship between absorbability of iron (as determined by dietary factors) and level of iron stores (the major physiological determinant), on iron absorption is illustrated in Figure 2.2. Individual data have been plotted from a series of iron absorption studies (Beard *et al.*, 1988b; Guindi *et al.*, 1988; Lynch *et al.*, 1984; Morck *et al.*, 1983) in which the absorbability of iron is expressed as the ratio of absorption of food iron to the reference iron

salt (3 mg ferrous ascorbate) and iron stores as plasma ferritin concentration. Although a greater number of data points would undoubtedly have smoothed out the surface plot, it is evident from Figure 2.2 that dietary factors are only important in subjects with low iron stores. When serum ferritin values exceed 25 μg/l, there are only small differences in the absorption of iron from foods containing iron of very different absorbability.

2.7 MECHANISMS OF ABSORPTION

The precise details of intestinal iron absorption remain unclear, both in terms of the specific biochemical mechanisms of transport as well as their regulation. Iron absorption consists of three steps:

- uptake into the intestinal mucosal cell;
- movement through the intestinal cell;
- release from the cell to the circulation.

2.7.1 Iron uptake from the intestine to the mucosal cell

There are at least three pathways of mucosal iron uptake:

- Ionic iron is taken across the brush border membrane on a carrier protein by means of receptor-mediated endocytosis. The carrier was originally believed to be transferrin, but this is unlikely since repeated studies have failed to identify transferrin receptors in the intestinal brush border membrane. Results from *in vitro* studies suggest that membrane lipids may play a role in iron uptake into the brush border membrane (Simpson and Peters, 1987) and also indicate that there may be more than one path of transport of Fe(III) (Raja *et al.*, 1988).
- Iron from haemoglobin is absorbed by a pathway distinct from that of ionic iron since it is largely unaffected by dietary factors known to influence non-haem iron absorption. The intestinal haem receptor has been partially characterized from brush border membranes (Grasbeck *et al.*, 1979), indicating that the haem moiety is absorbed intact. Once inside the cell the iron is released from haem by haem oxygenase and enters a common pool within the cell.
- Iron from lactoferrin may enter the mucosal cell by a specific pathway since receptors for lactoferrin have been isolated in brush border membranes (Cox *et al.*, 1979), but their role in iron absorption needs further clarification.

2.7.2 Movement of iron within the intestinal cell

The pathway of iron within the mucosal cell is not fully understood. Ionic iron cannot exist in the cell, so upon release from the carrier protein it is immediately bound to a protein already present in the cell, either transferrin, ferritin or other iron-binding proteins. Although the transferrin gene is not expressed in the intestine, transferrin can enter the cell from the plasma via transferrin receptors that occur in the basal and lateral membranes of intestinal cells. Whether such intestinal transferrin has any role in iron absorption remains to be determined.

The connection between mucosal cell ferritin and iron absorption has been recognized for some time (Granick, 1949). Oral iron can induce apoferritin synthesis (Charlton *et al.*, 1965), but the ease with which iron can be mobilized and subsequently transferred from ferritin to the circulation is not known.

2.7.3 Transfer of iron from the cell to the circulation

The presence of transferrin receptors in the baso-lateral membrane of intestinal cells and their demonstrated increase in iron deficiency might suggest a role for mucosal transferrin in iron absorption (Banerjee *et al.*, 1986). However, several observations make this very unlikely.

- The inappropriate pH for the release of transferrin-bound iron at the baso-lateral membrane.
- The fact that the transcapillary exchange rate of transferrin between the mucosal extravascular space and the circulation is too slow to account for the rapid transfer of iron to the portal blood (Morgan, 1980).
- The observation that iron absorption in hypotransferrinaemic mice is intact (Craven *et al.*, 1987).

Knowledge about iron transfer to the circulation is very limited and it is not known whether any intermediate acceptor is involved before binding to plasma transferrin in the portal circulation.

The most active sites of iron absorption are the duodenum and upper jejunum. Most iron taken up into the mucosal cells is transferred to the blood almost immediately, but after this rapid absorption phase, transfer continues at a much slower rate for up to 24 hours. The latter may be iron that has been temporarily stored within the cell as ferritin. Not all the iron that has entered the mucosa from the gastrointestinal tract is transferred to the plasma. It may be retained within the epithelial cells and eventually discarded largely in the form of ferritin, when the cells exfoliate.

2.8 REGULATION OF IRON ABSORPTION

2.8.1 Possible controlling factors

Iron absorption is directly related to both body stores and the amount of iron to which the intestinal mucosal cells have been exposed (Bothwell *et al.*, 1979), but mechanisms whereby information reaches intestinal absorptive cells to alter the efficiency of absorption and so maintain body homeostasis are unknown. Intestinal mucosal iron concentration has been implicated as the major regulating factor (Conrad and Crosby, 1963). The technique of isogeneic intestinal transplantation of iron-loaded and iron-deficient intestine into iron-deficient rats is a means of isolating the effects of body iron stores from the effects of intestinal mucosal iron concentration on iron absorption (Adams *et al.*, 1991); using this method, intestinal mucosal iron uptake was shown to regulate the uptake and transfer of iron in the intestine. On the other hand, the primary control of iron absorption may be via a circulating humoral mediator related to body stores (MacDermott and Greenberger, 1969); in experimental findings the serosal transfer of iron is the rate-limiting step in iron absorption (Huebers, 1986). Iron absorption may also be related to internal iron exchange, i.e. the relative size of intestinal and total exchangeable iron, as a function of plasma iron turnover (Cavill *et al.*, 1975).

2.8.2 Possible mechanisms

Iron absorption is regulated by two pathways, primary control being exerted according to the level of body stores, and 'fine tuning' according to the amounts of iron to which the intestinal mucosal cells are exposed.

A delayed response (several days) in the increase in iron absorption when animals are fed an iron-deficient diet is often described. This may be related to:

- a decrease in the amount of ferritin in the mucosal cell or a change in the partition of iron in the cell between ferritin and other iron-binding sites;
- an increase in the amount of iron carrier proteins.

The most likely explanation, however, is that the lag in iron absorption is related to the time taken for new cells, with a raised capacity to absorb iron, to become functional absorptive cells (Fairweather-Tait *et al.*, 1985). This strongly suggests that programming of mucosal cells takes place according to the state of body iron stores and previous exposure to iron. The mechanism may involve transferrin and/or ferritin receptors, since these are based on the serosal surface and would receive information about the amount of iron passing into circulation and also plasma ferritin levels, i.e. levels of body iron stores.

Although body iron content is the principal factor in the regulation of iron absorption, there are other physiological variables (Bothwell *et al.*, 1979). If the rate of erythropoiesis is stimulated by blood loss or acute haemolysis, iron uptake by the bone marrow is increased, plasma iron and transferrin saturation fall, and the efficiency of iron absorption is increased. Conversely, if erythropoiesis is inhibited by hypertransfusion, starvation or descent from high altitude to sea level, then iron absorption falls. There are, however, chronic dyserythropoietic anaemias such as those due to thalassaemia and sideroblastic anaemia in which transferrin saturation is normal, or even elevated. Such disease states are associated with a high efficiency of absorption, resulting in an accumulation of body stores of iron. On balance, it appears that erythropoiesis *per se* does not play a major role in the regulation of iron absorption in normal healthy individuals.

2.8.3 Genetic factors

In subjects with the iron-loading disorder, idiopathic haemochromatosis, genetic factors are responsible for the accumulation of excess iron from the diet. Current evidence suggests that there may be a defect in the mucosal and reticuloendothelial handling of iron. Inappropriately high rates of iron absorption occur from food (haem and non-haem iron) and from iron salts (Milder *et al.*, 1978; Bezwoda *et al.*, 1976). The fact that such enhanced absorption occurs in the presence of normal or high iron stores indicates a primary inherited abnormality in the regulation of iron balance. Some limited homeostatic regulation takes place since the increased absorption gradually decreases as body iron stores enlarge (Williams *et al.*, 1966).

2.9 EXAMPLES OF DIETS CONTAINING IRON OF LOW, MEDIUM AND HIGH BIOAVAILABILITY

Diets can be separated into three broad categories of 'low', 'intermediate' and 'high' bioavailability, with mean absorption (in individuals with very low iron stores but normal Hb concentrations) from the mixture of haem and non-haem iron of approximately 5, 10 and 15% respectively (FAO/WHO, 1988).

Low bioavailability diets (5% of iron absorbed)

contain cereals and root vegetables with negligible quantities of meat, fish or ascorbic acid-rich foods. Such diets contain a preponderance of foods that inhibit iron absorption (maize, beans, whole-grain flour) and are dominant in many developing countries, particularly among lower socio-economic groups.

Intermediate bioavailability diets (10% of iron absorbed) consist mainly of cereals and root vegetables but containing some ascorbic acid-rich foods and meat. A high bioavailability diet can be reduced to intermediate levels by the regular consumption of inhibitors of iron absorption, such as tea, coffee, cereal fibre, beans and/or high calcium foods with main meals.

High bioavailability diets (15% of iron absorbed) contain generous quantities of meat, poultry and fish. They also contain foods with high amounts of ascorbic acid such as citrus fruits and some vegetables. This is the type of diet often consumed by people in developed countries.

4

MECHANISMS OF CELLULAR IRON HOMEOSTASIS

4.1 PROTEINS OF IRON TRANSPORT

The study of iron homeostasis requires knowledge of the major forms of iron in the body, iron exchange between these components and iron intake and loss. This chapter considers the proteins of iron metabolism, extra- and intra-cellular iron exchange, and the regulation of synthesis and breakdown of the proteins of iron metabolism.

4.1.1 Transferrin

The iron-binding protein of the plasma is transferrin, which is very similar to lactoferrin found in granulocytes and in milk (reviewed by de Jong *et al.*, 1990). Both are monomeric glycoproteins with a molecular weight of about 80 kDa. The polypeptide chain of human transferrin has 679 amino acids organized in two homologous lobes – known as the N-terminal and C-terminal lobes. The protein contains about 6% carbohydrate on two branched heterosaccharide chains, both of which are in the C-terminal lobe (Figure 4.1). Each lobe has a single iron-binding site that requires both Fe(III) and an anion (usually carbonate or bicarbonate). The affinity of transferrin for iron is very high: at pH 7.4 in the presence of bicarbonate, the affinity constant for the binding of one iron atom is approximately $10^{20}M^{-1}$. However, iron can be released from both sites by lowering the pH to less than 5.5.

The plasma concentration of transferrin in adults is normally about 2.4 g/l and each mg of transferrin can bind 1.4 μg of iron. The protein is normally 20–40% saturated with iron.

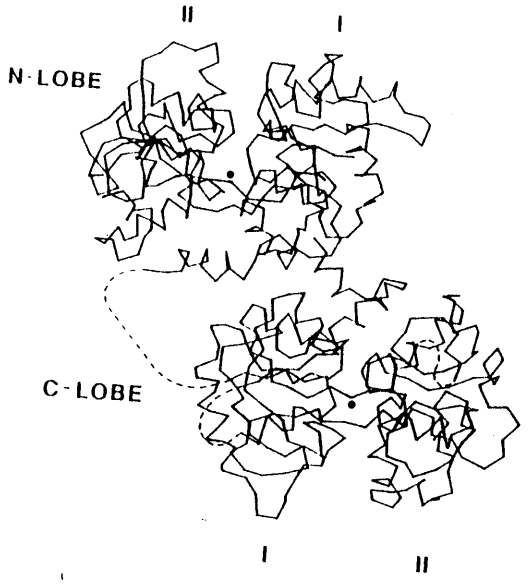

Figure 4.1 Overall organization of the rabbit serum transferrin molecule. The polypeptide chain is folded into two lobes, each containing some 330 amino acids and a single iron-binding site. The shape of each lobe can be described by a prolate ellipsoid of approximate semiaxial dimensions 21 × 25 × 36 Å with the major axes of the N- and C-lobes running antiparallel to one another at an angle of 155°. In turn each lobe comprises two dissimilar domains, I and II. Broken lines denote poorly defined regions in the current model. (From Bailey *et al.*, 1988, with permission.)

4.1.2 Transferrin receptor

Iron is released from transferrin on acidification, but delivery of transferrin iron to cells (particularly to immature red cells for haemoglobin synthesis) takes place by interaction with specific receptors in the cell membrane (Huebers and Finch, 1987) followed by receptor-mediated endocytosis and by removal of iron and release of apotransferrin within the cell. The transferrin receptor (Figure 4.2) is a transmembrane glycoprotein consisting of two identical subunits of molecular mass 95 kDa joined by a disulphide bond (Trowbridge and Shackelford, 1986). The genes for both transferrin and its receptor are found on the long arm of chromosome 3. Although there are structural differences between the two iron-binding sites of the transferrin molecule, there do not appear to be significant differences in the way in which each site delivers iron to the red cell (Huebers and Finch, 1987). However, recent studies *in vitro* have shown that iron release from the transferrin receptor complex takes place more readily from the C-terminal site on the transferrin molecule than the N-terminal site (Bali and Aisen, 1991), thus explaining the high prevalence of N-terminal monoferric transferrin in

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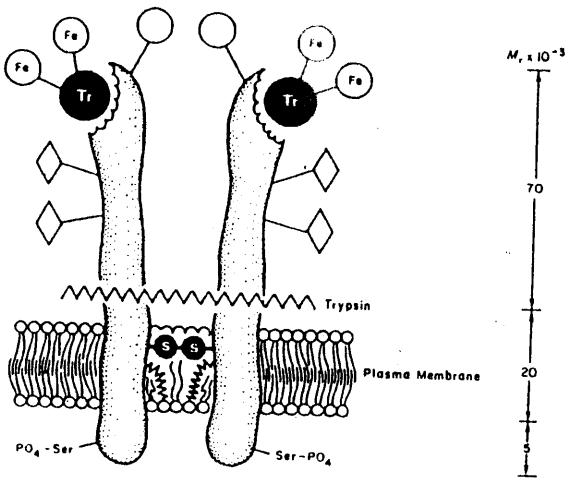

Figure 4.2 Schematic representation of the human transferrin receptor. ◇ = high-mannose oligosaccharide; o = complex-type oligosaccharide; Tr = transferrin.
(From Trowbridge and Shackelford, 1986, with permission.)

the circulation. Furthermore iron release from receptor bound transferrin at pH 7.4 is slower than for transferrin in solution, whereas at pH 5.6 iron release is faster. Thus non-specific release of transferrin iron at the cell surface is prevented and release in the endosome at more acidic pH is ensured.

4.2 IRON STORAGE PROTEINS

4.2.1 Ferritin

Iron is stored in cells as ferritin which is a soluble, spherical protein enclosing a core of iron. Particularly high concentrations are present in the liver, spleen and bone marrow. Ferritin is also found in low concentrations in plasma and urine (Worwood, 1986). Human apoferritin (i.e. the molecule devoid of iron) has a molecular mass of about 480 kDa and is composed of 24 subunits whose molecular mass is about 19 kDa. The subunits are roughly cylindrical in shape and form a nearly spherical shell that encloses a central core containing up to 4500 atoms of iron in the form of ferric hydroxyphosphate (Figure 4.3). Normally ferritin in liver, spleen, heart and kidney contains about 1500 atoms Fe/molecule (Wagstaff *et al.*, 1982).

The amino acid sequences of human spleen and liver ferritin are known and X-ray crystallographic analysis at 2.8 Å resolution has demonstrated the arrangement of the subunits within the molecule, as well as channels between the subunits through which iron enters and leaves (reviewed by Theil, 1990).

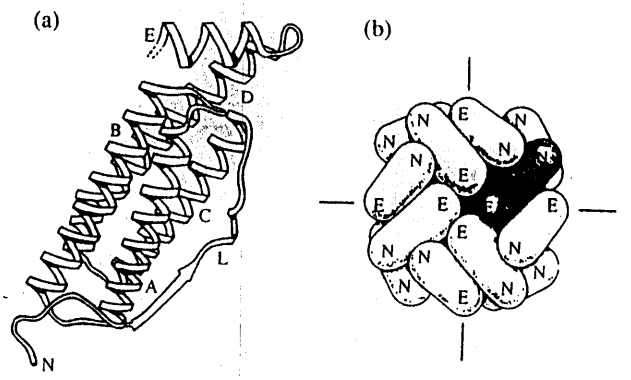

Figure 4.3 Schematic drawing of a ferritin subunit showing the five helices A to E and the long inter-helix loop L. The loop L and the N-terminal residues N lie on the outside of the protein shell. Helix E runs from outside to inside. The C terminus is on the inside. (b) The ferritin molecule with 24 subunits surrounding the iron core (visible at centre, shown in black). N = N-terminus; E = N-terminal end of E helix. (From Harrison, 1986, with permission.)

Human ferritins are made up of two types of subunit in varying proportions. In liver and spleen ferritin, the 'L' subunit predominates. In the more acidic isoferritins found in the heart and in red cells, the 'H' subunit predominates. There is about 55% homology between the two subunit sequences. The gene for the L subunit is located on chromosome 19q13.3-q13.4 and the gene for the H subunit is found on chromosome 11q13 (Worwood, 1990).

The various isoferritins appear to have different functions. In iron-loaded tissues it is the L-rich isoferritins which predominate although H-rich isoferritins have the highest rates of iron uptake *in vitro* (Wagstaff *et al.*, 1982). The production of recombinant ferritins has demonstrated that although L subunits promote nucleation of the iron core (Levi *et al.*, 1992), ferroxidase activity is a property of the H subunit. H-rich isoferritins display inhibitory activity for haemopoiesis (Broxmeyer, 1992).

4.2.2 Haemosiderin

Haemosiderin is a degraded form of ferritin in which the protein shells have partly disintegrated, allowing the iron cores to aggregate (Richter, 1984). It is usually found in lysosomes and may be seen under the light microscope after tissue sections have been stained with potassium ferrocyanide in the presence of hydrochloric acid (Prussian blue or Perl's reaction). In a normal human with adequate iron status most of the storage iron is present as ferritin, but with increasing iron accumulation the proportion present as haemosiderin increases.

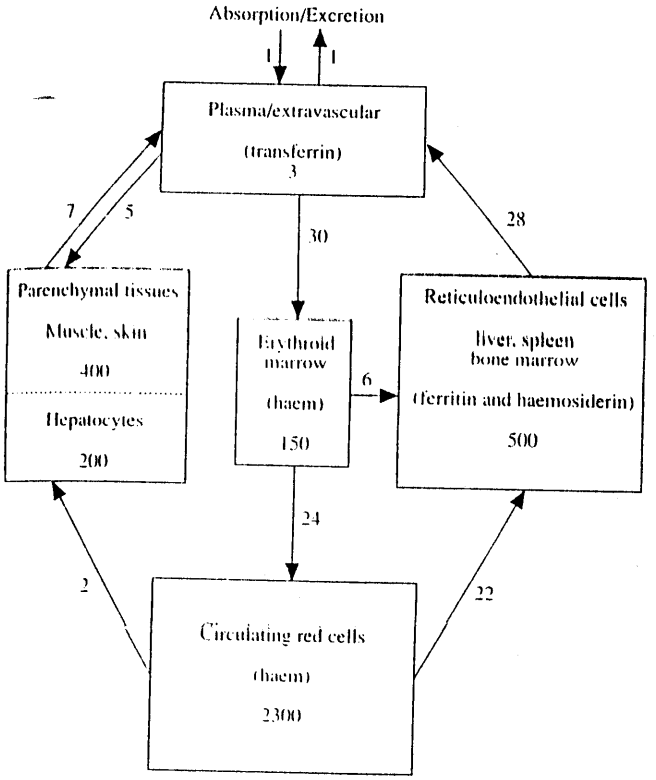

Figure 4.4 The major pathways of iron metabolism in humans. (Numbers against arrows and in boxes are mg Fe/day.) The iron in parenchymal tissues is largely haem (in muscle) and ferritin/haemosiderin (in hepatic parenchymal cells).

4.3 IRON TURNOVER IN THE PLASMA

4.3.1 Transferrin-bound iron

Iron turnover in the plasma takes place through transferrin and is largely directed to the synthesis and breakdown of haemoglobin (Figure 4.4). The plasma iron pool (transferrin-bound iron) is about 4 mg although the daily turnover is over 30 mg. Transferrin circulates through interstitial spaces in liver, spleen and bone marrow and more slowly in muscle and skin, and returns to the blood via the lymphatics. Most of the iron leaving the plasma is taken up by erythroblasts in the bone marrow for incorporation into haem. Some of the immature red cells are destroyed by phagocytic cells in the marrow ('ineffective erythropoiesis') but most of the iron re-enters the blood as haemoglobin in the erythrocytes. These are eventually destroyed in the reticulo-endothelial system, where haemoglobin is destroyed in lysosomes. Iron is then released from haem by haem oxygenase and is returned to the plasma. This cycle of iron metabolism may be investigated using radioactive iron (Jacobs and Wood, 1980). In addition there is an exchange between all other cells and tissues and the plasma, but the amounts involved are small.

4.3.2 Haptoglobin, haemopexin and their receptors

Haptoglobin is a serum glycoprotein which avidly binds haemoglobin released into the blood stream by haemolysis. The haemoglobin–haptoglobin complex is rapidly removed from the plasma by specific receptors for the complex which are found on liver parenchymal cells (Okuda *et al.*, 1992). The haptoglobin gene is located on chromosome 16 (16q22.1). The structure of the receptor is not known, neither is the chromosome location of the gene.

Haemopexin is a plasma glycoprotein with a molecular weight of about 60 kDa which binds haem and transports the haem to cells by a process that involves receptor-mediated endocytosis of haemopexin with recycling of the intact protein (a process similar to that of transferrin endocytosis). The murine haemopexin receptor appears to be an 85–90 kDa protein composed of two subunits of approximately 70 kDa (α subunit) and 20 kDa (β subunit). The subunits are linked by a single disulphide bond. Haemopexin appears to bind to the smaller subunit (Smith *et al.*, 1991). The gene for haemopexin is located on chromosome 11 (11p15.5-15.4).

4.3.3 Ferritin

In normal health, low concentrations of ferritin are found in the plasma, and ferritin concentrations reflect the level of body iron stores. Much of this ferritin appears to be glycosylated and has a relatively low iron content (Worwood, 1986). Such ferritin appears to have a relatively long survival in the blood ($t_{\frac{1}{2}}$, the time observed for a concentration of a substance to fall to half the initial level, is about 30 h). Ferritin is also released into the circulation as a result of tissue damage (most strikingly after necrosis of the liver). Tissue ferritin is cleared rapidly from the circulation ($t_{\frac{1}{2}}$ is about 10 min) by the liver. In the rat it has been shown that there is a ferritin receptor on hepatic parenchymal cells which has a higher affinity for tissue ferritins (such as liver or spleen ferritin) than for serum ferritin (Mack *et al.*, 1985). The role of the ferritin receptor would appear to be that of scavenging extracellular ferritin. However, some cultured human cell lines have receptors which are specific for ferritin molecules rich in 'H' subunits (Moss *et al.*, 1992) and these may play a part in the inhibition of haemopoiesis, immunosuppression and in the modulation of lymphocyte function by H-rich isoferritins by direct interference with cellular iron uptake.

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4.3.4 Non-transferrin iron

This describes a form of iron which is not bound to transferrin, is of low molecular mass, can be chelated by powerful chelators such as desferrioxamine, and is not haem or ferritin iron. Several assays have been described (Singh *et al.*, 1990) which have demonstrated such a fraction in plasma from patients with iron overload. The chemical form of this iron is unknown but it is probably rapidly removed from the circulation in the liver (Hershko, 1987).

4.4 PATHWAYS OF INTRACELLULAR IRON TRANSPORT

4.4.1 Introduction

The complex solution chemistry of iron is one reason why there is so little understanding of the mechanisms of membrane iron transport and of transport within the cytosol. Prokaryotes may produce iron chelators (siderophores) which bind iron and are then taken into the cell by specific receptors (Neilands and Nakamura, 1985). In yeasts there are external ferri-reductases which reduce iron, enhance its solubility and then allow transport into the cell. A similar ferri-reductase system may provide for iron transport from the endosome to cytosol during delivery of transferrin iron (Nunez *et al.*, 1990), transport into the mitochondrial membrane for haem synthesis, and passage from the lysosomal membrane to the cytosol. Breakdown of ferritin ($t_{\frac{1}{2}}$ of the protein portion is about 72 h) leads to haemosiderin formation in lysosomes but iron must eventually return to the cytosol for incorporation into new ferritin molecules. Almost nothing is known about this process.

There are only a few clues about the transport of iron within the cytosol. A small protein named mobilferrin has been described in the intestinal mucosa and it has been postulated that this is the intracellular transport protein which takes part in the process of iron transfer across the mucosal cell during iron absorption (Conrad *et al.*, 1992). Iron nucleotide complexes have been isolated from red cells and it is suggested that these comprise the low molecular weight pool in these cells (Weaver and Pollack, 1989).

4.4.2 Haem synthesis

Quantitatively, the major pathway of iron metabolism involves haem synthesis and breakdown, and in mammals this haem is largely present in haemoglobin. Haem synthesis and its control in the erythroid cell and the liver has been reviewed by Bottomley and Muller-Eberhard (1988). Figure 4.5 shows the metabolic pathway and the location of enzymes in cell cytoplasm or mitochondria. The rate-limiting enzyme in the liver is 5-amino levulinic acid (ALA) synthase and its synthesis is controlled by the level of 'free haem' in the cell. Erythroid haem biosynthesis is tightly linked to erythroblast development. There are two separate genes for

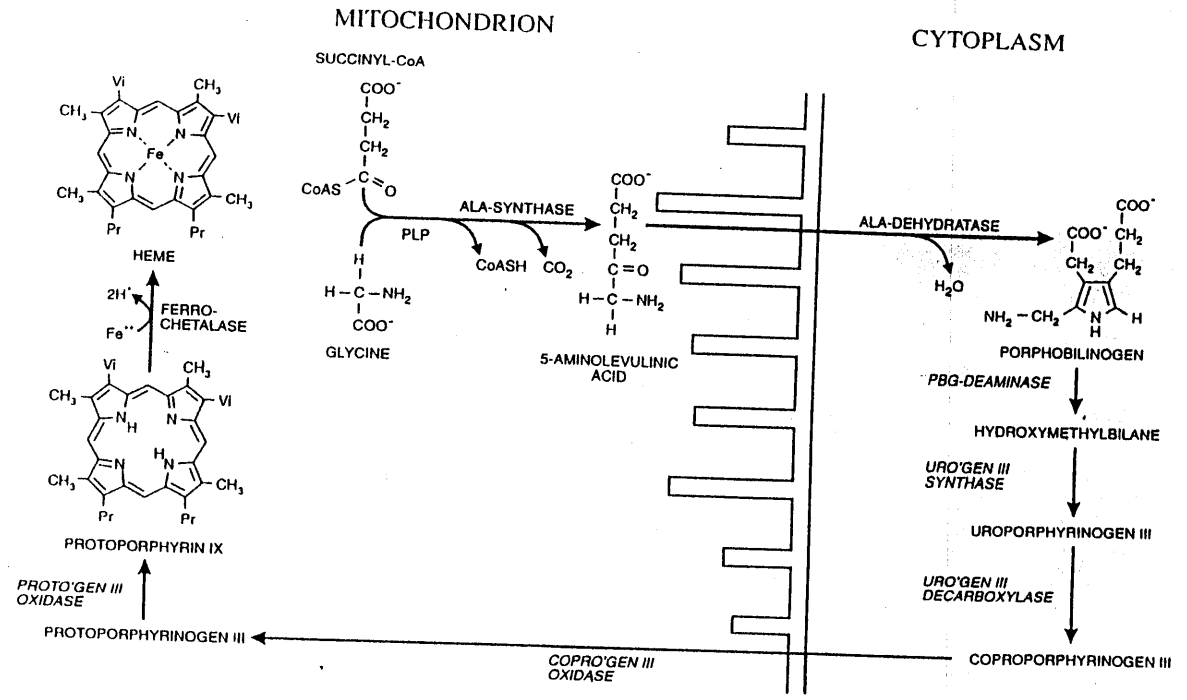

Figure 4.5 The haem biosynthesis pathway.

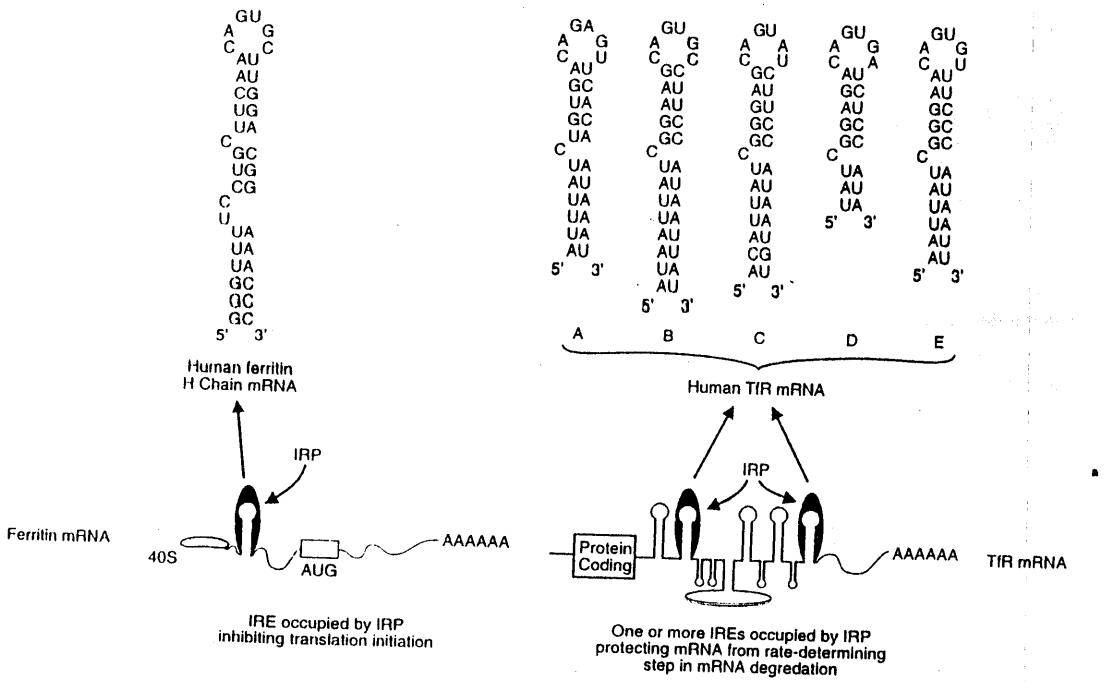

Figure 4.6 The interaction of the iron regulatory protein IRP (or IRE-BP) with 'stem-loop' structures on both ferritin and transferrin receptor (TfR) mRNA. Sequences for human H ferritin and human TfR mRNA are shown. (Redrawn from Klausner *et al.*, 1993.)

ALA synthase: the 'housekeeping' gene which lies at chromosome 3p21 and the erythroid-specific g[illegible] localized to Xp11.21 (Bishop, 1990; Cotter *et al.*, 92). The ferrochelatase gene (the last stage of the pathway) is located at chromosome 18q.22 (Whitcombe *et al.*, 1994).

4.4.3 Haem catabolism

Haem catabolism is an enzymatic process mediated by haem oxygenase, which is located in the endoplasmic reticulum. The enzyme requires NADPH and molecular O_2. Enzyme activity (in the rat) is highest in the spleen and then in the bone marrow, liver, brain, kidney and lung. There is also activity in the intestinal mucosa. The cellular distribution of enzyme activity is consistent with the role of haem oxygenase in haemoglobin catabolism.

The enzyme is a monomeric protein with a molecular mass of approximately 33 kDa and exists as two isoenzymes (Schacter, 1988). Enzyme activity is stimulated by administration of haem (as haemoglobin or methaemalbumin) as well as many other agents. The inducible enzyme (HMOX1) is located at chromosome 22q12 and the constitutive er[illegible]ne (HMOX2) at 16p13.3 (Kutty *et al.*, 1994).

[illegible] immediate fate of the iron released from haem is unknown but iron is rapidly returned to the plasma as well as being incorporated into ferritin in the cells breaking down haem.

4.5 SYNCHRONIZED REGULATION OF SYNTHESIS OF TRANSPORT AND STORAGE PROTEINS

In vitro, ferritin can be shown to have all the qualifications required for an iron storage protein. Apoferritin will bind and oxidize Fe(II) and deposit Fe(III) within the protein. Release of iron may be affected by reducing agents. Studies in both animals and cultured cells show that apoferritin is synthesized in response to iron administration. This control is exercised at the level of translation (Kuhn, 1991). The 5' untranslated region of the ferritin mRNA contains a sequence which forms a 'stem-loop' structure. This has been termed an 'iron response element' (IRE) (Figure 4.6). Cytoplasmic proteins which bind to this sequence and prevent translation have also been identified. In the presence of iron this repressor protein (iron regulatory protein; IRP) previously known as IRE-binding protein or iron regulatory factor, is unable to bind to the mRNA; polysomes form and translation proceeds. The iron regulatory protein has been purified and shown to be an iron–sulphur protein closely related to aconitase and encoded by a gene on chromosome 9 (and functioning as a cytosolic aconitase in its replete state). A model involving conformation changes which permit RNA binding has been proposed (Klausner *et al.*, 1993). There are now known to be two IRPs which bind specifically to the IREs. The functional significance of each protein is not yet known (Kim *et al.*, 1995).

A related mechanism operates in reverse for the transferrin receptor. Here there are stem-loop sequences in the 3' untranslated region and protein binding prevents degradation of mRNA. Hence iron deficiency enhances transferrin receptor synthesis. This translational regulation also applies to erythroid ALA synthase and aconitase.

Until recently control of transferrin synthesis had been considered in terms of transcriptional regulation involving not only iron but also developmental and tissue specific factors (Bowman *et al.*, 1988). Plasma transferrin levels increase in iron deficiency and decrease in iron overload but this latter change is not associated with a reduction in mRNA levels in the liver. Cox and Adrian (1993) have employed chimeric genes (human transferrin 5' regulatory region – chloramphenicol acetyl transferase transgene) to demonstrate post-transcription regulation by iron. They propose that IRP also binds to an IRE on transferrin mRNA. However, increased binding of IRP leads to an increase in transferrin mRNA translation rather than the decrease associated with binding to the ferritin IRE. The changes are also of a different magnitude, two-fold in the case of transferrin and up to 50-fold for ferritin. Thus post-transcriptional control by the IRE–IRP mechanism appears to be important for all three proteins regulating iron metabolism.

8 IRON OVERLOAD AND TOXICITY

8.1 INTRODUCTION

Since humans are unable to excrete significant quantities of iron, it is essential that the uptake of iron is carefully controlled by the intestinal mucosa. In certain pathological conditions iron overload may result from an increased absorption of dietary iron, by parenteral administration of iron, or both. The magnitude, rate and distribution of iron accumulation will influence the onset and severity of complications and differ for the various pathological conditions, a number of which have an inherited genetic basis.

8.2 CHRONIC IRON OVERLOAD

8.2.1 Genetic haemochromatosis

In genetic haemochromatosis, an inborn error of iron metabolism leads to an inappropriate increase in the absorption of iron from the diet for the levels of iron stores present. It results from the homozygous state for an abnormal gene closely linked to the HLA-A locus on chromosome 6. Iron is progressively stored in all tissues over a period of many years, particularly in the liver and pancreas in which the iron concentration may reach 50–100 × normal. A liver biopsy from a patient with symptomatic untreated genetic haemochromatosis will reveal heavy iron loading, frequently associated with fibrosis on light microscopy, and on electron microscopy will show the characteristic paracrystalline arrays of ferritin, eventually precipitating as haemosiderin (Figure 8.1). In addition, the iron content of other organs, particularly the endocrine glands and cardiac muscle, is elevated. The excessive amounts of accumulated iron are related to the clinical manifestations of cirrhosis, diabetes mellitus, heart disease and endocrine dysfunction, as well as the characteristic bronze skin pigmentation. Less clearly related to the iron overload is an arthropathy, which has been reported in 25–50% of patients with haemochromatosis. Arthralgia has been recognized as an early symptom, which may occur before the development of cirrhosis or diabetes mellitus; genetic haemochromatosis should be suspected in patients presenting with arthralgia before the age of 40 years. Arthropathy usually does not regress after phlebotomy treatment.

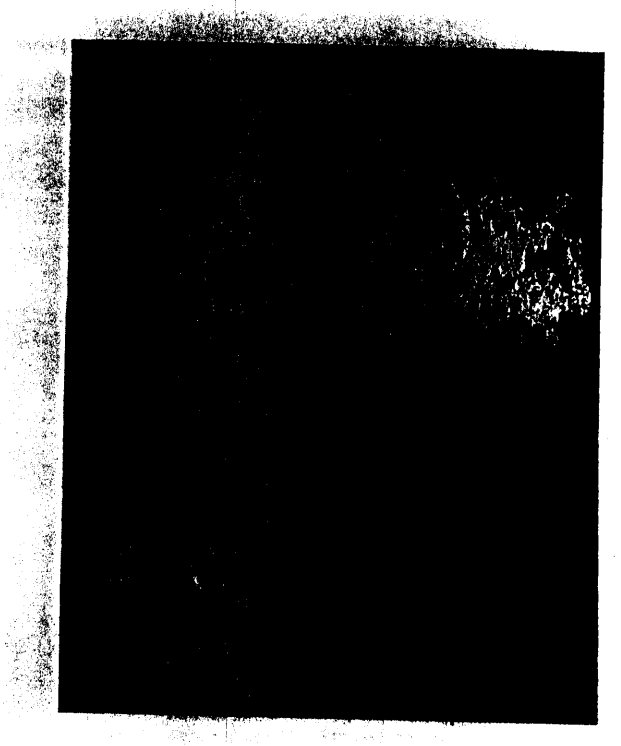

Figure 8.1 Electron micrograph of iron loaded liver. In the cytosol, ferritin can be seen as spherical dots which form paracrystalline arrays in certain circumstances. Within the two secondary lysosomes, deposits of haemosiderin are observed. (Unstained section: magnification × 60 000.)

Since the iron overload from excessive iron absorption takes place over many years, symptomatic genetic haemochromatosis does not usually develop until middle or later life. Expression is more common in men than women, presumably because of the protective effects of regular menstrual losses during the child bearing years. Once the disease is diagnosed, regular treatment by phlebotomy can remove the excessive iron stores, after which maintenance phlebotomy every few months will maintain iron stores at a normal level. Effective iron removal increases life expectancy, though in individuals presenting with symptomatic iron overload established tissue damage may not

be reversible and there is a greatly increased (20–30%) risk of carcinoma of the liver in those with established cirrhosis (Bomford and Williams, 1976; Niederau *et al.*, 1985). As homozygotes are increasingly identified at a presymptomatic stage, through family or more general screening programmes, the pattern of morbidity and mortality is changing: individuals with iron overload in the absence of tissue damage have a normal life expectancy after phlebotomy treatment.

The cause of the high iron absorption in genetic haemochromatosis has not yet been identified, the defect being ascribed to the intestinal mucosa, the liver or the reticuloendothelial system by various authors. A primary defect within the intestinal mucosa could be caused by a failure to switch from neonatal to adult control of iron absorption (Srai *et al.*, 1984), a decrease in ferritin expression (Pietrangelo *et al.*, 1992), alteration in the brush border membrane and soluble iron binding proteins (Teichmann and Stremmel, 1990; Conrad *et al.*, 1990) or by some as yet unidentified factor.

Genetic haemochromatosis has a gene frequency of approximately one in 20 in the Northern European countries, such that approximately one in every 300 individuals is affected. That makes this the most commonly occurring genetic disease in Caucasians – even more common than cystic fibrosis. It is an inherited autosomal recessive disorder, tightly linked to the HLA-A locus and showing allelic association with HLA-A3 histocompatibility antigen complex on chromosome 6 (Simon *et al.*, 1976). The identification of the gene for genetic haemochromatosis appears to be imminent. Using highly polymorphic markers to chromosome 6p, a recent study of 34 individuals from three large families affected by genetic haemochromatosis showed that the haemochromatosis allele is proximal to D6S89 and distal to D6S105 markers (Jaz Winska *et al.*, 1993).

8.2.2 Neonatal haemochromatosis

Neonatal haemochromatosis is an uncommon and generally fatal disorder of infancy. It is characterized by hepatic disease which is generally present at birth, and by stainable iron in the tissues with a distribution resembling that seen in HLA-linked haemochromatosis. First degree relatives of such patients do not appear to be at risk of iron overload (Dalhj *et al.*, 1990) and in a number of cases the extrahepatic siderosis appears to be caused by hepatic injury at a time of life when tissue iron concentrations are high, rather than a primary defect in iron metabolism, e.g. excessive transport of iron from mother to fetus (Hoogstraten *et al.*, 1990).

8.2.3 Secondary haemochromatosis

The disorders of erythropoiesis that may be associated with iron overload as a result of increased iron absorption and/or regular blood transfusions are discussed in Chapter 7. Parenteral administration of iron by multiple blood transfusion, although ameliorating anaemia (e.g. thalassaemias) will cause iron loading of a variety of tissues.

8.2.4 Thalassaemias

Several forms of thalassaemia exist. The disease is found mainly in a belt extending through southern Europe, North Africa and the Middle East to India, Indonesia and the Far East.

The thalassaemias are characterized by various genetic defects of α or β globin chain synthesis which is caused by changes in regulatory sequences in the gene or by gene deletions that result in decreased or absence of α- or β-chains. These are referred to as α or β thalassaemias, respectively, and are discussed, along with the problems of iron overload, in Chapter 7.

8.2.5 Sub-Saharan iron overload ('Bantu-type siderosis')

Gross iron overload resulting from excess absorption of orally ingested iron is very rare but has been described in Bantu people in South Africa. A high intake of iron over a prolonged period occurred in Bantu people who consume large amounts of 'Kaffir beer', an alcoholic beverage fermented in iron pots. The histological pattern of hepatic iron deposition in such patients is different from that of patients with HLA-linked haemochromatosis, i.e. the iron is more prominent in the cells of the mononuclear-phagocyte system (Brink *et al.*, 1976). The pattern of expression in family studies suggests that such iron overload is related to a gene distinct from any HLA-linked gene but that expression is also dependent on the environmental exposure to the high oral iron intake, both factors being required (Gordeuk *et al.*, 1992).

8.2.6 Alcohol misuse

Various liver diseases, especially cirrhosis and portal–systemic shunting, may increase the liver iron content. Patients with alcoholic liver disease often show increased stores of iron in the liver which may be caused in part by alcohol increasing the intestinal mucosa permeability to iron, and in part by the high amount of iron present in certain wines

and beers. The increased iron absorption may also be related to ineffective erythropoiesis associated with alcohol-related folate and sideroblastic abnormalities (Conrad and Barton, 1980). The extra amount of iron is usually moderate, and less than would be expected in patients of the same age with genetic haemochromatosis. Alcoholic subjects with excessive iron overload are almost always homozygous for the haemochromatosis gene and both iron accumulation and liver damage are accelerated by the alcohol misuse.

8.3 CHRONIC TOXICITY OF IRON IN IRON OVERLOAD

Extensive tissue damage often occurs in iron loaded tissues. In early studies, the pathogenesis of this lesion has been described in terms of increased levels of the iron storage proteins, ferritin and especially haemosiderin, and of iron catalysed lipid peroxidation.

Heterogeneity of haemosiderin, the iron storage protein, in genetic haemochromatosis and thalassaemias has been identified with respect to both the iron core and the associated protein shell (Mann *et al.*, 1988; Ward *et al.*, 1992, 1994b). Various mineralization products in addition to that of ferrihydrite have been identified, including amorphous ferric oxide and goethite, although it remains unresolved whether the presence of a certain form infers a greater toxicity to the iron loaded cell.

Initially, iron catalysed lipid peroxidation was an attractive hypothesis. The potential importance of iron in mediating oxidative damage by the production of radicals, via the Haber–Weiss reaction/Fenton chemistry, to a variety of macromolecules has been recognized *in vitro* for more than two decades. However, such a reaction *in vivo* will be dependent upon not only the availability of a low molecular weight 'catalytically active' iron, to participate in such a reaction, but also to overwhelming the capacity of the cell to combat reactive oxygen species by enzymes and antioxidants.

In normal circumstance iron is carefully sequestered into a variety of proteins (transport proteins or storage proteins) to ensure that there is little free iron either in solution or within the tissues. The nature of the free iron 'pool' remains unknown (Fontecave and Pierre, 1991): a variety of ligands have been suggested, including ATP, ADP, pyrophosphates, citrate and specific amino acids, but this remains to be resolved. It is debatable whether this pool increases in iron overload but it is more than likely that the flux through the pool is enhanced. This small iron pool could initiate and potentiate iron-catalysed lipid peroxidation, while the presence of the cytoprotective enzymes and antioxidants in the cytosol and membranes of the cell may play a vital role in scavenging and chain-stopping such reactions.

The distended lysosomes containing the bulk of the excessive iron in untreated genetic haemochromatosis patients can be observed by electron microscopy in liver biopsies (Stal *et al.*, 1990), or be measured by the increased activity of the lysosomal enzyme N-acetyl-β-glucosaminidase (Seymour and Peters, 1978) in such specimens. On completion of treatment by phlebotomy, the lysosomes revert to their normal size and the activities of lysosomal enzymes are within the normal range of values.

Damage to the mitochondria could be attributed to the ferrous ions initiating and propagating lipid peroxidation of the mitochondrial membrane, thus increasing permeability and allowing iron to accumulate within the mitochondria. This may alter the steric configuration of the mitochondrial membrane which is essential for the proper functioning of the electron transport system and therefore for aerobic respiration. Alternatively the mitochondrial swelling could result in the shunting of electrons away from the electron transport system. Ferric iron is reduced by an enzyme located on the inner mitochondrial membrane, to provide ferrous iron for insertion into protoporphyrin IX. In the presence of excessive iron this same enzyme may reduce the ferric iron to ferrous, which in turn would be rapidly oxidized back to the ferric state in the presence of intramitochondrial oxygen. Thermodynamic considerations of this system would favour the shunting of electrons away from the electron transport system, thereby diminishing oxidative phosphorylation and reducing ATP. There would be uncoupling of mitochondrial oxidative phosphorylation in which oxygen would be utilized without ATP being formed. The end result of this process would be cellular dysfunction and death due to impaired generation of ATP.

Even though subcellular organelles from experimentally iron-loaded rat livers show increased amounts of lipid peroxidation products, as assessed by thiobarbituric acid-reacting material and diene conjugate species (Britton *et al.*, 1990) or depletion of antioxidants (Ward *et al.*, 1991), to what extent such changes reflect actual damage to the cell is unresolved. Altered mitochondrial function (Bacon *et al.*, 1983, 1985) or increased lysosomal fragility in iron overloaded patients (Seymour and Peters, 1978) and in rats experimentally overloaded with iron (O'Connell *et al.*, 1987; Ward *et al.*, 1991) were considered to be a result of lipid peroxidation of the appropriate organelle membranes. As yet, there is no conclusive evidence that iron-catalysed lipid peroxidation is the cause of the cellular damage (Crichton and Ward,

1992) and it is therefore appropriate to view the problem of iron toxicity in a wider perspective with the possible target for iron or iron catalysed radicals being proteins, DNA, mRNA or Kupffer cell activation.

Highly reactive oxygen species, if generated by the iron species present, could also cause damage to DNA, initiating strand breaks and base modifications. *In vitro* the hydroxyl radical can induce strand breaks in the phosphodiester backbone of nucleic acids with the formation of 8-hydroxyguanine, 5-hydroxymethyuracil and thymine glycol. The modified base, 8-hydroxyguanine, will induce mutations. It is unlikely that the radicals are able to permeate the several nuclear membranes to access the DNA. Therefore it has been proposed that H_2O_2, generated in the cytosol during the dismutation of superoxide, could diffuse across the nuclear membranes to react with DNA-bound iron, generating hydroxyl radicals locally to damage DNA (Halliwell and Aruoma, 1991). *In vivo* studies of hepatic DNA isolated from iron loaded animals have not shown an increase in hydroxylated DNA bases (Ward *et al.*, 1995c).

Studies of the changes in expression of various mRNAs, from liver specific, growth related and stress induced genes, have identified selective activation of pro-α_2-collagen mRNA in addition to that of L-ferritin in the livers of iron loaded rats. This was true even though there was an absence of necrosis and nodular regeneration (Pietrangelo *et al.*, 1990). Other *in vivo* studies have not confirmed these results (Roberts *et al.*, 1993). Such results indicate that iron can specifically target genes in the liver. Previous studies have also shown that iron-complex induced lipid peroxidation may activate collagen expression in cultured fibroblasts.

More recently studies have been directed towards hepatic cells which undergo activation during experimental iron overload and cause the deposition of extracellular matrix proteins including collagen (Britton *et al.*, 1993). It is unknown what effect this might have in human iron overload but it may be one of the factors controlling the deposition of collagen.

8.4 ACUTE IRON POISONING

Accidental iron poisoning occurs predominantly in children who have consumed large numbers (10–50) of iron tablets, usually in the form of ferrous sulphate, over a period of a few hours or less. The pathophysiology of iron intoxication is complex with a variety of processes involved. The ingested iron enters the stomach, where there is a low pH. The ferrous sulphate will be mainly in a soluble form, although a small amount may precipitate, leading to irritation of the gastric mucosa with inflammation and haemorrhage. On leaving the stomach the pH will be drastically altered by the pancreatic bicarbonate in the duodenum. This leads to the formation of insoluble iron complexes, causing further mucosal damage. The severe intestinal lesions in the stomach and upper part of the small intestine cause erythema with areas of subepithelial haemorrhage and erosion. In addition, the increased vascular permeability caused by the inflamed gastrointestinal tract leads to the infiltration of many cells including polymorphonuclear leucocytes, macrophages, lymphocytes and plasma cells in addition to the release of cytokines. A variety of highly reactive oxygen species (ROS) including hypochlorous acid, superoxides and peroxides will be generated at the site of inflammation: these exacerbate the inflammatory response, increasing the permeability of the enterocyte and allowing toxins, in addition to the excess iron, to enter the cells and cause cell death. There are losses of intestinal fluid leading to systemic hypotension and circulatory failure. The marked increase in capillary permeability leads to a further plasma loss, a rise in haemocrit level and blood viscosity, while the blood volume, central venous pressure and tissue perfusion decrease. Subsequently decreased cardiac output leads to a state of shock and to circulatory failure and death within hours (Robontham and Lietman, 1980).

8.5 FURTHER STUDIES

Clearly it is essential to identify subjects with genetic haemochromatosis who are asymptomatic despite an increasing tissue burden of iron. At the moment such individuals can only be identified by the finding of an altered biochemical parameters, i.e. ferritin and transferrin saturation. Factors which prevent the toxicity of iron in such patients should be identified.

Within the next few years the gene for genetic haemochromatosis should be identified, its function elucidated and the explanation for the defect in the regulation of iron absorption understood. It would then be possible to screen the population, by amplifying the specific mutations within the gene which are associated with the disease.

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Suggestions/questions

- Further prospective studies are needed to explore the relationship between serum ferritin and tissue iron levels and the risk of CHD.

CHAPTER 13 IRON AND CANCER

Conclusions

- There are plausible scientific explanations for the increased incidence of hepatoma (liver cancer) in severe iron overload.
- The direct evidence associating modest iron overload conditions (i.e. high iron status) with cancer risk is very limited. There is a positive association between meat consumption and some sites of cancer, particularly breast cancer and colorectal cancer. The evidence is not consistent, however, and rests on the assumption that iron stores are directly related to meat consumption.

Suggestions/questions

- Is there a causal role for dietary iron rather than intake of meat in some cancers?
- The relative importance of iron overload *per se* versus cirrhosis in the aetiology of hepatoma requires further study.
- The differences in intracellular iron metabolism between tumour cells and normal cells requires elucidation.
- Further studies are needed on chelation and interference with iron delivery as a possible therapeutic regimen for cancer, with emphasis on protocols that will preferentially inhibit growth of tumour cells rather than normal cells.

CHAPTER 14 IRON, THE BRAIN AND NEURODEGENERATION

Conclusions

- Iron performs a crucial role in the functioning of the brain involving key metabolic enzymic reactions associated with mitochondrial oxidation, neurotransmitter synthesis and myelin formation.
- There is accumulating evidence that localized perturbations in iron-mediated free radical oxidative injury contribute to the pathogenic progression of a number of neurodegenerative disorders including Parkinson's and Alzheimer's diseases.
- Direct evidence of the injurious role of 'free' iron in the pathogenesis of neurodegenerative disease is still lacking.

Suggestions/questions

- There is a need to identify the non-transferrin mediated iron transport mechanisms and their quantitative contribution to iron uptake into the brain.
- Additional studies are necessary to determine the levels of iron distributed among the various iron-binding proteins, and in particular the location, concentration and identity of 'free' iron present in normal and diseased brains.

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CHAPTER 13

Iron

CARL-GUSTAF ELINDER

1 Abstract

Iron is an abundant metal, constituting 5% of the earth's crust.

Iron is essential and takes part in oxygen transport and utilization. Iron deficiency is common, especially among premenopausal women.

Absorption of ingested iron is adjusted to a fine homeostasis. Under normal conditions, about 5–15% of the iron is absorbed, but these values increase considerably in the presence of iron deficiency. Once absorbed, iron is lost mainly with desquamation of mucosal cells into the gastrointestinal tract. The rate of iron loss is 0.01% of the body burden per day.

Ingestion of soluble iron salts by children in doses exceeding 0.5 g of iron can give rise to severe lesions in the gastrointestinal tract, followed by metabolic acidosis, shock and toxic hepatitis. Long-term ingestion of excessive amounts of iron causes hemochromatosis which eventually leads to cirrhosis of the liver.

Occupational exposure to iron oxides during mining or refining of iron ore may give rise to hemosiderosis of the lung, which can be diagnosed by a roentgenological examination. Most reports regard this hemosiderosis as benign and therefore no cause for disability. Some reports indicate that long-term exposure to a mixture of iron and other metallic dusts may impair pulmonary function.

Increased mortality in lung cancer has repeatedly been reported for workers in hematite mines and iron foundries. Radon or other potentially carcinogenic substances have usually been present. Based on data from animal experiments it is suspected that iron oxide dust might serve as a cocarcinogenic substance, i.e. it enhances the development of cancer when combined with simultaneous exposure to carcinogenic substances.

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2 Physical and chemical properties

Iron (Fe): atomic weight 55.8; atomic number 26; density 7.9; melting point 1 535 °C; boiling point 2750 °C.

The magnetic properties of iron are superior to all other elements. The principal compounds of iron are ferrous (Fe^{2+}) and ferric (Fe^{3+}). Iron undergoes several structural changes when heated or mixed with other metals and these phenomena constitute the basis for the metallurgy of iron.

Iron occurs in a large number of inorganic compounds such as oxides, carbonates, disulfides, sulfates, and chlorides, and in some carbonyls, e.g. iron pentacarbonyl ($Fe(CO)_5$). Ferrous chloride and ferrous sulfate are water soluble. Iron carbonates, iron oxides, iron hydroxides, and iron sulfides have limited solubility in water (Hampel, 1968).

3 Methods and problems of analysis

The most commonly used methods for determination of small amounts of iron are colorimetric methods, using phenanthroline, thiocyanate and other substances as reagents (Sandell, 1959). Colorimetric methods can measure iron concentrations as low as 0.1 μg Fe/ml in water. At lower concentrations it is generally advisable to concentrate before analysis.

Atomic absorption spectrometry (AAS) techniques improve sensitivity considerably, and this method is nowadays frequently used for routine measurements of iron in biological materials (Tsalev, 1984). Electrothermal atomization (ET-AAS) is rarely needed due to the relatively high concentration of iron in most samples (Tsalev, 1984).

Less than 50 ng Fe/ml can be detected in water solution with conventional flame AAS (Sachdev et al., 1967; Pronk et al., 1974; Tsalev, 1984). An air concentration of 5 ng Fe/m³ can be detected employing AAS after digestion of air-sampling filters. Silica may, however, interfere with the measurement. This can be avoided by centrifugation (Kneip et al., 1974). AAS methods for determination of iron in biological materials are reviewed by Tsalev (1984).

Colorimetric and AAS methods for iron determination in serum have been compared for concentrations ranging between 0.1 and 1.6 μg Fe/ml and found to agree well, $r = 0.97$ (Pronk et al., 1974). Average iron content in diets, ranging from 7 to 30 μg Fe/g, was found to be similar, using both a colorimetric and an AAS method, though precision was less exact with the AAS method (Davies et al., 1972).

4 Production and uses

4.1 Production

Mining of iron ore takes place in many countries. World production in 1982 was 780 million metric tons (Klinger, 1982). The main producers of iron ore are the U.S.S.R. with 30% of the world production, Brazil 13%, Australia 11%, and China 9%. Abundant iron compounds are hematite (Fe_2O_3), magnetite (Fe_3O_4), limonite ($Fe_2O_3 \cdot H_2O$), and siderite ($FeCO_3$). Most iron ore is refined to produce steel, which is an iron alloy containing 0.02% to 1.5% carbon and often small quantities of certain other metals, such as chromium, manganese, molybdenum and nickel. World production of raw steel in 1982 was about 650 million metric tons, major producers being the U.S.S.R. (23%), Japan (15%) and the U.S.A. (11%) (Schottman, 1982).

4.2 Uses

Iron has been used by man for thousands of years and production of steel is one of the cornerstones of the industrialized world. Steel and iron products are used in the construction of ships, bridges, railroads, highways, buildings, etc. Large amounts of steel are also used in the production of vehicles and arms.

Iron compounds have a great number of applications even though they constitute less than 1% of the total iron consumption. Iron oxides are used as pigments in paints, plastics, etc.

Certain iron salts, mainly ferrous sulfate and ferrous succinate, are frequently used for the treatment and prevention of iron deficiency in humans.

5 Environmental levels and exposures

5.1 General environment

5.1.1 Food and daily intake

Due to the prevalence of iron deficiency in humans, quite a few reports have dealt with iron concentrations in different foodstuffs.

In general, liver, kidney, beef, ham, egg yolk, and soybeans have iron concentrations in the order of 30–150 mg Fe/kg fresh weight. Grains and fruits are low in iron, usually ranging from 1 to 20 mg Fe/kg (Documenta Geigy, 1970; Underwood, 1977). The boiling of vegetables, milling of grains and refin-

ing of sugar usually reduce their iron content considerably (Skeets et al., 1931; Czerniejewski et al., 1964; Hamilton and Minski, 1972/1973).

In both human and cow's milk, iron concentration is about 0.5 mg/l (Cavell and Widdowson, 1964; Murthy et al., 1972).

The daily intake of iron varies greatly with the total amount of food consumed and the proportions of iron-rich and iron-poor food in the diet. In general, reported daily intakes have ranged from 9 to 35 mg Fe/d (Underwood, 1977; Varo and Koivistoinen, 1980) and a typical European or North American diet can be considered to provide about 6 mg Fe per 1000 kcal (Callender, 1973).

In certain instances, contamination of food may occur, resulting in a higher daily intake of iron. Among rural inhabitants of Ethiopia the stable food is cakes of the cereal teff. The cereal teff has a high iron content. In addition, it is heavily contaminated with iron, mainly from the soil, but also during grinding, cooking and storage. Average daily intakes of iron in rural Ethiopia have been reported to be in the order of 450 mg Fe/d (Roe, 1966; Hofvander, 1968). Excessively high concentrations of iron (50–250 mg Fe/l) in locally brewed beer have been reported from South Africa and Zambia (Bothwell et al., 1964; Reilly, 1972). The beer, made from kafir corn, is fermented in iron pots which emit considerable amounts of iron into the acid beverage.

5.1.2 Water, soil and ambient air

Iron concentrations in water vary greatly. In the United States, freshwater and public water supplies, in general, have iron concentrations ranging from 0.01 to 1.0 mg/l (Davies et al., 1971). The median iron concentration in rivers has been reported to be 0.67 mg/l (Bowen, 1966). In seawater, iron concentrations vary between 1 and 60 μg/l (Bowen, 1966; Gupta, 1972).

Iron is one of the most common substances of the earth's crust with an average concentration of 50 mg/g (Hampel, 1968). Iron concentration in soil varies between 7 mg/g and extreme values of 550 mg/g (Bowen, 1966).

Levels of iron in air are low in non-industrialized areas. Considerably higher values have been reported from urban regions and especially areas where smelting takes place. From the South Pole, an average of 0.00084 μg Fe/m³ has been reported. This value is the average of ten three-day sampling periods (Zoller et al., 1974). Twenty-nine rural areas in the U.S. had iron concentrations in the air ranging from 0.08 to 0.7 μg Fe/m³, whereas 58 urban areas had values ranging from 0.3 to 4.2 μg Fe/m³ (Schroeder, 1970). Similar values have been reported from other places in the U.S. (Hwang, 1972) and the U.K. (Peirson et al., 1973; Salmon et al., 1977).

In Sweden, averages of up to 11 $\mu g/m^3$ (sampling time not given) have been reported close to iron- and steel-producing plants (Lindau and Sundberg, 1974).

5.2 Working environment

Occupational exposure to significant amounts of iron, mainly in the form of oxides, may occur during mining of iron ore, manufacturing of iron and steel products, arc welding, metal polishing, etc. Exposure to iron oxides is possible whenever these products are produced or used. In spite of the fact that tens of thousands of workers are exposed to iron oxides, data on workroom concentrations are sparse. Sentz and Rakow (1969) measured iron oxide concentrations at 6 powder-burning and 17 arc-air operations in 5 steel-manufacturing plants. Powder-burning operators were found to be exposed to an average of 31.1 mg Fe/m^3 in the breathing zone; and arc-air operators were exposed to an average of 21.5 mg Fe/m^3. Averages of about 1 mg Fe/m^3 have been reported from steel and iron foundries in Finland (Tossavainen, 1976).

6 Biological function and metabolism

6.1 Biological function

Iron is essential and vital to all living organisms. Iron together with protoporphyrin forms iron-porphyrin or heme. The heme is conjugated with four peptides forming hemoglobin, which in the red blood cells reversibly binds oxygen and serves as an oxygen transporter. Iron is also a necessary component of myoglobin, catalases, cytochromes, and peroxidases, which all play an essential role in the utilization of oxygen and for energy requirements of the cells (Gubler, 1956; Underwood, 1977).

The daily recommended iron requirement for humans is 10 mg for children, adult males and non-menstruating females. A daily amount of 15 to 18 mg of iron is recommended for rapidly growing children and menstruating females. During pregnancy it is recommended that iron supplement should be given in order to meet the increased requirements (NAS, 1974).

6.2 Iron deficiency

Iron deficiency is probably the most prevalent deficiency state affecting the human population. Due to iron loss during menstrual bleeding, the disorder is most common among young and middle-aged women. In the industrialized countries the prevalence of iron deficiency among young women is in the order of 10–25% (Rybo, 1966, 1973; Callender, 1973). In developing countries where the population relies heavily on vegetable and grain foodstuffs, the incidence of iron deficiency is even higher (Venkatachalam, 1968; Edgerton et al., 1979). Groups other than menstruating females who frequently suffer from iron deficiency are pregnant women (Pritchard and Hunt, 1958), and infants between 4 and 24 months of age (Sturgeon, 1954, 1956).

An early symptom of iron deficiency in humans is mild to moderate anemia, which may lead to lowered working capacity (Andersen and Barkve, 1970; Gardner et al., 1977). If the deficiency persists the anemia is exacerbated and clinical manifestations occur, including fatigue, headache, and anorexia. In more severe cases, abnormalities in epithelial tissues occur with sore mouth and tongue, angular stomatitis, etc. (Wintrobe and Lee, 1974).

Regarding signs and symptoms of iron deficiency in animals, reference is nade to Underwood (1977).

6.3 Metabolism

6.3.1 Absorption

No available data allow calculation of the pulmonary absorption of iron.

In both animals and humans, iron absorption from the gut is adjusted to a fine homeostasis with low iron stores resulting in increased absorption and, alternately, sufficient body stores of iron-decreasing absorption (Cox and Peters, 1978).

In humans with iron sufficiency, 2–15% of the iron ingested via food is absorbed (Pirzio-Biroli et al., 1958; Moore, 1965; Björn-Rasmussen et al., 1974). Based on fecal elimination of perorally given radioiron, Josephs (1958) estimated that in normal adults 2–20% of the administered dose was absorbed compared to 20–60% in patients with iron-deficiency anemia.

Apart from iron status, iron absorption is also influenced by factors such as condition of the gastrointestinal tract, chemical form of the ingested iron, and other substances in the diet (Hallberg, 1981).

In humans, it has been shown that iron from animal sources is taken up more effectively (10–25%) than iron from vegetables and grains (1–10%). The iron

from animal food largely exists as heme products. Heme fragments can be taken up directly without degradation (Moore, 1965; Hallberg and Sölvell, 1967; Underwood, 1977). Ascorbic acid and meat have been shown to markedly increase the absorption of non-heme iron (Layrisse et al., 1974; Hallberg, 1981).

In animals, it has further been shown that iron absorption is increased not only in conjunction with ascorbic acid, but also with certain other acids (Underwood, 1977). High levels of phosphate, cobalt, copper, zinc, and other trace metals decrease absorption (Hegsted et al., 1949; Forth and Rummel, 1971; Underwood, 1977).

The mechanisms of iron absorption have been studied extensively, but are not yet fully understood. Absorption is considered to be a two-step mechanism. In the first step, a chelate complex containing ferrous iron ions is taken up from the intestinal lumen by the mucosal cells. This is an energy-requiring process (Cox and Peters, 1978). In the second step, iron from the mucosal cells is transferred across the cell membrane to serum, where it is bound to transferrin (MacDonald, 1971).

Transferrin, a β_1-globulin with a molecular weight of 75,000, is produced in the liver. It binds iron and thus protects cells from the potential toxic effect of free iron ions. It also transports iron to the bone marrow and other storage tissues. In the event of an iron deficiency, transferrin in serum increases, thus enhancing transport across the mucosal cell membrane into the blood (Gubler, 1956; Wheby et al., 1964; MacDonald, 1971; Underwood, 1977). When transfer to serum does not occur, iron in mucosal cells is lost to feces by intestinal cell shedding.

6.3.2 Distribution

Normally, the human body contains about 3–5 g of iron. Two-thirds of this amount are bound to hemoglobin which is found almost entirely in blood. Less than 10% of the body iron is found in myoglobin and iron-requiring enzymes. Of the remaining amounts of iron, about 20–30% of the body pool is bound to iron-storage proteins: ferritin (soluble in water) and hemosiderin (insoluble in water). These iron-storage proteins are mainly found in liver, bone marrow and spleen.

The ferritin and hemosiderin pool of iron can be called upon for hemoglobin production when iron intake is insufficient or after bleeding. Iron stored as ferritin is regarded as more readily available than iron stored as hemosiderin. Transferrin plays a key role in iron metabolism as the iron transports protein in plasma.

The highest concentrations of iron are found in liver and spleen, followed by kidney, heart and skeletal muscle (Drabkin, 1951; Gubler, 1956; MacDonald, 1971; Underwood, 1977).

6.3.3 Excretion

Under normal conditions the total elimination of iron from the body is limited to 0.6–1.0 mg/d (Underwood, 1977). Disregarding the non-absorbed iron, about 0.2–0.5 mg Fe/d is eliminated via feces. This iron is derived from desquamized cells and bile (Ingalls and Johnston, 1954; Dubach et al., 1955). The mean urine excretion of iron has been reported to be about 0.1–0.3 mg/d (Barer and Fowler, 1937; McCance and Widdowson, 1938; Robinson et al., 1973). In addition, iron is lost via normal dermal losses in sweat, hair and nails. The total amount of iron eliminated each day via these routes has been estimated at 0.5 mg/d (Mitchell and Edman, 1962).

Considerable amounts of iron can be lost via bleeding. Each ml of blood contains about 0.5 mg of iron, and a normal menstrual bleeding of 40 ml thus results in a loss of 20 mg of iron per month (Rybo, 1966).

6.3.4 Biological half-time

Under normal conditions, very little absorbed iron is eliminated. The daily losses of iron are in the order of 0.01–0.02% of the body pool which corresponds to a biological half-time of 10–20 years. After intravenous administration of radioiron to volunteers, observed average fecal eliminations were in the order of 0.01% of the given dose per day (Dubach et al., 1955; Moore, 1955).

In rats it has been shown that inhaled and deposited iron oxide particles, with median aerodynamic diameter of 0.3 μm, are cleared slowly from the lung, $t_{1/2} = 33$ days (Hewitt and Hicks, 1972). Repeated exposure of hamsters to 40 mg Fe_2O_3/m^3 in air gives rise to a marked accumulation of iron in the lung (Creasia and Nettesheim, 1974).

In humans, Kalliomäki et al. (1978) estimated the yearly lung clearance of deposited iron dust to be in the order of 20–40% of the deposited amount. These values were estimated by comparing the iron content in lungs of retired iron welders with that of workers still-exposed (see Section 8.1.2 under 'Humans').

7 Levels in tissues and biological fluids

Apart from blood, which contains about 0.5 mg Fe/ml, high concentrations

of iron are found in liver and spleen where iron is stored in ferritin and hemosiderin. Under normal conditions, the concentrations of iron in these tissues is reported to be in the order of 0.5–0.8 mg/g wet weight (Butt et al., 1965; Mathies and Lund, 1973; Snyder et al., 1975). Considerably higher values, sometimes exceeding 10 mg/g in liver, have been found in cases of severe hemochromatosis (Drabkin, 1951; Bothwell and Bradlow, 1960).

In blood more than 99% of the iron is carried within the red blood cells bound to hemoglobin. The whole-blood concentration of iron is thus directly proportional to the hemoglobin concentration; the iron concentration in serum is about 1.3 mg/l. Infections or iron deficiency decrease this value considerably (Underwood, 1977). Serum also carries a low concentration of ferritin. The serum ferritin concentration reflects the total body stores of iron (Underwood, 1977) where each ng of ferritin per ml of serum corresponds to about 8 mg of storage iron (Walters et al., 1973).

In hair, iron concentrations range from 10 to 60 μg/g (Baumslag et al., 1974). Urinary concentration of iron is in the order of 0.1–0.3 mg/l (Barer and Fowler, 1937; Robinson et al., 1973).

8 Effects and dose–response relationships

8.1 Local effects and dose–response relationships

8.1.1 Gastrointestinal exposure

Iron is potentially toxic in all doses and forms. The incidence of accidental intoxication from iron has been increasing parallel to the increasing use of iron in medicine. According to Arena (1970), about 2000 intoxications occur in the U.S.A. each year. Intoxication is most frequent in children in the age group of 1–5 years due to their eating ferrous sulfate tablets with candy-like coatings. Severe poisoning in children may occur following ingestion of more than 0.5 g of iron, about 2.5 g as ferrous sulfate (Gleason et al., 1963; Crotty, 1971; Greenblatt et al., 1976; Krenzelok and Hoff, 1979). The symptoms usually occur within 1 or 2 h, but sometimes as late as 6 h after ingestion. The first sign of intoxication is vomiting, and due to ulceration of the gastrointestinal mucosa, vomitus frequently becomes bloody and the stool may turn black. Shortly afterwards, the patient begins to show signs of shock and metabolic acidosis. If the patient survives the initial crisis, liver damage with hepatitis and coagulation defects often occur within a couple of days. Renal failure, hepatic cirrhosis and pyloristenosis may occur as delayed effects (Gleason et al., 1963;

Green, 1971; Whitten and Brough, 1971)

The mechanism of acute iron poisoning is still uncertain, but the following hypothesis has been suggested: High concentrations of ferrous ions attack the mucosal cells and necrotize them. Due to mucosal damage the ferrous ions readily pass into the blood, i.e. absorption is enhanced and as a result free ions occur in serum. These free ions are toxic to the capillary walls and the liver, giving rise to shock and hepatitis (Gleason et al., 1963; Whitten and Brough, 1971).

8.1.2 Pulmonary exposure

Animals Acute exposure of rats to iron oxide in air at concentrations exceeding 500 mg Fe/m³ for periods exceeding 30 min resulted in coughing, respiratory difficulties and nasal irritation. Microscopical examination of the lungs showed numerous macrophage cells densely packed with granular material, most probably iron oxide, in all exposed rats (Hewitt and Hicks, 1972).

Repeated intratracheal installations of ferric oxide to hamsters, 10 times 5 mg Fe per animal, gave rise to losses of ciliated cells and hyperplasia and proliferation of non-ciliated epithelial cells. The tracheobronchial epithelium, however, returned to normal 7 weeks after completion of the treatment (Port et al., 1973).

Hamsters exposed to ferric oxide dust with a mean particle size of 0.11 μm at a concentration of 40 mg/m³, 6 h/d, 5 days a week, accumulated iron in the lung. After 1 month of exposure the concentration of Fe_2O_3 in the lung was 0.5 mg/g, and after 2 years 9.5 mg/g. Microscopical examination of lung specimens obtained from hamsters exposed to iron for long periods revealed respiratory tract cell injury and alveolar fibrosis (Creasia and Nettesheim, 1974).

It is suspected that the pulmonary lesions induced by iron oxides enhance the development of lung cancer when carcinogenic substances are given simultaneously (Creasia and Nettesheim, 1974).

Humans Exposure to iron, mainly in the form of oxides, occurs in both mining and smelting industries, but also during welding of iron and steel materials. It should be pointed out that during mining and also during the smelting and welding process, workers are often exposed to dust containing iron oxides and silica, as well as other metals and substances. In iron mines α-particles emitted from radon gas and radon daughters are often present, too.

It was early recognized that inhalation of iron fumes, principally in the form of iron oxides, could give rise to roentgenological changes in the lung due to deposition of inhaled iron particles (Doig and McLaughlin, 1936). The roent-

genological picture was similar to that seen in silicosis or miliary tuberculosis. The occurrence of these roentgenological findings among workers exposed to iron has been confirmed in hematite miners (Faulds, 1957), silver polishers (McLaughlin et al., 1945), workers engaged in the manufacture of iron oxide (McLaughlin, 1951; Teculescu and Albu, 1973), iron and steel workers (Dunner and Hermon, 1944; Pendergrass and Leopold, 1945), and arc welders (Schuler et al., 1962).

The roentgenological changes, attributable to iron oxide exposure, have been named: siderosis, iron pneumoconiosis, hematite pneumoconiosis, iron pigmentation of the lung, and arc welder lung. The prevalence of siderosis among iron workers who were exposed to iron for periods exceeding five years was reported to be in the order of 5–15% (Buckell et al., 1946; Schuler et al., 1962; Sentz and Rakow, 1969). Dose levels were not given in the two earlier studies, but exceeded 10 mg Fe/m^3 in the latter study (Sentz and Rakow, 1969). In a Romanian industry producing iron oxide (Fe_2O_3), the prevalence of siderosis was 34% (Teculescu and Albu, 1973). Total dust concentrations ranged from 10 to 770 mg/m^3 in different rooms of the plant. There was no evidence of lung fibrosis among the men with X-ray changes, but many of them (80%) complained about chronic cough (Teculescu and Albu, 1973).

A method for determining the exact amount of iron deposited in the lung has been developed (Cohen, 1973; Kalliomäki et al., 1976). The method, which is based on the magnetic properties of the iron dust deposited in the lung, has shown that less than 4 mg of magnetic dust is present in non-exposed normals and that the amount of iron increases with time of exposure. The total amount of magnetic dust in lungs of arc welders who were exposed to iron oxide for 18 years has been reported to range from 30 to 2000 mg (Kalliomäki et al., 1978).

Reviewing the literature on occupational exposure to iron oxide fumes, Stokinger (1963, 1984), the ACGIH (1971) and Parkes (1982) concluded that most authors regarded the roentgenological pulmonary changes secondary to inhalation of iron dust, i.e. siderosis, as benign and did not suspect them to progress to fibrosis.

In three reports it has, however, been suggested that pulmonary dysfunction may occur as a result of long-term exposure to iron oxides from welding fumes (Charr, 1956; Friede and Rachow, 1961; Stanescu et al., 1967).

Charr (1956) reported on three cases of severe pulmonary changes related to iron oxide exposure from welding fumes. The three men in this study suffered from cough and shortness of breath, X-ray examination revealed diffuse fibrosis. In 1961, Friede and Rachow described another case with similar expo-

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

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Appendix A

ALL PAGES OF APPENDIX A (PAGES 1 THROUGH 8) HAVE BEEN CBI-DELETED

ROOT & LEAF Co.

2635 SW Luradel Street
Portland, OR 97219
503-452-1593 Phone
503-452-1927 Fax

Availability of Mined Ferric Phosphate

Prepared by John Wohler
March 22, 2001

I used a three-pronged approach to research and prepare this report. I searched the World Wide Web, contacted commodity companies trading in agricultural minerals and phosphates and talked with the United States Geological Survey (USGS) offices. This gave me the greatest chance to find an industrial source of ferric phosphate.

All three of these avenues gave the same result. Either they could not find or did not know of any large-scale sources or indicated by their knowledge of phosphate chemistry and geology that deposits large enough to economically develop were not possible.

The Web

A search of the World Wide Web gives information on many minerals that contain iron and phosphate most of these listings are for collectors and dealers of minerals and crystals. I spoke with Tony Nikischer[1] of Excalibur Mineral Company. He indicates that ferric phosphate does not occur in large quantities. It accumulates in small voids where the crystals of the ferric phosphate develop. Strengite is the crystal of ferric phosphate. It is listed on the Web and as a rare mineral. Tony Nikischer said that even Beraunite, which is a combination of ferric and ferrous phosphate, which is more common than Strengite, would not be found in quintiles large enough to mine on an industrial scale.

There are about 150 different minerals with iron and phosphate plus other elements. These are all secondary minerals they develop in much the same way as Strengite with the same sparse distribution. The only pure ferric phosphate would be Strengite all others would be contaminated with other elements.

The USGS

I contacted the USGS through a number of different avenues. I sent emails to the general information line as well as directly contacting Steve Jasinski[2] the phosphate rock & peat commodity specialist. All attempts to contact the USGS directed me back to Mr. Jasinski. He stated, "Iron phosphate is not mined because there are no deposit that would be economically feasible to develop." He also suggested that I contact the Florida Institute of Phosphate Research[3] (FIPS). I contacted Karen Stuart at the FIPS. She gave me several contacts to follow up with. The ones that I was able to contact had no knowledge of any mines for ferric phosphate.

Phosphate & Agricultural Mineral Trading Companies

I contacted IMC Global the largest phosphate supplier in North America. Dennis Michalski[4] returned my faxed request for information. He indicated, "To the best of my

knowledge, there are no large scale deposits of ferric phosphate." He also directed me back to the Florida Institute of Phosphate Research.

I spoke to three different mineral trading companies Frit Industries[5], Universal Minerals[6] and North Pacific Trading[7]. None of these companies could locate a mined source of ferric phosphate.

South America

There was rumor of a ferric phosphate source in Brazil. I contacted the Institute for Technological Research in Brazil. They are the foremost technical research institutes in Latin America. I was put in contact with Mr. Edson Monte of their geology department. He did not know of any sources of ferric phosphate nor did any of the other specialists at IPT. He checked with his contacts at other companies in Latin America, none of them knew of a source.

Conclusion

There are no sources of ferric phosphate that could be economically mined for industrial uses.

References

1. Mr. Tony Nikischer Owner
Excalibur Mineral Company
1000 N. Division St
Peekskill, NY 10655 USA
www.excaliburmineral.com

2. Stephen M. Jasinski
Commodity Specialist - Phosphate Rock & Peat
USGS
983 National Center
Reston, VA 20192
Phone: 703-648-7711
FAX: 703-648-7722
email: sjasinsk@usgs.gov
Web: minerals.usgs.gov/minerals

3. Florida Institute of Phosphate Research
1855 West Main Street
Bartow, FL 33830
Telephone: (863) 534-7160
FAX: (863) 534-7165
Karen Stewart – Librarian

4. Dennis Michalski
DHMichalski@imcglobal.com

5. Universal Mineral
dans@universalmineral.com

6. North Pacific Trading Co
Darren MacFarlane
dmcfarl@north-pacific.com

7. Frit Industries, Inc
P.O. Box 1589
Ozark, Alabama 36361-1589
Jimmy Wyatt
jwyatt@fritinc.com

8. Institutes for Technological Research
São Paulo, Brazil
sac@ipt.br
www.ipt.br

983 National Center
Reston, VA 20192
Phone: 703-648-7711
FAX: 703-648-7722
email: sjasinsk@usgs.gov
Web: minerals.usgs.gov/minerals

2.20.01
Dear Mr. John Wohler,

we are SAC - Customer Service of IPT and we are sending your message to our researcher, Mr. Edson Monte, mailto:edmonte@ipt.br .

Best Regards,

Katia K. Crespo
SAC - IPT

3/5/01
Mr. Wohler,

To the best of my knowledge, there are no large-scale deposits of ferric phosphate. Most of the iron in our products is from the mineral Goethite a ferric oxide hydroxide. The Florida Institute of Phosphate Research (FIPR) is the best authority to check. They have information on phosphate deposits world wide. Their telephone number is 863-534-7160 and their web site is www.FIPR.STATE.FL.US

Good luck in your search and if we can help in the future don't hesitate to call.

Dennis Michalski

Michalski, Dennis H - New Wales [DHMichalski@imcglobal.com]

3/6/01
Dear John:
OMRI does not currently have a listed source of mined ferric phosphate. You can find our entire Brand Name Product List on our website at www.omri.org. Sorry we couldn't help further.
Sincerely,
Scott Rice, Projects Coordinator
****
Organic Materials Review Institute (OMRI)
Box 11558, Eugene OR 97440 USA
541-343-7600, fax 541-343-8971
srice@omri.org, www.omri.org
The Organic Materials Review Institute's mission is to provide professional, independent, and transparent review of materials and compatible processes allowed to produce, process, and handle organic food and fiber.

Dear Mr. Wohler,

GeoRef is the most comprehensive database in the geosciences. The GeoRef database covers the geology of North America from 1785 to the present and the geology of the rest of the world from 1933 to the present. It's a database that I can search through our affiliation with the University of South Florida. Unfortunately, it isn't available for searching online by the general public. However, if you are near a university you might be able to go to their library and search it from there. (A public library would not have access to it.)

There are a few phosphate geologists I could recommend to you:

Mr. Henry J. Lamb, Consulting Geologist
501 Church Ave. N.
Mulberry, FL
Phone (863) 425-4092

Mr. John Maddry
Geologist
IMC Phosphates
P.O. Box 2000
Mulberry, FL 33860
Phone (863) 428-2500, ext. 4473

Dr. Stanley R. Riggs
Distinguished Professor
East Carolina University
http://www.geology.ecu.edu/geology/riggs/

Your question about whether iron phosphate occurs in large enough deposits to be economically recoverable is one that occurred to me also. Unfortunately, I really can't give you a good answer, but I'm sure one of the geologists listed above could.

Best of luck in your inquiries,

Karen Stewart
Assistant Librarian

2/22/01
Dear Mr. Wohler,

I've done some searching for you, but unfortunately I can't find a source of mined ferric phosphate. Our Research Director of Chemical Processing doubts there is any, unless someone is mining for something else and produces it as a waste product.

There are any number of iron phosphate minerals, and the largest deposits
of them seem to be in Africa. However, I don't know whether they are presently being mined (or for that matter, have ever been).

I have a printout of a GeoRef search on several iron phosphate minerals:
vivianite, wavellite, rockbridgeite, beraunite, strengite, and cacoxenite.
In the printout are citations telling where many of these mineral deposits
are located, but whether these have ever been mined is another matter.

I'm sorry I can't be more helpful, but this is about all I could find. Here in Florida, we try to remove the iron from our phosphoric acid during
processing (it's considered a contaminant).

With best regards,

Karen Stewart
Assistant Librarian

Jimmy Wyatt Frit industries
2/21/01

John, we have never encountered ferric phosphate in sourcing iron materials but I will look for it. How much of this material do you anticipate purchasing? The reason that mined ferric phosphate is not readily available could be due to the fact that phosphorous is a "bad" contaminate in steel, so any iron ore with a high phosphate would be avoided.

2/20/01
Iron phosphate isn't mined because there are no deposits that would be economically feasible to develop.

The Florida Institute of Phosphate Research has an extensive library of phosphate materials and may be able to provide some more information. Requests can be sent via to kstewart@helios.acomp.usf.edu or by phone at 863-534-7160. FIPR also has a website, www.fipr.state.fl.us

Other possible source of information:

International Fertilizer Industry Association (IFA)
Paris, France
Email: ifa@fertilizer.org
Web: www.fertilizer.org
Phone: +33-153-930-500
Fax: +33-153-930-545

Stephen M. Jasinski
Commodity Specialist - Phosphate Rock & Peat
USGS

John Wohler

From: sjasinsk@usgs.gov
Sent: Tuesday, February 20, 2001 11:43 AM
To: John Wohler
Subject: RE: Iron Phosphate

Iron phosphate isn't mined because there are no deposits that would be economically feasible to develop.

The Florida Institute of Phosphate Research has an extensive library of phosphate materials and may be able to provide some more information. Requests can be sent via to kstewart@helios.acomp.usf.edu or by phone at 863-534-7160. FIPR also has a website, www.fipr.state.fl.us

Other possible source of information:

International Fertilizer Industry Association (IFA)
Paris, France
Email: ifa@fertilizer.org
Web: www.fertilizer.org
Phone : +33-153-930-500
Fax: +33-153-930-545

==========

Stephen M. Jasinski
Commodity Specialist - Phosphate Rock & Peat
USGS
983 National Center
Reston, VA 20192
Phone: 703-648-7711
FAX: 703-648-7722
email: sjasinsk@usgs.gov
Web: minerals.usgs.gov/minerals

==========

John Wohler

From: sjasinsk@usgs.gov
Sent: Tuesday, February 20, 2001 5:43 AM
To: John Wohler
Subject: Re: Iron Phosphate

Mr. Wohler,

I don't know of mined source for ferric phosphate, but the Organic Materials Review Institute (OMRI) may be able to help. They have a directory of suppliers on their website at http://omri.org/ or you can send an email to info@omri.org or contact by phone at 541-343-7600 or fax, 541-343-8971.

==========

Stephen M. Jasinski
Commodity Specialist - Phosphate Rock & Peat
USGS
983 National Center
Reston, VA 20192
Phone: 703-648-7711
FAX: 703-648-7722
email: sjasinsk@usgs.gov
Web: minerals.usgs.gov/minerals

==========

From: Maddalena,Rino [Rmaddalena@nma.org]
Sent: Tuesday, February 20, 2001 10:20 AM
To: 'John Wohler'
Subject: RE: iron Phosphate

john, try the phosphate council http://www.flaphos.org/, they most likely to help you find this information.

-----Original Message-----
From: John Wohler [mailto:jawohler@home.com]
Sent: Monday, February 19, 2001 1:59 PM
To: rmaddalena@nma.org
Subject: iron Phosphate

This is a strange request. I am looking for a mined source of ferric Phosphate. I have been searching the web and have been able to find many gem quality iron phosphates that seem to only be available in small quantities. We will need a larger source.

My company manufactures a low impact slug and snail bait made with ferric phosphate as the active ingredient. We are looking for a natural mined source of the material so we can apply for an organic certification.

If you can not help me can you please suggest some other resources for me.

Thank you for your help.

hn Wohler
... Neudorff GmbH KG
2635 SW Luradel Street
Portland, Oregon 97219
Phone 503 452-1593
Fax 503 452-1927
Cell 503 706-7961
jawohler@home.com

John Wohler

From: jlswartz@usgs.gov on behalf of ask@usgs.gov
Sent: Tuesday, February 27, 2001 10:32 AM
To: jawohler@home.com
Subject: In Response to Your Inquiry

In response to your inquiry:
= = = = = = = = = = = = = = =

This is a strange request. I am looking for a mined source of ferric Phosphate. I have been searching the web and have been able to find many gem quality iron phosphates that seem to only be available in small quantities. We will need a larger source.

My company manufactures a low impact slug and snail bait made with ferric phosphate as the active ingredient. We are looking for a natural mined source of the material so we can apply for an organic certification.

If you can not help me can you please suggest some other resources for me.

Thank you for your help.

John Wohler
W. Neudorff GmbH KG
2635 SW Luradel Street
Portland, Oregon 97219
Phone 503 452-1593
Fax 503 452-1927
Cell 503 706-7961
jawohler@home.com

= = = = = = = = = = = = = = =
Thank you for your inquiry.

For information on Phosphate Rock please view the following USGS Web site at:
http://minerals.usgs.gov/minerals/pubs/commodity/phosphate_rock

For information on Iron Ores please view the following USGS Web site at:
http://minerals.usgs.gov/minerals/pubs/commodity/iron_ore

The USGS state representatives for the state of Oregon are:

Arnold Tanner ARNIE CALLED 3/6/01
U.S. Geological Survey 3/8 CALLED BACK DIRECTED ME TO STEVE JASINSKI
Minerals Information
984 National Center
Reston, VA 20192 USA
Phone: 703-648-4758
Fax: 703-648-4995
Email: atanner@usgs.gov

J. Roger Loebenstein CALLED 3/6-01
U.S. Geological Survey 3/8 CALLED BACK SAID TO CALL JASINSKI
Minerals Information
National Center
Reston, VA 20192 USA
Phone: 703-648-4752
Fax: 703-648-4995

Email: rloebens@usgs.gov

Or you may contact the Oregon Department of Geology and Mineral Industries.

egon Department of Geology and Mineral Industries
800 NE Oregon St., #28
Portland, OR 97232
Phone: (503)731-4100
Fax: (503)731-4066
Email: Nature.of.NW@state.or.us

3/8 SPOKE W/ RON GRITCH NO SOURCES IN OREGON DID NOT KNOW OF ANY IN THE US SUGGESTED USGS

If you have further questions regarding this response, please contact me.

Jennifer Swartz
Information Technician
Reston/ESIC
507 National Center
Reston, VA 20192
jlswartz@usgs.gov
703-648-4345
888-ASK-USGS

If you have any other questions please direct them to:

Reston/ESIC
507 National Center
Reston, VA 20192
ask@usgs.gov
888-ASK-USGS

John Wohler

To: edmonte@ipt.br
Subject: ferric Phosphate

Katia K. Crespo of SAC - IPT customer service sent you a copy of my request. I am looking for a source of mined Ferric Phosphate for a Product that we manufacture that kills slugs and Snails.

I am not sure that there are any ferric phosphate sources in the world that are economically viable to mine. I did hear that there was a mine in Brazil. Would you be able to confirm this? Any information that you could share would be appreciated. If you could confirm that there are no source or that this mineral is not present in economically recoverable amounts this would also be good information to have.

Thank you for your time and trouble.

John Wohler
W. Neudorff GmbH KG
2635 SW Luradel Street
Portland, Oregon 97219
Phone 503 452-1593
Fax 503 452-1927
Cell 503 706-7961
jawohler@home.com

John Wohler

ent: Edson Del Monte [edmonte@ipt.br]
To: Tuesday, March 13, 200
Cc: John Wohler
Subject: Marsis Gabral Junior; Luiz Carlos Tanno; Jose Francisco M
Krasnikovicius Crespo
Re: ferric Phosphate

Dear Mr. Wohler

We asked for the ferric phosphat among specialist in IPT as well as in other companies, and infortunately their answer was negative. They don't know any ferric phosphate in Brasil.
One of them said that iron and aluminiun would common occur as secondary and insoluble phosphate in the deposits but he doesn't know a specific mine. He told about aluminum phosphate that occurs in Senegal. If you interest it is named Lam-Lam Mine, from which they produce termo phosphate to be used in grape crops in France.

Sincerely

Edson

-----Mensagem original-----
De: John Wohler <jawohler@home.com>
Para: Edm <edmonte@ipt.br>
Data: Terça-feira, 6 de Março de 2001 15:34
Assunto: RE: ferric Phosphate

>Wondering if you have had any luck finding information on ferric phosphate?
>Thank you for your time and trouble helping me.
>
>Sincerely
>
>John Wohler
>
>-----Original Message-----
>From: Edm [mailto:edmonte@ipt.br]
>Sent: Thursday, March 01, 2001 5:56 AM
>To: John Wohler
>Subject: Re: ferric Phosphate
>
>
>I received your e-mail related to ferric phosohate and I'm looking for some
>answer for that issue.
>As fast as possible I'll return this answer.
>
>Sincerely
>Yours
>
>
>Edson
>
>

----Mensagem original-----
>De: John Wohler <jawohler@home.com>
>Para: edmonte@ipt.br <edmonte@ipt.br>
>Data: Terça-feira, 27 de Fevereiro de 2001 13:51

>Assunto; ferric Phosphate
>
>
>>Katia K. Crespo of SAC - IPT customer service sent you a copy of my
>request. I am looking for a source of mined Ferric Phosphate for a Product
>that we manufacture that kills slugs and Snails.
>>
>>I am not sure that there are any ferric phosphate sources in the world
that
>>are economically viable to mine. I did hear that there was a mine in
>>Brazil. Would you be able to confirm this? Any information that you
could
>>share would be appreciated. If you could confirm that there are no source
>>or that this mineral is not present in economically recoverable amounts
>this
>>would also be good information to have.
>>
>>Thank you for your time and trouble.
>>
>>John Wohler
>>W. Neudorff GmbH KG
>>2635 SW Luradel Street
>>Portland, Oregon 97219
>>Phone 503 452-1593
>>Fax 503 452-1927
>>Cell 503 706-7961
>>jawohler@home.com
>>
>

Mr. Wobler,

To the best of my knowledge, there are no large-scale deposits of ferric phosphate. Most of the iron in our products is from the mineral Goethite a ferric oxide hydroxide. The Florida Institute of Phosphate Research (FIPR) is the best authority to check. They have information on phosphate deposits world wide. Their telephone number is 863-534-7160 and their web site is www.FIPR.STATE.FL.US

Good luck in your search and if we can help in the future don't hesitate to call.

Dennis Michalski

John Wohler

From: Riggs, Stanley Robert [RIGGSS@MAIL.ECU.EDU]
Sent: Monday, March 05, 2001 4:47 AM
To: 'John Wohler'
Subject: RE: Ferric Phosphate

John Wohler,

Sorry, I don't know anything about ferric phosphate, nor do I know anyone that could help you. Good luck.

Cheers,
Stan Riggs

-----Original Message-----
From: John Wohler
To: riggss@mail.ecu.edu
Sent: 2/26/01 6:22 PM
Subject: Ferric Phosphate

Karen Stewart at the Florida Institute of Phosphate research suggested that
I contact you.
This is a strange request. I am looking for a mined source of ferric Phosphate. I have been searching the web and following up many leads. I
have been able to find many gem quality iron phosphates but they seem to only be available in small quantities. We will need a larger more industrial source.

My company manufactures a low impact slug and snail bait made with ferric
phosphate as the active ingredient. We are looking for a natural mined source of the material so we can apply for an organic certification. The
source can be any where in the world.

Give some of the feed back that I have been getting I am starting to think
that Ferric Phosphate does not exist in large enough deposits to be economically mined. My back ground is in horticulture and I would appreciate an opinion on if this is true from an expert in geology.

If you can not help me can you please suggest some other resources for me.

Thank you for your help.

John Wohler
W. Neudorff GmbH KG
2635 SW Luradel Street
Portland, Oregon 97219
Phone 503 452-1593
Fax 503 452-1927
Cell 503 706-7961
jawohler@home.com

John Wohler

Sent: Wyatt, Jimmy [jwyatt@fritinc.com]
To: Tuesday, March 06, 2001 11:37 AM
Subject: John Wohler
RE: Ferric Phosphate

I have not found any at this time. Our Brazilian company is looking into a source in Brazil, but the deposit may be very small.

-----Original Message-----
From: John Wohler [mailto:jawohler@home.com]
Sent: Tuesday, March 06, 2001 12:35 PM
To: Wyatt, Jimmy
Subject: Ferric Phosphate

I was just following up to see if you had been able to find a source of ferric phosphate. You had indicated that you would be checking some of your
sources. Thank you for your help.

John Wohler

To: Wyatt, Jimmy
Subject: RE: iron phosphate

We are looking at 25,000 to 100,000 pounds first year if the product is nearly pure, more if it is less pure. Thanks for your help! Let me now how your search goes. John Wohler

-----Original Message-----
From: Wyatt, Jimmy [mailto:jwyatt@fritinc.com]
Sent: Wednesday, February 21, 2001 8:34 AM
To: jawohler@home.com
Subject: RE: iron phosphate

John, we have never encountered ferric phosphate in sourcing iron materials but I will look for it. How much of this material do you anticipate purchasing? The reason that mined ferric phosphate is not readily available could be due to the fact that phosphorous is a "bad" contaminate in steel, so any iron ore with a high phosphate would be avoided.

-----Original Message-----
From: John Wohler [mailto:jawohler@home.com]
Sent: Tuesday, February 20, 2001 3:41 PM
To: frit
Subject: iron phosphate

This is a strange request. I am looking for a mined source of ferric Phosphate. I have been searching the web and have been able to find many
gem quality iron phosphates that seem to only be available in small quantities. We will need a larger source.

My company manufactures a low impact slug and snail bait made with ferric
phosphate as the active ingredient. We are looking for a natural mined source of the material so we can apply for an organic certification.

If you can not help me can you please suggest some other resources for me.

Thank you for your help.

John Wohler
W. Neudorff GmbH KG
2635 SW Luradel Street
Portland, Oregon 97219
Phone 503 452-1593
Fax 503 452-1927
Cell 503 706-7961
jawohler@home.com

John Wohler

From: Darren MacFarlane [dmacfarl@north-pacific.com]
Sent: Thursday, February 22, 2001 7:38 AM
To: jawohler@home.com
Subject: Your e-mail

Hi, John. Sure I remember you. Thanks for remembering me!

Could you relay any specifics regarding the Ferric Phosphate? I understand it is used in fertilizers and as a feed and food additive.

Ferric phosphate is produced by adding a solution of sodium phosphate to a solution of ferric chloride. It is then filtered and dried. Do I understand you are looking for a natural, mined source rather than a chemically manufactured product?

If you would like to call me I'm at 800-461-3477.

Look forward to your reply.

Regards - Darren MacFarlane
www.gypsumsales.com

ROOT & LEAF Co.

2635 SW Luradel Street
Portland, OR 97219
503-452-1593 Phone
503-452-1927 Fax

Fax

To: **Mr. Hermann H. Wittje** From: **John Wohler**

Fax: **847.607.3304** Date: **February 20, 2001**

Phone: Pages: **1** **(including cover)**

CC:

Re: **Iron Phosphate**

This is a strange request. I am looking for a mined source of ferric Phosphate. I have been searching the web and have been able to find many gem quality iron phosphates that seem to only be available in small quantities. We will need a larger source.

My company manufactures low impact slug and snail bait made with ferric phosphate as the active ingredient. We are looking for a natural mined source of the material so we can apply for an organic certification.

If you cannot help me can you please suggest some other resources for me.

Thank you for your help.

John Wohler
Cell 503 706-7961
jawohler@home.com

This fax is intended only for the use of the individual or entity named above. If you have received this transmission in error, please immediately notify me by telephone to arrange for return of the documents.

John Wohler

From: sdanner@ppi-far.org
Sent: Tuesday, February 20, 2001 12:59 PM
To: John Wohler
Subject: Re: iron Phosphate

Dear Mr. Wohler:

Thank you for your inquiry. I have checked with one of agronomists on staff and he suggests you might want to contact the following micronutrient company:

Frit Industries, Inc.
P. O. Box 1589
Ozark, Alabama 36361-1589
Phone: 334/774-2515
Fax: 334/774-9306

Another person who might know of other contacts is out of town at the moment. If I hear anything further from him, I will let you know.

Good luck with your search.

Sincerely,
Sheryl Danner
770/825-8062
sdanner@ppi-far.org

"John Wohler" <jawohler@home.com>

02/20/2001 02:01 PM

To: <ppi@ppi-ppic.org>
cc:
Subject: iron Phosphate

This is a strange request. I am looking for a mined source of ferric Phosphate. I have been searching the web and have been able to find many gem quality iron phosphates that seem to only be available in small quantities. We will need a larger source.

My company manufactures a low impact slug and snail bait made with ferric phosphate as the active ingredient. We are looking for a natural mined source of the material so we can apply for an organic certification.

If you can not help me can you please suggest some other resources for me.

Thank you for your help.

John Wohler
W. Neudorff GmbH KG
2635 SW Luradel Street
Portland, Oregon 97219
Phone 503 452-1593
Fax 503 452-1927
2/20/01

Cell 503 706-7961
jawohler@home.com

2/20/01

NEU1165M
SLUG AND SNAIL BAIT

Active Ingredient:	By weight
Iron phosphate	1.0%
Inert Ingredients:	99.0%
Total	100.0%

KEEP OUT OF REACH OF CHILDREN

CAUTION

NET WEIGHT XX LBS

EPA registration #67702-3 **EPA establishment #67702-WG-1**

FIRST AID
If in eyes: Flush eyes with plenty of water. Call a physician if irritation persists.

PRECAUTIONARY STATEMENTS - HOME AND GARDEN

Hazards to Humans and Domestic Animals: Caution. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling.

Environmental Hazards: For terrestrial uses. Do not apply directly to water. Do not contaminate water when disposing of equipment washwaters or rinsate.

PRECAUTIONARY STATEMENTS - COMMERCIAL AGRICULTURE

Hazards to Humans and Domestic Animals: Caution. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling.

Personal Protective Equipment (PPE) Requirements: Applicators and other handlers must wear: long-sleeved shirts and long pants; and shoes plus socks. Follow manufacturer's instructions for maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

Environmental Hazards: For terrestrial uses. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when cleaning equipment or disposing of equipment wastes.

DIRECTIONS FOR USE - HOME AND GARDEN
It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

DIRECTIONS FOR USE - COMMERCIAL AGRICULTURE
It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

Do not apply this product in a manner that will contact workers or other persons, either directly or through drift. Only protected workers may be in the area during application. For any requirements specific to your State or Tribe, consult the agency representative responsible for pesticide regulation.

AGRICULTURAL USE REQUIREMENTS

Use this product in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. This standard contains requirements for the protection of agricultural workers on farms, forests, nurseries, and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification, and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE), restricted-entry interval, and notification to workers. The requirements in this box only apply to uses of this product that are covered by the Worker Protection Standard (WPS).

There is a restricted-entry interval of zero hours for this product.

Conflicting Instructions: If the requirements of the WPS conflict with instructions listed elsewhere on this product label, users must obey the more protective requirements.

NON-AGRICULTURAL USE REQUIREMENTS

The requirements in this box apply to uses of this product that are not within the scope of the Worker Protection Standard for agricultural pesticides (40 CFR Part 170). The WPS applies when this product is used to produce agricultural plants on farms, forests, nurseries, or greenhouses.

There is a restricted-entry interval of zero hours for this product.

HOME AND GARDEN

HOW TO APPLY: The slug and snail bait granules should be scattered on the soil around or near the plants to be protected. For broadcast application standard broadcast spreaders may be used. For row application standard granular spreaders may be used. Apply bait evenly at approximately 1 lb. per 1000 square feet (0.15 oz., or about 1 level teaspoon, per square yard) and reapply as the bait is consumed or at least every two weeks. Do not place in piles. If the ground is dry, wet it before applying bait. The soil should be moist but with little or no standing water.

Reapply as the bait is consumed or at least every two weeks. Apply more heavily if the infestation is severe, if the area is heavily watered or after long periods of heavy rain. See specific directions for different plant types and for inside greenhouses.

WHEN TO APPLY: Evening is the best time to apply the bait, as slugs and snails travel and feed mostly by night or early morning.

WHERE TO APPLY: All likely areas of infestation should be treated, especially around the perimeter of garden plots because these pests travel into plant areas from daytime refuges. They favor damp places around vegetable plants such as beans, tomatoes, lettuce, cabbage, celery and squash. Other favorite areas are flower gardens, rockeries, hedges, dichondra lawns, citrus groves, ivy patches, and other ground cover where they obtain shelter by day.

COMMERCIAL AGRICULTURE

HOW TO APPLY: The slug and snail bait granules should be scattered on the soil around or near the plants to be protected. For broadcast application standard broadcast spreaders may be used. For row application standard granular spreaders may be used. Apply bait evenly at 24-44 lbs. per acre (apply the higher rates if the infestation is severe or if the area is heavily watered or after long periods of heavy rain). Reapply as the bait is consumed or at least every two weeks.

Do not place in piles. If the ground is dry, wet it before applying bait. The soil should be moist but with little or no standing water. See specific directions for different plant types and for inside greenhouses.

WHEN TO APPLY: Evening is the best time to apply the bait, as slugs and snails travel and feed mostly by night or early morning.

WHERE TO APPLY: All likely areas of infestation should be treated, especially around the perimeter of garden plots because these pests travel into plant areas from daytime refuge sites. They favor damp places around vegetable plants such as beans, tomatoes, lettuce, cabbage, celery and squash, and in weeds or ditches around field margins. Other favorite areas are flower gardens, rockeries, hedges, dichondra lawns, citrus groves, ivy patches, and other ground cover where they obtain shelter by day.

HOME AND GARDEN

Vegetables

The bait can be used to protect any vegetables from slug and snail damage, including (but not limited to): artichokes, asparagus, beans, beets, blackeyed peas, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, corn, cucumbers, eggplants, garlic, lettuce, onions, peas, peppers, potatoes, radishes, rutabagas, spinach, squash, Swiss chard, tomatoes and turnips. Scatter the bait around the perimeter of the vegetable plot at approximately 1 lb. per 1000 square feet to provide a protective "barrier" for slugs and snails entering the garden plot. If slugs or snails are inside the rows, then scatter the bait on the soil around the base of the plants and between the rows.

Fruits Including Citrus

The bait can be used to protect fruits from slugs and snails, including (but not limited to): apples, avocados, apricots, cherries, grapes, melons, peaches, plums, citrus, pears. For seedlings spread the bait around the base of the stem. Apply at 0.15 oz., or 1 level teaspoon, per square yard, in a 6 inch circular band around the base of the plants to be protected. For older trees, spread the bait around the base of the tree to intercept slugs and snails traveling to the trunk. Apply the bait at approximately 1 lb. per 1000 square feet for orchards using standard fertilizer granular spreaders.

Berries

The bait can be used to protect berries from slugs and snails, including (but not limited to): strawberries, blackberries, blueberries, boysenberries, loganberries, raspberries. Spread the bait around the perimeter of the plot to intercept slugs and snails migrating toward the berries. Use a rate of approximately 1 lb. per 1000 square feet and scatter by hand or with granular spreaders. If slugs and snails are already in the plots, then

carefully spread bait between the furrows near the base of the plants. For small plots, treat around the base of the plants to be protected. Do not spread over the entire area but apply selectively.

Outdoor Ornamentals

Scatter bait in a 6 inch circular band around the base of the plants to be protected at 0.15 oz., or 1 level teaspoon, per square yard. If plants are next to a grassy area, spread the bait between the ornamentals and the grass. Slugs and snails traveling to the plants will encounter the bait before reaching the plant. In these situations, scatter the bait around the perimeter of the plot at approximately 1 lb. per 1000 square feet to intercept snails and slugs traveling to the plot.

Greenhouses

Where slugs or snails are a problem in greenhouses, scatter the bait in the plant pots of plants being damaged or around pots on greenhouse benches. Apply about ½ teaspoon per 9 inch pot.

Lawns

The bait can be used to protect lawns. When slugs or snails are detected, scatter the bait at a rate of approximately 1 lb. per 1000 square feet. Scatter by hand or with a granular spreader where the slugs or snails are observed.

COMMERCIAL AGRICULTURE

Vegetables

The bait can be used to protect any vegetables from slug and snail damage, including (but not limited to): artichokes, asparagus, beans, beets, blackeyed peas, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, corn, cucumbers, eggplants, garlic, lettuce, onions, peas, peppers, potatoes, radishes, rutabagas, spinach, squash, Swiss chard, tomatoes and turnips. Scatter the bait around the perimeter of the vegetable plantings at the rate of 24-44 lbs per acre to provide a protective "barrier" for slugs and snails entering the vegetable plantings. If slugs or snails are inside the rows, then scatter the bait on the soil around the plants and between the rows.

Fruits Including Citrus

The bait can be used to protect fruits from slugs and snails, including (but not limited to): apples, avocados, apricots, cherries, grapes, melons, peaches, plums, nectarines, citrus, pears. For seedlings spread the bait around the base of the stem. Apply at 0.15 oz., or 1 level teaspoon, per square yard, in a 6 inch circular band around the base of the plants to be protected. For older trees, spread the bait around the base of the trees to intercept slugs and snails traveling to the trunk. Apply the bait at 24-44 lbs. per acre in orchards, using standard fertilizer granular spreaders. Use the higher rates for heavy infestations.

Berries

The bait can be used to protect berries from slugs and snails, including (but not limited to): strawberries, blackberries, blueberries, boysenberries, loganberries, raspberries. Spread the bait around the perimeter of the plot to intercept slugs and snails migrating toward the berries. Use a rate of 24-44 lbs. per acre and scatter by hand or with granular spreaders. If slugs and snails are already in the plots, then carefully spread bait between the furrows near the base of the plants. For small plots, treat around the base of the plants to be protected. Do not spread over the entire area but apply selectively.

Field Crops

The bait can be used to protect field and seed crops from slugs and snails, including: artichokes, beans, field corn, sweet corn, soybeans, sugarbeets, sugar cane, asparagus, beets, broccoli, Brussels sprouts, cabbage, carrots, cauliflower, cucumbers, lettuce, onions, peas, peppers, potatoes, radishes, strawberries, tomatoes, turnips and wheat. At the seedling and later stages, apply the bait between the rows and around the perimeter of the field. Scatter pellets at a rate of 24-44 lbs. per acre. Use the higher dosage rate for heavy infestations.

Outdoor Ornamentals

Scatter bait in a 6 inch circular band around the base of the plants to be protected at 0.15 oz., or 1 level teaspoon, per square yard. If plants are next to a grassy area, spread the bait between the ornamentals and the grass. Slugs and snails traveling to the plants will encounter the bait before reaching the plant. In these situations, scatter the bait around the perimeter of the plot at approximately 1 lb. per 1000 square feet to intercept snails and slugs traveling to the plot.

Greenhouses

Where slugs or snails are a problem in greenhouses, scatter the bait in the plant pots of plants being damaged or around pots on greenhouse benches. Apply about ½ teaspoon per 9 inch pot.

Outdoor Container-Grown Nursery Plants

Where slugs or snails are a problem in outdoor nurseries, scatter the bait in the plant containers at the rate of 1 tablespoon per container of plants being damaged, or scatter around the soil near the containers at the rate of 1 teaspoon per square yard (24-44 lbs. per acre).

Lawns and Grass Grown for Seed Production

The bait can be used to protect lawns and grass seed crops. When slugs or snails are detected, scatter the bait at a rate of approximately 1 lb. per 1000 square feet (24-44 lbs. per acre). Use the higher rate for heavy infestations. Scatter by hand or with a granular spreader where the slugs or snails are observed.

STORAGE AND DISPOSAL - HOME AND GARDEN
Do not contaminate water, food or feed by storage or disposal.

PESTICIDE STORAGE: Store this product in its original container and keep in a secure storage area out of reach of children and domestic animals.

CONTAINER DISPOSAL:
If empty: Do not reuse this container. Place in trash or offer for recycling if available.
If partly filled: Call your local solid waste agency or 1-800-CLEAN-UP for disposal instructions. Never place unused product down any indoor or outdoor drain.

STORAGE AND DISPOSAL - COMMERCIAL AGRICULTURE

Do not contaminate water, food or feed by storage or disposal.

PESTICIDE STORAGE: Store this product in its original container and keep in a secure storage area out of reach of children and domestic animals.

PESTICIDE DISPOSAL: Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility.

CONTAINER DISPOSAL: Completely empty drum, bag, box or tote into application equipment. Then dispose of empty drum, bag, box or tote in a sanitary landfill, or by incineration, or if allowed by State and local authorities, by burning. If burned, stay out of smoke.

The registrant may use one or both of these two optional statements, either:

"WARRANTY
Seller warrants that this product conforms to the chemical description on this label and is reasonably fit for purposes stated on this label only when used in accordance with directions under normal use conditions. This warranty does not extend to use of this product contrary to label directions, or under abnormal use conditions, or under conditions not reasonably foreseeable to seller. Buyer assumes all risk of any such use. Seller makes no other warranties, either expressed or implied."

or

"WARRANTY
The directions for use of this product are believed to be reliable and should be followed carefully. However, it is impossible to eliminate all risks inherently associated with use of this product. Crop injury, ineffectiveness or other unintended consequences may result because of such factors as timing and method of application, weather and crop conditions, presence of other materials, or other influencing factors, all of which are beyond the control of W. Neudorff GmbH KG and the Seller. Buyer and user acknowledge and assume all risks and liability resulting from the handling, storage and use of this material not in strict accordance with directions given herewith. In no case shall W. Neudorff GmbH KG or the Seller be liable for consequential, special, indirect, or incidental damages or losses resulting from the handling or use of this product. The foregoing is a condition of sale by W. Neudorff GmbH KG and is accepted as such by the Buyer.

or

OUR COMMITMENT TO YOUR SATISFACTION: If you are not happy with the way this product works in your garden, please let us know. We will be happy to replace the product or refund your money. Simply send your name, address and proof of

purchase to [insert name and address of supplemental registrant]."

[The following claims and product information, may or may not be presented on the product's label and labeling:
-**NOTE:** This package is sold by weight. Contents may have settled during shipment.
- US Patent number 5,437,870.
-This container is made from XX% recycled materials.
-The highly compressed granules (pellets) are easy to use, clean to handle and economical.
- Patented technology. Patented snail & (and) slug killer.
-Unique, patented formula.
-Easy-to-use (ready-to-use) (RTU) granular (pellet) formulation.
-Kills snails & (and) slugs.
-Treats (will treat) x,xxx sq. ft.
-Remains effective after rain or sprinkling.
-Proven snail & (and) slug killer (kill, control).
-Convenient. Easy-to-use. Requires no mixing, spraying, or special applicators.
-SATISFACTION GUARANTEED.
-Can be used in vegetable gardens.
-For use around vegetables, fruit trees, citrus, berries, ornamentals, shrubs, flowers, trees, lawns, gardens, and in greenhouses.
-Iron phosphate occurs naturally in soil.
-Can be used around domestic animals (pets) and wildlife.
-Read Entire Container Label Before Using This Product.
-The active ingredient in this product is exempt from the requirement for a tolerance when used as a molluscicide in or on all food commodities.
-For broadcast application standard broadcast applicators may be used, such as (but not limited to): Cyclone.
-For row application standard granular spreaders may be used, such as (but not limited to): Gandy and Clampco.
-Unconditionally guaranteed by [insert name of supplemental registrant].
-Baits and Kills
-For household home garden use.
-The slugs and snails controlled by this product include (but are not limited to): *Deroceras reticulatum* (Field slug), *Deroceras laeve* (Smooth slug), *Arion subfuscus* (Dusky slug), *Arion circumscriptus* (Gray garden slug), *Arion hortensis* (Black field slug), *Arion rufus* (Large red slug), *Arion ater* (Large black slug), *Limax flavus* (Spotted garden slug), *Limax tenellus* (Slender slug), *Ariolimax columbianus* (Banana slug), *Helix* spp., *Helicella* spp., and *Cepaea* spp.]
-Contains Ferramol™, a trademark of W. Neudorff GmbH KG
-Made with Ferramol™, a trademark of W. Neudorff GmbH KG

-Ferramol™ is a trademark of W. Neudorff GmbH KG, Germany.
-www.neudorff.de
-Manufactured under a license of W. Neudorff GmbH KG, Germany.

GENERAL INFORMATION (WHY SLUG AND SNAIL BAIT IS EFFECTIVE) - HOME AND GARDEN

This product is a unique blend of an iron phosphate active ingredient, originating from soil, with slug and snail bait additives. It is used as an ingredient in fertilizers. The bait which is not ingested by snails and slugs will degrade and become a part of the soil.

The bait is attractive to slugs and snails and lures them from their hiding places and plants. Ingestion, even in small amounts, will cause them to cease feeding. This physiological effect of the bait gives immediate protection to the plants even though the slugs and snails may remain in the area. After eating the bait, the slugs and snails cease feeding, become less mobile and begin to die within three to six days. Dead slugs and snails may not be visible as they often crawl away to secluded places to die. Plant protection will be observed in the decrease in plant damage.

This product is effective against a wide variety of slugs and snails and will give protection to home lawns, gardens, greenhouses, outdoor ornamentals, vegetable gardens, fruits, berries, citrus and crop plants. The bait can be scattered on the lawn or on the soil around any vegetable plants, flowers or fruit trees or bushes to be protected.

GENERAL INFORMATION (WHY SLUG AND SNAIL BAIT IS EFFECTIVE) - COMMERCIAL AGRICULTURE

This product is a unique blend of an iron phosphate active ingredient, originating from soil, with slug and snail bait additives. It is used as an ingredient in fertilizers. The bait which is not ingested by snails and slugs will degrade and become part of the soil in your garden.

The bait is attractive to slugs and snails and lures them from their hiding places and plants. Ingestion, even in small amounts, will cause them to cease feeding. This physiological effect of the bait gives immediate protection to the plants even though the slugs and snails may remain in the area. After eating the bait, the slugs and snails cease feeding, become less mobile and begin to die within three to six days. Dead slugs and snails may not be visible as they often crawl away to secluded places to die. Plant protection will be observed in the decrease in plant damage.

This product is effective against a wide variety of slugs and snails and will give protection to home lawns, gardens, greenhouses, outdoor ornamentals, vegetable gardens, fruits, berries, citrus, crop and seed plants. The bait can be scattered on the lawn or on the soil around any vegetable or seed crops, flowers or fruit trees or bushes to be protected.

Registrant: W. Neudorff GmbH KG, Postfach 1209, an der Mühle 3, D-31860 Emmerthal, Germany

FIRST CHOICE®

SLUGGO®

SNAIL and SLUG BAIT

THE ACTIVE INGREDIENT IN THIS PRODUCT IS EXEMPT FROM THE REQUIREMENT FOR A TOLERANCE WHEN USED AS A MOLLUSCICIDE IN OR ON ALL FOOD COMMODITIES.

READ ENTIRE CONTAINER LABEL BEFORE USING THIS PRODUCT

Active Ingredient:	
Iron Phosphate	1.0%
Inert Ingredients	99.0%
Total	100.0%

Net Weight 25 lbs.

EPA REG. NO. 67702-3-11656 EPA EST. NO. 67702-WG-1
CA REG. NO. 67702-3-AA-11656

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID: If in eyes: Flush eyes with plenty of water. Call a physician if irritation persists.

GENERAL INFORMATION
WHY FIRST CHOICE® SLUGGO SNAIL AND SLUG BAIT IS EFFECTIVE

This product is a unique blend of an iron phosphate active ingredient, originating from soil, with slug and snail bait additives. It is used as an ingredient in fertilizers. The bait which is not ingested by snails and slugs will degrade and become a part of the soil.

The bait is attractive to slugs and snails and lures them from their hiding places and plants. Ingestion, even in small amounts, will cause them to cease feeding. This physiological effect of the bait gives immediate protection to the plants, even though the slugs and snails may remain in the area. After eating the bait, the slugs and snails cease feeding, become less mobile and begin to die within three to six days. Dead slugs and snails may not be visible as they often crawl away to secluded places to die. Plant protection will be observed in the decrease in plant damage.

This product is effective against a wide variety of slugs and snails and will give protection to home lawns, gardens, greenhouses, outdoor ornamentals, vegetable gardens, fruits, berries, citrus, crop and seed plants. The bait can be scattered on the lawn or on the soil around any vegetable or seed crops, flowers or fruit trees to be protected.

**KILLS SLUGS AND SNAILS.
CAN BE USED AROUND DOMESTIC ANIMALS AND WILDLIFE.
IRON PHOSPHATE OCCURS NATURALLY IN SOIL.**

The slugs and snails controlled by this product include (but are not limited to): *Deroceras reticulatum* (Field slug), *Deroceras laeve* (Smooth slug), *Arion subfucus* (Dusky slug), *Arion circumscriptus* (Gray garden slug), *Arion hortensis* (Black field slug), *Arion rufus* (Large red slug), *Arion ater* (Large black slug), *Limax flavus* (Spotted garden slug), *Limax tenellus* (Slender slug), *Ariolimax columbianus* (Banana slug), *Helix* spp., *Helicella* spp., and *Cepaea* spp.

NON-AGRICULTURAL USE REQUIREMENTS

The requirements in this box apply to uses of this product that are not within the scope of the Worker Protection Standard for agricultural pesticides (40 CFR Part 170). The WPS applies when this product is used to produce agricultural plants on farms, forests, nurseries or greenhouses.
There is a restricted-entry interval of zero hours for this product.

AGRICULTURAL USE REQUIREMENTS

Use this product in accordance with its labeling and with the Worker Protection Standard, 40 CFR part 170. This standard contains requirements for the protection of agricultural workers on farms, forests, nurseries, and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification, and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE), restricted-entry interval, and notification to workers. The requirements in this box only apply to uses of this product that are covered by the Worker Protection Standard (WPS).
There is a restricted-entry interval of zero hours for this product.
Conflicting instructions: If the requirements of the WPS conflict with instructions listed elsewhere on this product label, users must obey the more protective requirements.

PRECAUTIONARY STATEMENTS
COMMERCIAL AGRICULTURE

Hazards to Humans and Domestic Animals: CAUTION. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling.
Personal Protective Equipment (PPE) Requirements: Applicators and other handlers must wear: long-sleeved shirts and long pants; and shoes plus socks. Follow manufacturers instructions for maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.
Environmental Hazards: For terrestrial uses. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when cleaning equipment or disposing of equipment wastes.

STORAGE AND DISPOSAL
COMMERCIAL AGRICULTURE

Do not contaminate water, food or feed by storage or disposal.
PESTICIDE STORAGE: Store this product in its original container and keep in a secure storage area out of reach of children and domestic animals.
PESTICIDE DISPOSAL: Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility.
CONTAINER DISPOSAL: Completely empty drum, bag, box or tote into application equipment. Then dispose of empty drum, bag, box or tote in a sanitary landfill, or by incineration, or if allowed by State and local authorities, by burning. If burned, stay out of smoke.

WARRANTY

Seller warrants that this product conforms to the chemical description on this label and is reasonably fit for purposes stated on this label only when used in accordance with directions under normal use conditions. This warranty does not extend to use of this product contrary to label directions, or under abnormal use conditions, or under conditions not reasonably foreseeable to seller. Buyer assumes all risk of any such use. Seller makes no other warranties, either expressed or implied.

DIRECTIONS FOR USE
COMMERCIAL AGRICULTURE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

Do not apply this product in a manner that will contact workers or other persons, either directly or through drift. Only protected workers may be in the area during application. For any requirements specific to your State or Tribe, consult the agency representative responsible for pesticide regulation.

COMMERCIAL AGRICULTURE

HOW TO APPLY: The slug and snail bait granules should be scattered on the soil around or near the plants to be protected. For broadcast application standard broadcast spreaders may be used, such as (but not limited to): Cyclone. For row application, standard granular spreaders may be used, such as (but not limited to): Gandy and Clampco. Apply bait evenly at 24-44 lbs. per acre (apply at the higher rates if the infestation is severe or if the area is heavily watered or after long periods of heavy rain). Reapply as the bait is consumed or at least every two weeks. Do not place in piles. If the ground is dry, wet it before applying bait. The soil should be moist but with little or no standing water. See specific directions for different plant types and for inside greenhouses.

WHEN TO APPLY: Evening is the best time to apply the bait, as slugs and snails travel and feed mostly by night or early morning.

WHERE TO APPLY: All likely areas of infestation should be treated, especially around the perimeter of garden plots because these pests travel into plant areas from daytime refuge sites. They favor damp places around vegetable plants such as beans, tomatoes, lettuce, cabbage, celery, and squash, and in weeds or ditches around field margins. Other favorite areas are flower gardens, rockeries, hedges, dichondra lawns, citrus groves, ivy patches, and other ground cover where they obtain shelter by day.

COMMERICAL AGRICULTURE

VEGETABLES

The bait can be used to protect any vegetables from slug and snail damage, including (but not limited to): artichokes, asparagus, beans, beets, blackeyed peas, broccoli, brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, corn, cucumbers, eggplants, garlic, lettuce, onions, peas, peppers, potatoes, radishes, rutabagas, spinach, squash, swiss chard, tomatoes, and turnips. Scatter the bait around the perimeter of the vegetable plantings at the rate of 24-44 lbs. per acre to provide a protective "barrier" for slugs and snails entering the vegetable plantings. If slugs or snails are inside the rows, then scatter the bait on the soil around the plants and between the rows.

FRUITS INCLUDING CITRUS

The bait can be used to protect fruits from slugs and snails, including (but not limited to): apples, avocados, apricots, cherries, grapes, melons, peaches, plums, nectarines, citrus, pears. For seedlings spread the bait around the base of the stem. Apply at 0.15 oz., or 1 level teaspoon, per square yard, in a 6 inch circular band around the base of the plants to be protected. For older trees, spread the bait around the base of the trees to intercept slugs and snails traveling to the trunk. Apply the bait at 24-44 lbs. per acre in orchards using standard fertilizer granular spreaders. Use the higher rates for heavy infestations.

BERRIES

The bait can be used to protect berries from slugs and snails, including (but not limited to): strawberries, blackberries, blueberries, boysenberries, loganberries, raspberries. Spread the bait around the perimeter of the plot to intercept slugs and snails migrating toward the berries. Use a rate of 24-44 lbs. and scatter by hand or with granular spreaders. If slugs and snails are already in the plots, then carefully spread bait between the furrows near the base of the plants. For small plots, treat around the base of the plants to be protected. Do not spread over the entire area, but apply selectively.

FIELD CROPS

The bait can be used to protect field and seed crops from slugs and snails, including: artichokes, beans, field corn, sweet corn, soybeans, sugar beets, sugar cane, asparagus, beets, broccoli, brussels sprouts, cabbage, carrots, cauliflower, cucumbers, lettuce, onions, peas, peppers, potatoes, radishes, strawberries, tomatoes, turnips, and wheat. At the seedling and later stages, apply the bait between the rows and around the perimeter of the field. Scatter pellets at a rate of 24-44 lbs. per acre. Use the higher dosage rate for heavy infestations.

OUTDOOR ORNAMENTALS

Scatter bait in a 6 inch circular band around the base of the plants to be protected at 0.15 oz., or 1 level teaspoon, per square yard. If plants are next to a grassy area, spread the bait between the ornamentals and the grass. Slugs and snails traveling to the plants will encounter the bait before reaching the plant. In these situations, scatter the bait around the perimeter of the plot at approximately 1 lb. per 1,000 square feet to intercept snails and slugs traveling to the plot.

GREENHOUSES

Where snails or slugs are a problem in greenhouses, scatter the bait in the plant pots of plants being damaged or around pots on greenhouse benches. Apply about ½ teaspoon per 9 inch pot.

OUTDOOR CONTAINER-GROWN NURSERY PLANTS

Where slugs or snails are a problem in outdoor nurseries, scatter the bait in the plant containers at the rate of 1 teaspoon per container of plants being damaged, or scatter around the soil near the containers at the rate of 1 teaspoon per square yard (24-44 lbs. per acre).

LAWNS AND GRASS GROWN FOR SEED PRODUCTION

The bait can be used to protect lawns and grass seed crops. When slugs or snails are detected, scatter the bait at a rate of approximately 1 lb. per 1,000 square feet (24-44 lbs. per acre). Use the higher rate for heavy infestation. Scatter by hand or with a granular spreader where the slugs or snails are observed.

NOTE: This package is sold by weight. Contents may have settled during shipment.

-US Patent number 5,437,870
-The highly compressed pellets are easy to use, clean to handle and economical.
-Patented technology. Patented snail and slug killer.
-Easy-to-use granular formulation.
-Treats 25,000 sq. ft.
-Remains effective after rain or sprinkling.
-Proven snail and slug kill, control.
-Convenient. Easy-to-use. Requires no mixing, spraying, or special applicators.
-SATISFACTION GUARANTEED
-Can be used in vegetable gardens.
-For use around vegetables, fruit trees, citrus, berries, ornamentals, shrubs, flowers, trees, lawns, gardens, and in greenhouses.

Sold under a license of W. Neudorff GmbH KG, Germany.

MADE IN GERMANY

Manufactured for:
WESTERN FARM SERVICE, INC.
P.O. BOX 1168
FRESNO, CA 93711
(559) 436-2800

First Choice® and Sluggo® are registered trademarks of Western Farm Service, Inc.

6/01(01) dhf

GENERAL INFORMATION

WHY SLUG AND SNAIL BAIT IS EFFECTIVE

This product is a unique blend of an iron phosphate active ingredient, originating from soil, with slug and snail bait additives. It is used as an ingredient in fertilizers. The bait which is not ingested by snails and slugs will degrade and become part of the soil.

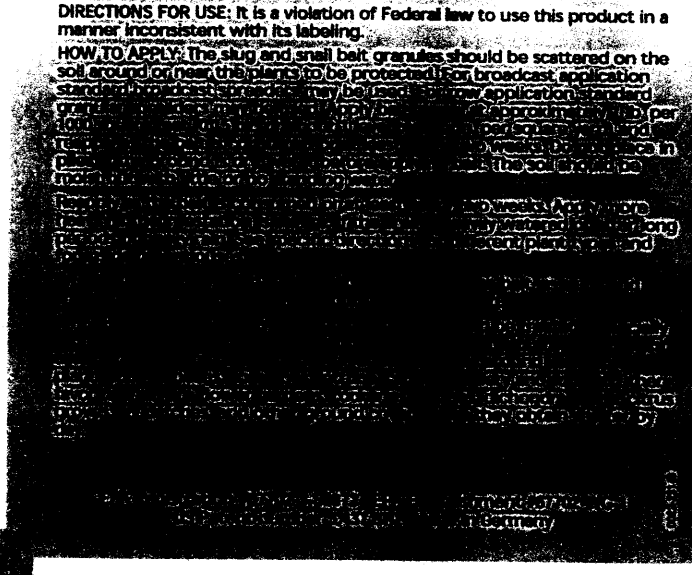
The bait is attractive to slugs and snails and lures them from their hiding places and plants. Ingestion, even in small amounts, will cause them to cease feeding. This physiological effect of the bait gives immediate protection to the plants even though the slugs and snails may remain in the area. After eating the bait, the slugs and snails cease feeding, become less mobile and begin to die within three to six days. Dead slugs and snails may not be visible as they often crawl away to secluded places to die. Plant protection will be observed in the decrease in plant damage.

This product is effective against a wide variety of slugs and snails and will give protection to lawns, gardens, greenhouses, outdoor ornamentals, vegetable gardens, fruits, berries, citrus and crop plants. The bait can be scattered on the lawn or on the soil around any vegetable plants, flowers or fruit trees or bushes to be protected.

The slugs and snails controlled by this product include (but are not limited to): Deroceras reticulatum (Field slug), Deroceras laeve (Smooth slug), Arion subfuscus (Dusky slug), Arion circumscriptus (Gray garden slug), Arion hortensis (Black field slug), Arion rufus (Large red slug), Arion ater (Large black slug), Limax flavus (Spotted garden slug), Limax tenellus (Slender slug), Ariolimax columbianus (Banana slug), Helix spp., Helicella spp. and Cepaea spp.

DIRECTIONS FOR USE: It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

HOW TO APPLY: The slug and snail bait granules should be scattered on the soil around or near the plants to be protected. For broadcast application [illegible]



Greenhouses: Where slugs or snails are a problem in greenhouses, scatter the bait in the plant pots of plants being damaged or around pots on greenhouse benches. Apply about ½ teaspoon per 9-inch pot.

Lawns: The bait can be used to protect lawns. When slugs or snails are detected, scatter the bait at a rate of approximately 1 lb. per 1000 square feet. Scatter by hand or with a granular spreader where the slugs or snails are observed.

Satisfaction Guaranteed

FIRST AID: If in eyes: Flush eyes with plenty of water. Call a physician if irritation persists.

PRECAUTIONARY STATEMENTS: Hazards to Humans and Domestic Animals: Caution. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling.

Environmental Hazards: For terrestrial uses. Do not apply directly to water. Do not contaminate water when disposing of equipment washwaters or rinsates.

STORAGE AND DISPOSAL:
Do not contaminate water, food or feed by storage or disposal.

PESTICIDE STORAGE:
Store this product in its original container and keep in a secure storage area out of reach of children and domestic animals.

CONTAINER DISPOSAL:
Do not reuse container. Securely wrap original container in several layers of newspaper and discard in trash.

Escar-Go!®

SLUG AND SNAIL BAIT

Escar-Go!®

SLUG AND SNAIL BAIT

Kills snails and slugs.
Can be used around domestic animals and wildlife.
Iron phosphate occurs naturally in soil.

Active Ingredient:	By weight
Iron phosphate	1.0%
Inert Ingredients	99.0%
Total	100.0%

KEEP OUT OF REACH OF CHILDREN

CAUTION

NET WEIGHT 2¼ LBS
Treats 2,250 sq. ft.a

Vegetables: The bait can be used to protect any vegetables from slug and snail damage, including (but not limited to): artichokes, asparagus, beans, beets, blackeyed peas, broccoli, Brussel sprouts, cabbage, cantaloupe, carrots, cauliflower, corn, cucumbers, eggplants, garlic, lettuce, onions, peas, peppers, potatoes, radishes, spinach, squash, Swiss chard, tomatoes and turnips. Scatter the bait around the perimeter of the vegetable plot at approximately 1 lb. per 1000 square feet to provide a protective "barrier" for plants and when entering the garden slugs or snails or rows, then apply the soil around the of the plants and between the rows.

Fruits include citrus: The bait used to protect fruits slugs and snails including (but not limited to): apples, avocados, apricots, cherries, grapes, melons, citrus, peaches, pears, plums. For seedlings spread the bait around the base of the stem. Apply at 0.15 oz, or 1 level tea-spoon, per square yard, in a 6 inch circular band around the base of the plants to be protected. For older trees, spread the bait around the base of the tree to intercept slugs and snails traveling to the trunk. Apply the bait at approximately 1 lb. per 1000 square feet for orchards using standard fertilizer granular spreaders. [illegible]

SLUGGO® SNAIL AND SLUG BAIT

2(ee) Recommendation

For use in all states where crop and pest(s) exist and where 2(ee) recommendations are recognized.

FIRST CHOICE®

For Agricultural or Commercial Use Only
EPA Reg. No. 67702-3-11656 Emergency Calls: 800-331-3148

IT IS A VIOLATION OF FEDERAL LAW TO USE THIS PRODUCT IN A MANNER INCONSISTENT WITH ITS LABELING.
FOR USE ONLY IN THE STATE OF: OREGON

[redacted]

FIELD CROPS Wheat, clover **GRASS SEED** Ryegrass, Bentgrass, Bluegrass, Fescue grass seed	**Slugs and Snails including but not limited to:** *Deroceras reticulatum* (Field Slug) *Deroceras laeve* (Smooth slug) *Arion subfucas* (Dusky slug) *Arion circumscriptus* (Gray garden slug) *Arion hortensis* (Black field slug) *Aropm* rufus (Large red slug) *Arion ater* (Large black slug) *Limax flavus* (Spotted garden slug) *Limax tenellus* (Slender slug) *Ariolimax columbianus* (Banana slug) *Helilx* spp. *Helicella* spp. *Cepaea* spp.	10-44 lbs/A

DIRECTIONS FOR USE:
First Choice Sluggo Snail and Slug Bait is a unique blend of iron phosphate and bait additives. For control of slugs and snails, use 10 to 44 pounds of formulated product per acre as noted in above label. Product may be applied by hand broadcast equipment or standard ground equipment.

Important:
This product bulletin contains new or additional directions for use which are recommended by Western Farm Service Inc .
All applicable directions, restrictions and precautions on the EPA registered label are to be followed.
Personal protective equipment and reentry intervals on the basic label must be followed.

2(ee) Recommendation 10/28/02

Western Farm Service, Inc.
P.O. Box 1168
Fresno, CA 93715

FIRST CHOICE® is a registered trademark of Western Farm Service, Inc.
SLUGGO® is a registered trademark of W. Neudorff GmbH KG.

SLUGGO® SNAIL AND SLUG BAIT

FIRST CHOICE®

2(ee) Recommendation

For use in all states where crop and pest(s) exist and where 2(ee) recommendations are recognized.

For Agricultural or Commercial Use Only
EPA Reg. No. 67702-3-11656 Emergency Calls: 800-331-3148

IT IS A VIOLATION OF FEDERAL LAW TO USE THIS PRODUCT IN A MANNER INCONSISTENT WITH ITS LABELING.
FOR USE ONLY IN THE STATES OF: CA and AZ

VEGETABLES **Including, but not limited to:** (artichokes, asparagus, beans, beets, black-eyed peas, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, corn, cucumbers, eggplant, garlic, lettuce, onions, peas, peppers, potatoes, radishes, rutabagas, spinach, squash, Swiss chard, tomatoes, and turnips) **FRUITS INCLUDING CITRUS** **but not limited to:** (apples, avocados, apricots, cherries, grapes, melons, peaches, plums, nectarines, citrus, and pears) **BERRIES Including, but not limited to:** (strawberries, blackberries, blueberries, boysenberries, loganberries, and raspberries) **FIELD CROPS** **Including but not limited to:** beans, field corn, sweet corn, soybeans, sugar beets, sugar cane, wheat)	**Slugs and Snails including but not limited to:** *Deroceras reticulatum* (Field slug) *Deroceras laeve* (Smooth slug) *Arion subfucas* (Dusky slug) *Arion circumscriptus* (Gray garden snail) *Arion hortensis* (Black field slug) *Arion rufus* (Large red slug) *Arion ater* (Large black slug) *Limax flavus* (Spotted garden slug) *Limax tenellus* (Slender slug) *Ariolimax columbianus* (Banana slug) *Helix* spp. *Helicella* spp. *Cepaea* spp.	20 lbs/A

DIRECTIONS FOR USE:
First Choice Sluggo Snail and Slug Bait is a unique blend of iron phosphate and bait additives. For control of slugs and snails, use a minimum of 20 pounds of formulated product per acre as noted in above label. Product may be applied by hand broadcast equipment or standard ground equipment.

Important:
This product bulletin contains new or additional directions for use which are recommended by Western Farm Service Inc .
All applicable directions, restrictions and precautions on the EPA registered label are to be followed.
Personal protective equipment and reentry intervals on the basic label must be followed.

2(ee) Recommendation

Western Farm Service, Inc.
P.O. Box 1168
Fresno, CA 93715

FIRST CHOICE® is a registered trademark of Western Farm Service, Inc.
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MONTEREY

SLUGGO® - AG

KILLS SNAILS & SLUGS

- **Remains Effective After Rain Or Sprinkling**
- **Easy-To-Use Granular Formulation**
- **Can Be Used Around Pets & Wildlife**

ACTIVE INGREDIENTS:

Iron Phosphate	1.0%
INERT INGREDIENTS:	99.0%
TOTAL	100.0%

EPA Reg. No. 67702-3-84705 **MADE IN GERMANY**
EPA Est. No. 48498-CA-1 **U.S. Patent Number 5,437,870**
® Registered Trademark of Western Farm Service, Inc.
Sold under a license of W. Neudorff GmbH, Germany

KEEP OUT OF REACH OF CHILDREN

CAUTION

FIRST AID

IF IN EYES: Flush eyes with plenty of water. Call a physician if irritation persists.

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

CAUTION. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling.

Personal Protective Equipment (PPE) Requirements:
Applicators and other handlers must wear: long-sleeved shirts and long pants; and shoes plus socks. Follow manufacturer's instructions for maintaining PPE. If no such instructions for washables, use detergent and hot water. Keep and wash PPE separately from other laundry.

ENVIRONMENTAL HAZARDS

For terrestrial uses. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Do not contaminate water when cleaning equipment or disposing of equipment washes.

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

Do not apply this product in a manner that will contact workers or other persons, either directly or through drift. Only protected workers may be in the area during application. For any requirements specific to your State or Tribe, consult the agency representative responsible for pesticide regulation.

AGRICULTURAL USE REQUIREMENTS
Use this product in accordance with its labeling and with the Worker Protection Standard, 40 CFR Part 170. This standard contains requirements for the protection of agricultural workers on farms, forests, nurseries, and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification, and emergency assistance. It also contains specific instructions and exceptions pertaining to the statements on this label about personal protective equipment (PPE), restricted-entry interval, and notification to workers. The requirements in this box only apply to uses of this product that are covered by the Worker Protection Standard (WPS).

There is a restricted-entry interval of zero hours for this product.

Conflicting Instructions: If the requirements of the WPS conflict with instructions listed elsewhere on this product label, users must obey the more protective requirements.

NON-AGRICULTURAL USE REQUIREMENTS
The requirements in this box apply to uses of this product that are not within the scope of the Worker Protection Standard for agricultural pesticides (40 CFR Part 170). The WPS applies when this product is used to produce agricultural plants on farms, forests, nurseries, or greenhouses.

There is a restricted-entry interval of zero hours for this product.

GENERAL INFORMATION
(Why SLUGGO® - AG Is Effective)

This product is a unique blend of an iron phosphate active ingredient, originating from soil, with slug and snail bait additives. It is used as an ingredient in fertilizers. The bait which is not ingested by snails and slugs will degrade and become part of the soil in your garden.

The bait is attractive to slugs and snails and lures them from their hiding places and plants. Ingestion, even in small amounts, will cause them to cease feeding. This physiological effect of the bait gives immediate protection to the plants even though the slugs and snails may remain in the area. After eating the bait, the slugs and snails cease feeding, become less mobile and begin to die within three to six days. Dead slugs and snails may not be visible as they often crawl away to secluded places to die. Plant protection will be observed in the decrease in plant damage.

This product is effective against a wide variety of slugs and snails and will give protection to home lawns, gardens, greenhouses, outdoor ornamentals, vegetable gardens, fruits, berries, citrus, crop and seed plants. The bait can be scattered on the lawn or on the soil around any vegetable or seed crops, flowers or fruit trees or bushes to be protected.

The slugs and snails controlled by this product include (but are not limited to): *Deroceras reticulatum* (Field slug), *Deroceras laeve* (Smooth slug), *Arion subfuscus* (Dusky slug), *Arion circumscriptus* (Gray garden slug), *Arion hortensis* (Black field slug), *Arion rufus* (Large red slug), *Arion ater* (Large black slug), *Limax flavus* (Spotted garden slug), *Limax tenellus* (Slender slug), *Ariolimax columbianus* (Banana slug), *Helix* spp., *Helicella* spp., and *Cepaea* spp.

HOW TO APPLY:

The slug and snail bait granules should be scattered on the soil around or near the plants to be protected. For broadcast application, standard broadcast applicators may be used such as (but not limited to): Cyclone. For row application, standard granular spreaders may be used, such as (but not limited to): Gandy and Clampco. Apply bait evenly at 24-44 lbs. per acre (apply the higher rates if the infestation is severe or if the area is heavily watered or after long periods of heavy rain). Reapply as the bait is consumed or at least every two weeks. Do not place in piles. If the ground is dry, wet it before applying bait. The soil should be moist with little or no standing water. See specific directions for different plant types and for inside greenhouses.

WHEN TO APPLY:

Evening is the best time to apply the bait, as slugs and snails travel and feed mostly by night or early morning.

WHERE TO APPLY:

All likely areas of infestation should be treated, especially around the perimeter of garden plots because these pests travel into plant areas from daytime refuge sites. They favor damp places around vegetable plants such as beans, tomatoes, lettuce, cabbage, celery and squash, and in weeds or ditches around field margins. Other favorite areas are flower gardens, rockeries, hedges, dichondra lawns, citrus groves, ivy patches and other ground cover where they obtain shelter by day.

VEGETABLES: The bait can be used to protect any vegetables from slug and snail damage, including (but not limited to): artichokes, asparagus, beans, beets, blackeyed peas, broccoli, Brussels sprouts, cabbage, cantaloupe, carrots, cauliflower, corn, cucumbers, eggplants, garlic, lettuce, onions, peas, peppers, potatoes, radishes, rutabagas, spinach, squash, Swiss chard, tomatoes and turnips. Scatter the bait around the perimeter of the vegetable plantings at the rate of 24-44 lbs. per acre to provide a protective "barrier" for slugs and snails entering the vegetable plantings. If slugs or snails are inside the rows, then scatter the bait on the soil around the plants and between the rows.

FRUITS Including Citrus: The bait can be used to protect fruits from slugs and snails, including (but not limited to): apples, avocados, apricots, cherries, grapes, melons, peaches, plums, nectarines, citrus, pears. For seedlings, spread the bait around the base of the stem. Apply at 0.15 oz., or 1 level teaspoon, per square yard, in a 6-inch circular band around the base of the plants to be protected. For older trees, spread the bait around the base of the trees to intercept slugs and snails traveling to the trunk. Apply the bait at 24-44 lbs. per acre in orchards using standard fertilizer granular spreaders. Use the higher rates for heavy infestations.

BERRIES: The bait can be used to protect berries from slugs and snails, including (but not limited to): strawberries, blackberries, blueberries, boysenberries, loganberries, raspberries. Spread the bait around the perimeter of the plot to intercept slugs and snails migrating toward the berries. Use a rate of 24-44 lbs. per acre and scatter by hand or with granular spreaders. If slugs and snails are already in the plots, then carefully spread bait between the furrows near the base of the plants. For small plots, treat around the base of the plants to be protected. Do not spread over the entire area, but apply selectively.

FIELD CROPS: The bait can be used to protect field and seed crops from slugs and snails, including: artichokes, beans, field corn, sweet corn, soybeans, sugarbeets, sugar cane, asparagus, beets, broccoli, Brussels sprouts, cabbage, carrots, cauliflower, cucumbers, lettuce, onions, peas, peppers, potatoes, radishes, strawberries, tomatoes, turnips and wheat. At the seedling and later stages, apply the bait between the rows and around the perimeter of the field. Scatter pellets at a rate of 24-44 lbs. per acre. Use the higher dosage rate for heavy infestations.

OUTDOOR ORNAMENTALS: Scatter bait in a 6-inch circular band around the base of the plants to be protected at 0.15 oz., or 1 level teaspoon, per square yard. If plants are next to a grassy area, spread the bait between the ornamentals and the grass. Slugs and snails traveling to the plants will encounter the bait before reaching the plant. In these situations, scatter the bait around the perimeter of the plot at approximately 1 lb. per 1,000 square feet to intercept snails and slugs traveling to the plot.

GREENHOUSES: Where slugs or snails are a problem in greenhouses, scatter the bait in the plant pots of plants being damaged or around pots on greenhouse benches. Apply about 1/2 teaspoon per 9 inch pot.

OUTDOOR CONTAINER-GROWN NURSERY PLANTS: Where slugs or snails are a problem in outdoor nurseries, scatter the bait in the plant containers, at the rate of 1 tablespoon per container of plants being damaged, or scatter around the soil near the containers at the rate of 1 teaspoon per square yard (24-44 lbs. per acre).

LAWNS and GRASS GROWN FOR SEED PRODUCTION: The bait can be used to protect lawns and grass seed crops. When slugs or snails are detected, scatter the bait at a rate of approximately 1 lb. per 1,000 square feet (24-44 lbs. per acre). Use the higher rate for heavy infestations. Scatter by hand or with a granular spreader where slugs or snails are observed.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal. **Pesticide Storage:** Store this product in its original container and keep in a secure storage area out of reach of children and domestic animals. **Pesticide Disposal:** Wastes resulting from the use of this product may be disposed of on site or at an approved waste disposal facility. **Container Disposal:** Completely empty drum, bag, box or tote into application equipment. Then dispose of empty drum, bag, box or tote in a sanitary landfill, or by incineration, or if allowed by State and local authorities, by burning. If burned, stay out of smoke.

WARRANTY: Seller warrants that this product conforms to the chemical description on this label and is reasonably fit for purposes stated on this label only when used in accordance with directions under normal use conditions. This warranty does not extend to use of this product contrary to label directions, or under abnormal use conditions, or under conditions not reasonably foreseeable to seller. Buyer assumes all risk of any such use. Seller makes no other warranties, either express or implied.

NET WEIGHT: 40 LBS / 18 kgs

Distributed By:
MONTEREY
LAWN AND GARDEN PRODUCTS, INC.
P.O. Box 35000 Fresno, CA (559) 499-2100
www.montereylawn.com

(UPC Code)

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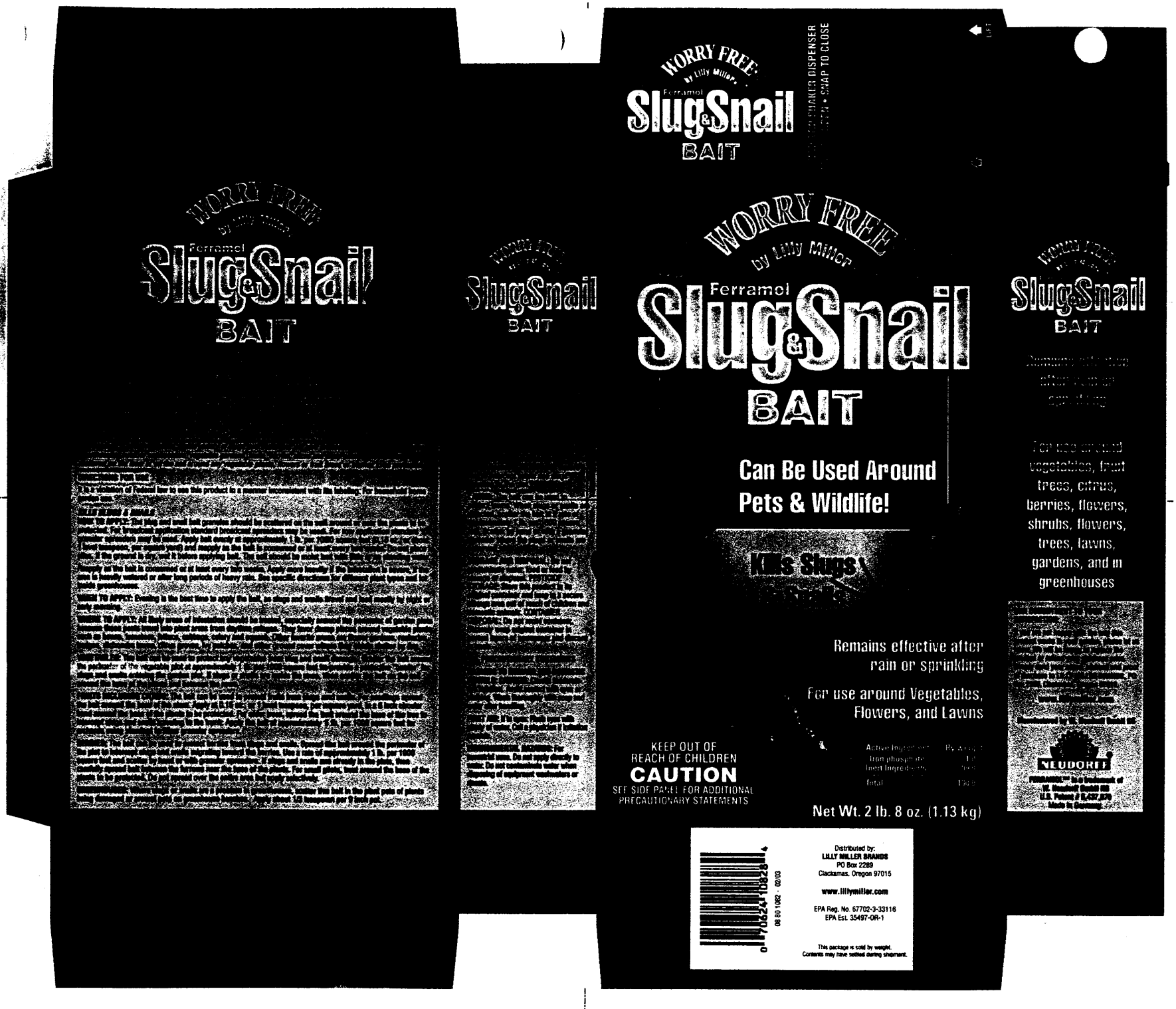
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BAIT
Can Be Used Around
Pets & Wildlife!
Kills Slugs
Remains effective after
rain or sprinkling
For use around Vegetables,
Flowers, and Lawns
KEEP OUT OF
REACH OF CHILDREN
CAUTION
SEE SIDE PANEL FOR ADDITIONAL
PRECAUTIONARY STATEMENTS
Net Wt. 2 lb. 8 oz. (1.13 kg)
Distributed by:
LILLY MILLER BRANDS
PO Box 2289
Clackamas, Oregon 97015
www.lillymiller.com
EPA Reg. No. 67702-3-33116
EPA Est. 35497-OR-1
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WORRY FREE
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Ferramol
Slug&Snail
BAIT
For use around
vegetables, fruit
trees, citrus,
berries, flowers,
shrubs, flowers,
trees, lawns,
gardens, and in
greenhouses
NEUDORFF

SAFETY DATA SHEET
91/155/EEC

Dr. Paul Lohmann
Chemische Fabrik seit 1806 GmbH KG

Print date: 17.08.1998

Version of: 09.01.1998

Trade name: Ferric Phosphate

1. Name of company

Manufacturer/supplier
Dr. Paul Lohmann GmbH KG
Hauptstr. 2
D-31860 Emmerthal

Tel.: (49) 5155 - 630
Fax: (49) 5155 - 63118
Telex: 92858 lohma d

Contact department: QC/Kn

2. Composition/information on ingredients

CAS-No.	Name of substance	Hazard symbol	R-phrases
10045-86-0	Ferric Phosphate		
Chemical characterisation (preparation)		EINECS-No.	Code-No.
FePO4*xH2O		233-149-7	H33

3. Hazard risks

Specific information on human and environmental hazards

Not classified as hazardous. When used in accordance with good manufacturing practices it should present no significant hazard to users.

4. First aid measures

General informations

Change clothings if contaminated with the product.

Inhalation

Remove to fresh air.

Skin contact

Wash with soap and plenty of water.

Eye contact

Flush with copious quantities of water and obtain medical attention.

Ingestion

Refer for medical treatment.

Advice for physicians

None

5. Fire-fighting measures

Suitable extinguishing media

Product itself is non-combustible; use any means suitable for extinguishing

Dr. Paul Lohmann GmbH D-31860 Emmerthal
SAFETY DATA SHEET 91/155/EEC

Trade name Ferric Phosphate

5. Fire-fighting measures (continued)

6. Accidental spillage measures

Personal precautions

See under section 8.

Clean up and disposal measures

Spills should be mechanically collected in a suitable container for proper disposal or recovery. Wash area with sufficient water.
Avoid raising dust.

7. Handling and storage

Advice on safe handling

Usual safety precautions should be observed to ensure safe handling.
Adequate exhaust system in areas where workers are exposed to dusting.

Further information on storage conditions

To be kept in well-closed containers in a cool and dry place.

8. Exposure controls/personal protection

Requirements for technical facilities

Provision of adequate exhaust system in working areas.

General protective and hygienic measures

Wash thoroughly after handling.

Respiratory protection

Dust mask

Hand protection

Protective gloves

Eye protection

Goggles

Body protection

Rubber or plastic apron.

9. Physical and chemical properties

Form	Powder	
Colour	Yellowish to buff	
Odour	Practically odourless	
Flash point		n.d. °C
Ignition temperature		n.d. °C
Upper explosion limit		n.d. Vol %
Lower explosion limit		n.d. Vol %

Dr. Paul Lohmann GmbH D-31860 Emmerthal
SAFETY DATA SHEET 91/155/EEC

Trade name Ferric Phosphate

9. Physical and chemical properties (continued)

Further information

Practically insoluble in water.
The product is non-combustible.
n.d. = no data available

10. Stability and reactivity

no relevant data known

11. Toxicological information

Acute toxicity
For classification relevant values

no relavent data known

Subacute / chronic toxicity
Longterm tests

no information available

Human experience

no information available

12. Ecological information

Information on elimination (persistancy and biodegradability)

Environmental effects

Water hazard class: 1 (see section 15)

Ecotoxical effects
Aquatic toxicity

no relevant data available

Effect on water treatment process

no relevant data available

Further information

no relevant data available

13. Disposal considerations

Product disposal

As permitted under appropriate Federal, State, and Local Regulations.

Contaminated packaging

As permitted under appropriate Federal, State, and Local Regulations.

Recommended cleansing agent

no information available

Dr. Paul Lohmann GmbH D-31860 Emmerthal
SAFETY DATA SHEET 91/155/EEC

Print date: 17.08.1998 Version of: 09.01.1998 page 4 of 4

Trade name Ferric Phosphate

13. Disposal considerations (continued)

14. Transport information

ADR/RID-GGVS/E class	Figure	Hazard-No.	Substance-No.
ADNR class	Figure	Categorie	
IMDG/GGVSee class	UN-No.	EMS-No.	MFAC-No.
ICAO/IATA class	UN-No.		

Further information

Not classified for conveyance.

15. Regulatory information

Labelling according to EEC Directives

National regulations

Water hazard class (Germany)

- 1 - weakly hazardous to water

Own classification

16. Other information

no information available

The data provided herein are based upon information believed to be reliable. This information is not to be considered as a warranty or quality specification and we do not assume any responsibility, including injury or damage, resulting from its use as such or in combination with other materials.

Toxicity of Iron Phosphate

CAS#: 10045-86-0

Synonyms: Ferric phosphate; Fe(+3) phosphate; Ferric orthophosphate; Iron (III) phosphate; Phosphoric acid, iron(3+) salt (1:1)

Summary: Almost no toxicity information is available for iron phosphate. Consequently, potential adverse health effects from exposure to this form of inorganic iron are inferred from related inorganic iron species. All forms of inorganic iron salts have low toxicity by oral exposure, whether from single, acute exposure or from repeated, chronic exposure (Stokinger, 1981). Iron phosphate is not expected to be absorbed through the skin in toxic amounts and, generally, would present an inhalation hazard only as a nuisance dust (see repeat dose section for inhalation effects).

Many toxicity summaries of iron compounds indicate that inorganic compounds of iron have low acute toxicity. Moreover, the water insoluble forms which have been tested have even lower toxicity because they are less likely to be absorbed from the gastrointestinal tract. Because of it's very low solubility, iron phosphate is not expected to be absorbed in large quantities from the gastrointestinal tract into the systemic circulation. Consequently, it may be concluded that iron phosphate will have low acute toxicity.

Very little chronic toxicity data is available for iron phosphate. Based on other forms of iron, it is possible that heavy, prolonged inhalation exposure to this compound might cause siderosis, (iron pigmentation) of the lungs, liver, spleen, and, possibly, other organs. This syndrome is generally benign, even in the lungs and requires years of heavy exposure to develop. Thus, iron phosphate is considered to presents a low order of toxicity by chronic inhalation exposure. Regarding chronic oral exposure, iron phosphate has low toxicity. Iron phosphate has been a GRAS (generally recognized as safe) substance for many years, used nutritionally to fortify bread and other foods for human consumption.

Symptoms of Overexposure: In cases of massive acute overdose (by ingestion) to iron compounds, symptoms may include; vomiting, hemorrhagic gastritis, and diarrhea in an initial phase (Ellenhorn, 1988). This may be followed by a period of apparent recovery that leads to a third phase characterized by hematemesis, perforation of the gastrointestinal tract, lethargy, coma, convulsions, pulmonary edema, cyanosis, and vascular collapse. Metabolic acidosis accompanies these symptoms and liver and kidney failure occur in severe cases. Death may ensue if the dose is large enough. For soluble iron salts (e.g., ferrous sulfate), the lethal dose for a human is estimated to be between 180 and 300 mg/kg. Note that higher (perhaps much higher) doses might be required to elicit these effects for an iron compound that is as insoluble as iron phosphate.

Information Sources: Although a great deal of toxicity literature is available for iron compounds in general, almost none is available for iron phosphate specifically. This compound was not found in such databases as RTECS (Registry for the Toxic Effects of Chemical Substances) (1995). An HSDB (Hazardous Substances Databank) file was found for iron phosphate but it also did not contain specific toxicity information for this compound (1995). NIOSHTIC contained a small amount of iron phosphate-specific information. Several summaries on general iron toxicity were found, including; Patty's (both the 3rd and 4th editions), Bryson (1984), Ellenhorn (1988), Goodman and Gilman (1985), Gosselin (1984), Goyer (1991), and the TLV Documentation (ACGIH, 1991).

Acute Toxicity: No acute toxicity information, not even an LD50, was located for iron phosphate. Thus, acute toxicity of this form of iron must be inferred from knowledge of other iron compounds.

Iron is an essential trace element so some exposure and absorption via the diet is required for normal health. At low to moderate oral doses, the water solubility of the various iron salts determines their bioavailability (i.e., propensity to be absorbed from the gastrointestinal tract into the body) which, in turn, governs toxicity. Thus, the more water soluble the salt, the more it presents a potential for toxic overdose. Goodman and Gilman (1985) relate: "Ferrous salts are absorbed about three times as well as ferric salts, and the discrepancy becomes even greater at high dosage." Iron phosphate is a ferric salt that has particularly low water solubility (Beliles, 1994; Hawley, 1994). This suggests even lower toxicity for iron phosphate than for the more water soluble forms. In fact, phosphate salts have been shown in rats to reduce the toxicity of more water soluble forms of iron, presumably by precipitating the iron within the gastrointestinal tract, rendering it non-absorbable (Goodman and Gilman, 1985).

Iron phosphate is a GRAS (Generally Recognized as Safe) substance added to foods such as bread for nutritional fortification (HSDB, 1995). Thus, at least some absorption of iron in this form is evident. Even this ferric salt has sufficient solubility in acidic solutions, such as stomach acid, to be absorbed and maintain needed body iron reserves (although more water soluble forms are required to correct frank iron deficiency). This means that, despite it's low solubility, iron phosphate may have the potential to cause toxicity if a single large dose were ingested. If a very large dose were to be ingested, all iron salts, perhaps even iron phosphate, may be lethally toxic because they can corrode the mucosal lining of the stomach and intestinal tract. This facilitates absorption of massive amounts of solubilized iron salts directly into the circulation. It may be concluded that iron phosphate has very low acute toxicity although it is possible that a massive dose may present a serious threat to health and life.

Repeat Dose Toxicity: Chronic exposure to soluble iron salts has caused a syndrome known as siderosis (a.k.a., iron pigmentation) which is the accumulation of a reddish-colored iron-protein complex in tissues such as the lung, spleen, and liver (Stokinger, 1981). From inhalation exposure, the lungs take on a mottled appearance in workers occupied in electric-arc welding and other metallurgical occupations, only after years of exposure. This syndrome is considered benign since, in the lungs, no progressive fibrosis occurs and, as a rule, pulmonary function is not significantly impaired. Siderosis is less common in modern times presumably due to better industrial hygiene practices and observance of relevant occupational exposure limits. A number of epidemiological surveys in the iron refining and mining industries have been conducted (Beliles, 1992). Some of these studies reveal a correlation between exposure to iron and progressive lung disease and certain forms of cancer. However, excess cancers have been attributed mostly to co-exposure to contaminants such as crystalline silica and radon (ibid). The only cancers in humans attributed definitively to any form of iron have been injection site tumors resulting from injection of iron dextran in patients suffering from anemia.

For inhalation exposure, no chronic data was found relating to iron phosphate specifically. Predicting the chronic inhalation toxicity of this compound from that observed for the other forms of iron described above, is problematic. However, prudence would require the inference that this insoluble form of iron also may cause siderosis if high levels are inhaled over prolonged periods. A single study was located that assessed iron phosphate's ability to cause fibrosis of the lung after intratracheal instillation in rats up to one year after injection (Stacy et al., 1959 as cited in NIOSHTIC). While materials such as alumina and various forms of silica caused fibrosis, iron phosphate did not. The more severe lung diseases might

also occur with heavy exposure but only if iron phosphate were contaminated with silicates or radon, similar to mining/refining exposures. Otherwise, only siderosis might reasonably be predicted.

Orally, iron phosphate is a GRAS substance added to flour for nutritional fortification. After many years, no toxicity has been reported from this usage. By either inhalation or ingestion, it may be concluded that iron phosphate presents a low order of toxicity from chronic exposure.

Target Organs: In cases of massive acute overdose, lungs, liver, kidneys, central nervous system, and blood may be affected. In chronic over-exposure, the lungs, liver, spleen may become pigmented with a mottled appearance.

Regulatory Information: No ACGIH TLV or OSHA PEL have been established specifically for iron phosphate. Occupational standards do exist for general classes of iron, such as iron oxide dust and fume, iron pentacarbonyl, and soluble iron salts (ACGIH, 1995). Since it is inorganic and not water soluble, perhaps the class most relevant for iron phosphate is iron oxide and fume. The 8 hr TWA for this form of iron is 5 mg/m^3 (as Fe) and the PEL is 10 mg/m^3 (as total particulate) (ibid).

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IRON OXIDE

CAS: 1309-37-1

Ferric oxide

Fe_2O_3

Dust and Fume

TLV–TWA, 5 mg/m³, as Fe

1946–1947: MAC–TWA, 15 mg/m³

1948–1966: TLV–TWA, 15 mg/m³

1965: TLV–TWA, 10 mg/m³, proposed

1967–1974: TLV–TWA, 10 mg/m³

1973: TLV–TWA, 5 mg/m³, proposed

1975–present: TLV–TWA, 5 mg/m³

1976–1985: TLV–STEL, 10 mg/m³

1986: TLV–STEL, deleted

1992: Documentation revised

Chemical and Physical Properties

The appearance and color of iron oxide are dependent upon the shape and size of the particles and the degree of hydration.[1] The fume of iron oxide is red–brown in color, and exposure can produce a metallic taste. Chemical and physical properties of iron oxide include:

Molecular weight: 159.70
Specific gravity: 5.24
Melting point: 1565°C
Vapor pressure: 0 torr at 20°C
Solubility: insoluble in water; slightly soluble in nitric acid; soluble in sulfuric and hydrochloric acids

Major Uses or Sources of Occupational Exposure

The principle iron ores are composed of the oxides. Iron oxide is used in polishing compounds (e.g., jeweler's rouge), pigments, magnetic tapes, and metallurgy. Its fume may be encountered during the arc-welding of ferrous alloys.

Animal Studies

The toxicology of iron and its oxides has been reviewed by Beliles,[2] Herbert,[3] and the U.S. National Academy of Sciences.[4]

Chronic/Carcinogenicity

Experimental work in animals exposed by intratracheal injection or by inhalation of iron oxide and to iron oxide mixed with less than 5% silica has shown no evidence of fibrosis produced in lung tissue.[5] Another study reported that intratracheal administration of iron oxide particles alone occasionally induced interstitial fibrosis.[6]

Inhalation or intratracheal exposure to iron oxide dust in mice, hamsters, and guinea pigs provided no evidence for the carcinogenicity of iron oxide.[6,7] The International Agency for Research on Cancer (IARC)[8] determined that the evidence suggested a lack of carcinogenicity of ferric oxide in animals.

The injection of high doses of an iron–polysaccharide complex (iron–dextran) was shown to induce local sarcomas at the site of injection in mice, rats, and rabbits;[6,8,9] however, this experimental route of administration is not considered relevant to occupational exposure.

Human Studies

In 1939, Doig and McLaughlin[10] reported that some electric arc welders exposed mainly to iron oxide fume showed generalized discrete densities in their chest X-ray films. None of these welders, however, showed any demonstrable clinical disability. Similar X-ray changes were also noted in British hematite miners;[11] carbon arc and oxyacetylene welders,[12] silver polishers using rouge (a finely divided iron oxide),[13] workers engaged in the manufacture of electrolytic iron oxide,[14] iron and steel grinders in foundries,[15] and boiler scalers.[16] Occupational exposures in many of these groups were mixed. In the case of the hematite miners, foundry workers, and boiler scalers, the iron oxide exposure was associated with exposure to significant amounts of silica. Hematite miners in many cases were also exposed to radioactivity as demonstrated by mine field surveys.[2]

A number of workers with mixed exposure developed a disabling pneumoconiosis. McLaughlin and Harding[17] noted that workers exposed to iron oxide fume and silica may develop a "mixed dust pneumoconiosis." Stokinger[18] suggested that freshly formed iron oxide fume, produced at high temperatures, might act in the same way as freshly formed alumina and silica fume which, after chronic exposure, can produce a condition commonly known as Shaver's disease.

McLaughlin[19] noted that little or no physical disability was associated with the presence of iron oxide fume and dust in the lungs, although "it cannot be assumed that it is harmless." McLaughlin's opinion on the pulmonary effects of inhaled iron oxide fume and dust is the one most generally accepted. The deposition and collection of iron oxide in the lung, which is responsible for the chest X-ray changes noted above, has been termed "siderosis," although Sander[20] preferred the term "iron pigmentation." Siderosis is considered a benign condition and does not progress to fibrosis. Six to 10 years of exposure to iron oxide fume is generally required in order to produce siderosis. Little or no clinical changes are found upon physical examination of workers diagnosed with siderosis.[21–23]

No studies have been reported that would permit a

correlation between exposure concentr... to iron oxide and the occurrence or incidence of X-r... hanges in the lungs. Weber[24] was of the opinion th... siderosis occurred in workers exposed to iron oxide ... the region of 15 mg/m^3" and recommended that exposure to iron oxide fume be controlled to a level of 5 mg/m^3. Kleinfeld et al.[25] found evidence of siderosis in welders with recent exposures below 10 mg/m^3, but with probable higher past exposures. Sentz and Rakow[26] found exposures to iron oxide fume well over 10 mg/m^3 in electric arc and powder-burning operations. Chest X-rays revealed no significant changes in these workers, but relatively few of the workers had long exposure histories and none had worked with iron oxide fume for more than 12 years.

Faulds[27] reported that some British hematite miners exposed to mixed dust developed massive pulmonary fibrosis. He also reported an increased incidence of lung cancer in this group. Dreyfus[28] had suggested in 1936 that inhalation of iron oxide was a factor leading to the development of lung cancer. Increase in the incidence of lung cancer in hematite miners was also reported by Boyd et al.[29] in England, Braun et al.[30] and Monlibert and Roubille[31] in France, and Jorgensen[32] in Sweden.

Studies[33,34] in foundry workers exposed to iron oxide have shown an increase in lung cancer incidence among these workers. In the case of the hematite miners, mixed exposures including silica, radon gas, and diesel exhaust occurred. In the case of the foundry workers, there was also mixed exposure including exposure to silica, core oils, and the thermal decomposition products of synthetic resins. In its 1987 review of hematite mining and ferric oxide, IARC[6] found inadequate evidence for the carcinogenicity to humans from occupational exposure to hematite and ferric oxide but found sufficient evidence of carcinogenicity to humans from underground hematite mining with concomitant exposure to radon. Stokinger[35] reviewed the world literature of studies in hematite and taconite mining, ferrous foundry workers, welders, and magnetic tape industry and concluded that occupational exposure to iron oxide per se was not carcinogenic. At this time, it is not generally accepted that inhalation or dermal exposure to iron oxide dust or fume poses a carcinogenic risk in human beings.

TLV Recommendation

Inhalation of iron oxide dust or fume can cause a benign pneumoconiosis. No studies were reported that would permit a correlation between exposure level and the occurrence of X-ray changes in the lungs. Accordingly, a TLV–TWA of 5 mg/m^3, measured as Fe, for iron oxide dust and fume is recommended to minimize the potential for development of X-ray changes in the lung on long-term exposure. These changes are not considered to be associated with any physical impairment of lung function. At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV–TWA, even when the 8-hour TWA is within the recommended limits. The reader should also consult the Documentation on Welding Fumes and the "Substances of Variable Composition" Appendix in the TLV/BEI Booklet for a discussion of welding fume mixtures.

Other Recommendations

OSHA PEL: OSHA established a PEL–TWA for iron oxide dust and fume of 10 mg/m^3 (as Fe), measured as total particulate. Based on the evidence currently available, OSHA concluded that this limit would protect workers from developing siderosis, a benign pneumoconiosis that occurs after many years of exposure to levels of iron oxide or fume in excess of 15 mg/m^3, and from accumulation of iron dust in the lungs associated with ferric oxide exposure.[36]

NIOSH REL/IDLH: NIOSH [Ex 8-47, Table N1] established a REL–TWA of 5 mg/m^3, total particulate, for iron oxide dust and fume by concurrence with OSHA's originally proposed limit.[36] NIOSH has not established an IDLH value for iron oxide dust and fume.

ACGIH Rationale for TLVs that Differ from the PEL or REL: The TLV was established on the basis of the prevention of the development of X-ray changes in the lung on long-term exposure. These changes are not considered to be associated with any physical impairment of lung function, although more sophisticated physiologic testing, including measurement of the lung's mechanical properties and expiratory air flow, is required prior to reaching a firm and final conclusion. No studies are available whereby a correlation can be made between exposure level and the appearance of siderosis on X-ray films. ACGIH believes that any occupational exposure which permits the deposition and retention of particles in the lung should be controlled to minimize such effects.

NTP Studies: NTP has not conducted genetic toxicology, short-term toxicity, or long-term toxicology and carcinogenesis effects studies on iron oxide.

Carcinogenic Classification

IARC: Group 3, not classifiable as to its carcinogenicity to humans.

Other Nations

Australia: fume 5 mg/m^3, as Fe (1990); Federal Republic of Germany: 6 mg/m^3, fine dust (short-term exposure values in preparation) (1991); Sweden: 3.5 mg/m^3,

respir[illegible] (1989); United King[illegible] n: 5 mg/m³ (as Fe), 10-min[illegible] EL 10 mg/m³ (as Fe) 991)

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TLV Documentation '91

IRON SALTS (Soluble)

Ferric chloride

AS: 7705-08-0

Ferric nitrate

CAS: 10421-48-4

Ferric sulfate

CAS: 10028-22-5

Ferrous chloride

CAS: 7758-94-3

Ferrous sulfate

CAS: 7720-78-7

TLV–TWA, 1 mg/m^3, as Fe

1967: TLV–TWA, 1 mg/m^3, proposed

1969–present: TLV–TWA, 1 mg/m^3

1976–1985: TLV–STEL, 2 mg/m^3

1986: TLV–STEL, deleted

1992: Documentation revised

Chemical and Physical Properties

A large proportion of iron salts are water-soluble; exceptions are carbonates, oxides, hydroxides, phosphates, sulfides, and ferrous fluoride. Soluble iron salts include: ferric chloride ($FeCl_3$), nitrate [$Fe(NO_3)_3$], and sulfate [$Fe_2(SO_4)_3$] and the ferrous compounds, chloride ($FeCl_2$) and sulfate ($FeSO_4$). $FeCl_3$ is a black-brown solid; $Fe(NO_3)_3$ is a pale violet, green, or white, odorless solid in a lumpy crystalline form; $Fe_2(SO_4)_3$ is a grayish-white or yellow solid in a powder or lumpy crystalline form; $FeCl_2$ is a pale greenish, salt-like crystal or powder; and $FeSO_4$ is a greenish or yellow solid in fine or lumpy crystalline form. Chemical and physical properties include:[1–3]

Molecular weight: 162.21 ($FeCl_3$)
241.87 [$Fe(NO_3)_3$]
399.88 [$Fe_2(SO_4)_3$]
127.76 ($FeCl_2$)
151.91 ($FeSO_4$)

Specific gravity: 2.90 at 25°C ($FeCl_3$)
1.68 at 21°C [$Fe(NO_3)_3$]
3.097 at 18°C [$Fe_2(SO_4)_3$]
3.16 at 25°C ($FeCl_2$)
1.897 ($FeSO_4 \cdot 7H_2O$)

Melting point: 306°C ($FeCl_3$)
47°C [$Fe(NO_3)_3$]
674°C ($FeCl_2$)

Boiling point: decomposes at 315°C ($FeCl_3$); decomposes at < 100°C [$Fe(NO_3)_3$]; 1023°C ($FeCl_2$)

Solubility: soluble in water (744 g/L at 0°C); very soluble in ethanol, methanol, and ether ($FeCl_3$); soluble in water, ethanol, and acetone [$Fe(NO_3)_3$]; soluble in water, sparingly soluble in ethanol, and insoluble in acetone [$Fe_2(SO_4)_3$]; soluble in water, ethanol, and acetone ($FeCl_2$); soluble in water but insoluble in ethanol ($FeSO_4$)

Major Uses or Sources of Occupational Exposure

$FeCl_3$ is used to treat sewage and industrial waste. It is also used in engraving, textiles, and photography; as a disinfectant; and as a feed additive. $Fe(NO_3)_3$ is used in textile dyeing, tanning, and weighting silk. $Fe_2(SO_4)_3$ is used in pigments, textile dyeing, water treatment, and metal pickling. $FeCl_2$ is used in textile dyeing, metallurgy, the pharmaceutical industry, and sewage treatment. $FeSO_4$ is used as a fertilizer; as a food or feed additive; and in herbicides, process engraving, dyeing, and water treatment.[2] Ferrous salts (including the most widely used form, ferrous sulfate U.S.P., which contains 300 mg $FeSO_4 \cdot 7H_2O$ or an equivalent amount of anhydrous material, 60 mg) are used in treatment of iron-deficiency anemias.

Animal Studies

Acute

Iron salts on oral ingestion are of moderate to low toxicity. On the other hand, iron salts, especially the ferric salts, such as $FeCl_3$ and $Fe_2(SO_4)_3$, are highly toxic after parenteral injection in animals. For example, the intraperitoneal LD_{50} of anhydrous $FeCl_3$ for the mouse is 68 mg/kg, but after an oral dose, the value increased to 400 mg/kg. In mice, the intraperitoneal LD_{50} of the hexahydrate, $FeCl_3 \cdot 6H_2O$, was reported as 260 mg/kg. In the older literature, the intravenous lowest lethal dose of $FeCl_3$ for rabbits was reported as 7 mg/kg.[3] Elemental iron is far less toxic than soluble iron salts, and the acute toxicity data gathered in animals are consistent with its designation as a moderately toxic agent for the five iron salts.[4]

Human Studies

The clinical toxicology of ingested iron salts has been reviewed in detail by Gosselin et al.[4] The probable oral lethal dose for a 70-kg person is expected to be between 1 ounce to 1 pint (or 0.25 to 1 lb). Ingestion of ten tablets (approximately 0.3 g/tablet) by children causes a mild poisoning; severe intoxication occurs after ingestion of some 20 iron tablets.[5] Death can occur when serum iron concentrations reach 500 µg/100 ml or higher.[4]

The lowest toxic oral dose of $FeSO_4$ for an infant is reported as 600 mg/kg, with effects on the gastrointesti-

nal tract; for an adult female, the value is 60 mg/kg, with effects primarily on the gastric mucosa, cardiovascular/peripheral circulation, metabolic acidosis, and on the central nervous system (CNS) where shock, coma, and death can result.[3] In an overview of 474 cases of acute iron poisoning after ingestion, the overall mortality rate was 1%.[6]

In contrast to the wealth of data available on the human toxicology of ingested iron salts (including details of postmortem examinations in cases where the dose is known), the data on the potential for adverse health effects after inhalation or dermal contact is scant. Inhalation of ferric salts as dusts and mists had been considered irritating to the respiratory tract and the dusts and mists of ferric salts are regarded as skin irritants.[7]

TLV Recommendation

A TLV–TWA of 1 mg/m^3, as Fe, is recommended in order to reduce the likelihood of respiratory irritation and skin irritation from exposure to aerosols and mists of soluble iron salts. At this time, no STEL is recommended until additional toxicological data and industrial hygiene experience become available to provide a better base for quantifying on a toxicological basis what the STEL should be. The reader is encouraged to review the section on *Excursion Limits* in the "Introduction to the Chemical Substances" of the current TLV/BEI Booklet for guidance and control of excursions above the TLV–TWA, even when the 8-hour TWA is within the recommended limits.

Other Recommendations

OSHA PEL: OSHA established a PEL–TWA of 1 mg/m^3, measured as iron, for the soluble salts of iron. OSHA concluded that employees are at risk of skin and mucous membrane irritation from exposure to aerosols and mists of soluble iron salts at levels above the PEL.[8] The OSHA PEL is consistent with the recommended ACGIH TLV.

NIOSH REL/IDLH: NIOSH [Ex 8-47, Table N1] established a REL–TWA of 1 mg/m^3, measured as iron, for the soluble salts of iron by concurrence with the OSHA PEL.[8] NIOSH has not established an IDLH value for this substance.

NTP Studies: NTP has not conducted short-term toxicology or long-term toxicology and carcinogenesis effects studies on soluble iron salts. $FeCl_3$, which was negative in the mouse lymphoma assay, is the only soluble iron salt that has been tested by the NTP for its genetic toxicologic properties.

Other Nations

Australia: 1 mg/m^3 (1990); United Kingdom: 1 mg/m^3, 10-minute STEL 2 mg/m^3 (1991).

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PATTY'S INDUSTRIAL HYGIENE AND TOXICOLOGY

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Toxicology

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Volume II of this series is dedicated to Paul D. Halley, past president of the American Industrial Hygiene Association, former Director of Environmental Health Services for AMOCO, (Industrial Hygiene, Safety and Toxicology), and Editor-in-Chief for eight years of the *AIHA Journal*, who, after retirement from the latter position, initiated contacts for the fourth revision of this volume, but was forced to relinquish its editorship because of illness.

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16 IRON, Fe

16.1 Sources, Uses, and Industrial Exposures (1, 3)

Iron [CAS # 1309-97-1] is a silver white solid metal of Group VIII, the transition elements of the periodic table. The chemical symbol, Fe, is from *ferrum*, the Latin word for iron. Elemental iron has been known since prehistoric times. Around 1200 BC, iron was obtained from its ores; this achievement marks the beginning of the Iron Age. Even with the development of other materials, iron and its alloys remain crucial in the economies of modern countries. Iron is also critical to life. It is an essential element and a component of hemoglobin.

Iron is the fourth most abundant element (5.1 percent) in the earth's crust. The molten core of the earth is primarily elemental iron. Iron occasionally occurs in its pure form; however, it is abundant in combination with other elements as oxides, sulfides, carbonates, and silicates. Iron ore reserves are found worldwide. Areas with more than 1 billion metric tons of reserves include Australia, Brazil, Canada, the United States, Venezuela, South Africa, India, the former Soviet Union, Gabon, France, Spain, Sweden, and Algeria. The ore exists in varying grades, ranging from 20 to 70 percent iron content. North America has been fortunate in its ore deposits. There are commercially usable quantities in 22 U.S. states and in six Canadian provinces. In the United States the most abundant supplies, discovered in the early 1890s, are located in the Lake Superior region around the Mesabi Range. Other large deposits are found in Alabama, Utah, Texas, California, Pennsylvania, and New York. These deposits, particularly the Mesabi Range reserves, seemed inexhaustible in the 1930s when an average of 30 million tons of ore was produced annually from that one range. The tremendous demand for iron ore during World War II virtually tripled the output of the Mesabi Range and severely depleted its deposits of high-grade ore. The major domestic (U.S.) production is now from crude iron ore, mainly taconite, a low-grade ore composed chiefly of hematite ($FeO(OH)\cdot H_2O$) and silica found in the Great Lakes region.

After the war an intensive search revealed large quantities of rich ore, acceptable for blast-furnace use, in newly discovered deposits. Most of these discoveries involved reserves located close to the surface, allowing the use of open-pit mining

rather than the more costly underground mining that had been necessary to reach many of the older reserves. In addition, new ore upgrading techniques were developed to exploit the large reserves of low-grade ores such as taconites and jaspers.

These techniques include sintering and pelletizing. Sintering is used when ore and other iron-bearing materials are too fine to be charged directly into the furnace. These materials are agglomerated with a mixture of coal and coke fines, or powders, which, when ignited, provide the heat for the sinter process. The result is a porous, clinker-like mass that enhances the upward flow of hot gases through the blast furnace burden.

Pelletizing is used to increase the iron content of low-grade (20 to 30 percent iron) ores. After being crushed, screened, and concentrated, the ore fines are formed into small balls or pellets with an iron content of 60 percent or more. The pellets are then hardened by heating to increase their strength and durability for subsequent processing. Thus ores that were once considered unsuitable now supply a substantial portion of the industry's requirements.

Perhaps the most important alloy of iron is steel, which contains up to approximately 2 percent carbon. Steels that contain about 0.25 percent carbon are called mild steels; those with about 0.45 percent carbon are medium steels; and those with 0.60 percent to 2 percent carbon are high-carbon steels. Within this range, the greater the carbon content, the greater the tensile strength of the steel. The hardness of steel may be substantially increased by heating the metal until it is red hot and then quickly cooling it, a process known as quench hardening. An important component of many steels is cementite, a carbon–iron compound. Mild steels are ductile and are fabricated into sheets, wire, or pipe. The harder medium steels are used to make structural steel. High-carbon steels, which are extremely hard and brittle, are used in tools and cutting instruments.

Wrought iron, which is nearly pure iron, has a lower carbon content than steel. Because of its low carbon content (usually below 0.035 percent), it is forgeable and nonbrittle. Iron of high carbon content (3 to 4 percent), obtained when pig iron is remelted and cooled, is called cast iron. If cast iron is cooled quickly, hard but brittle white cast iron is formed; if it is cooled slowly, soft but tough gray cast iron is formed. Because it expands while cooling, cast iron is used in molds.

The addition of other materials in alloys—for example, manganese or silicon—also increases the hardness of steel. The inclusion of tungsten permits high-speed drills and cutting tools to remain hard even when used at high temperatures. The inclusion of chromium and nickel improves the corrosion resistance of the steel and, within certain limits of composition, is called stainless steel. A common stainless steel contains 0.15 percent C, 18 percent Cr, and 8 percent Ni. It is used in cooking utensils and food-processing equipment. The inclusion of silicon, ranging from 1 to 5 percent, results in an alloy that is hard and highly magnetic. An alloy with cobalt is used for permanent magnets.

In the United States, steel ranks among the 10 largest industries. Steel producers fall into two major categories. Integrated steel makers convert iron ore into steel through a lengthy process that employs a blast furnace to produce iron from iron ore, and a basic oxygen or open hearth furnace to transform the iron into steel.

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Nonintegrated steelmakers melt steel scrap in electric arc furnaces to produce liquid steel in facilities that are sometimes referred to as minimills. Given the very large size of many nonintegrated steel facilities, however, the term "scrap-based mill" is also used to describe a steel plant that does not convert iron ore to iron; and "ore-based mill" has become another term to describe an integrated steelmaker.

The rapid expansion of foreign steel industries created unprecedented competition for the U.S. industry, which must increase its investment in new technologies to reduce costs, improve steel quality, and meet more demanding performance specifications. However, foreign steel, much cheaper than domestic steel, resulted in many older mills closing. The reduction of demand for domestic steel and the reduction of man-hours required to produce steel in modernized plants have reduced the number of workers exposed in this industry.

Mining and handling of iron ores provide exposure to dusts of SiO_2 and iron oxides. Carbon monoxide is a hazard in the operation of blast furnaces for the production of pig iron. The use of fluorspar (CaF_2) in steelmaking gives rise to gases containing SiF_4 and other fluorine-containing substances. The manufacture of alloy steels introduces hazards attendant on the use of metals such as chromium, manganese, nickel, vanadium, tungsten, molybdenum, and copper. "Pickling" of iron containing arsenic and phosphorus liberates arsine and phosphine. Certain grades of ferrosilicon used in steelmaking decompose with explosive violence on contact with moist air, evolving various toxic gases such as acetylene, H_2S, SiH_4, AsH_3, and PH_3. Fatal intoxications have occurred from such accidents during transportation, particularly at sea (546).

Because iron is essential to health, iron supplements are frequently used in the treatment of iron deficiency or iron malabsorption syndromes. Iron dextran is a complex of ferric hydroxide with dextran. It is injected to treat iron deficiency anemia in humans and in baby pigs. Exposure occurs in manufacturing and repacking, and use is limited. Slightly more than 1000 workers may be so exposed; about half are women (113). A great many more workers are exposed in the manufacture of oral iron preparations.

Iron in its various oxidation states readily combines with many carbon compounds to form organometallic compounds. Finely divided iron reacts with carbon monoxide under pressure to form the yellow liquid iron pentacarbonyl, $Fe(CO)_5$. This transition-metal carbonyl, like many others, contains the metal in a zero oxidation state. The compound is the starting material for iron compounds in unusually low oxidation states. On decomposition, iron pentacarbonyl yields pure iron. Iron pentacarbonyl is used as a gasoline additive (0.2 percent) in Europe, similar to the use of tetraalkyl lead in the United States.

A new type of organometallic compound was discovered in 1951. If ferrous chloride is reacted with cyclopentadiene in the presence of a strong organic base, the orange crystalline compound ferrocene (CAS # 102-54-5) is the product. This compound, which has a highly stable structure, is called a "sandwich" compound because the iron atom is strongly held between the two flat C_5H_5 rings. In this case, it is not useful to attempt to assign an oxidation state to iron. The characterization of this compound has led to extensive transition metal organometallic

Table 27.21. Chemical and Physical Characteristics of Iron and Some of Its Salts

Form	At. or Mol. Wt.	Sp. Gr.	M.P. (°C)	B.P. (°C)	Solubility
Iron, Fe	55.85	7.86	1535	2750	Insol. water; sol. acids
Ferrous oxide, black, FeO	71.85	5.7	1420	—	Insol. water; sol. acid; insol. alcohol, alkalies
Iron oxide, magnetite, red, F_3O_4	231.54	5.19	Dec. 1538	—	Insol. water; sol. conc. acid; insol. alcohol, ether
Ferric chloride, $FeCl_3$	162.21	2.898 (25°C)	306	Dec. 315	5.35 kg/l (100°C); v. sol. EtOH, MeOH, ether
Ferric sulfate, $Fe_2(SO_4)_3$	399.87	3.097 (18°C)	—	—	Sl. sol. cold water; dec. hot water; insol. H_2SO_4
Ferrous sulfate, $FeSO_4 \cdot H_2O$	169.96	2.97 (25°C)	—	—	Sl. sol. cold water
Ferrocene, $C_5H_5FeC_5H_5$	186.04	—	172.5	Subl.	Insol. water; sol. EtOH, ether, MeOH
Iron carbonyl, $Fe(CO_5)$	195.9	1.46	−20	103	Insol. water, dilute acids; sol. most organic acids

chemistry. Ferrocene (dicyclopentadienyl iron) is a relatively volatile, organometallic compound used as a chemical intermediate, a catalyst, and as an antiknock additive in gasoline.

16.2 Physical and Chemical Characteristics

The chemical and physical characteristics of iron and some of its compounds have been listed in Table 27.21.

The physical properties of iron, the metal, are profoundly affected by impurities and by changes in temperature and treatment. Iron is superior to all other elements in magnetic properties. Iron, in an almost pure state, loses its magnetism when removed from an electric field; when iron contains small amounts of carbon, cobalt, or nickel, the retention of magnetism is increased. When heated to 770°C, iron

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loses its magnetism; on cooling, it retains this property. Iron undergoes a variety of structural changes (transformations) on heating that form the basis of the heat treatment of ferrous metals.

The principal compounds of iron are ferrous (Fe^{2+}) and ferric (Fe^{3+}). In general, ferrous and ferric forms are mutually interconvertible. The oxidation potential against the normal hydrogen electrode for the ferrous form is −0.43 V, and for the ferric form, +0.77 V. Ferrous compounds are more stable than ferric when ionized, less stable when covalent.

A large proportion of iron salts are water soluble; exceptions are carbonates, oxides, hydroxides, phosphates, sulfides, and ferrous fluoride. Iron of both valences tends to form complexes in which the most common coordination number is 6. Iron has a strong tendency to combine with oxygen, as in the form of hydroxyl groups, with resultant stable compounds, especially as chelates. Iron compounds exhibit marked catalytic activity in the promotion of oxidations, which are of both chemical and biologic importance. Iron forms several carbonyls; their properties and uses are discussed.

An interesting aspect of iron chemistry is the array of compounds that bond to carbon. Cementite, Fe_3C, is a component of steel. The cyanide complexes of both ferrous and ferric iron are very stable and are not strongly magnetic in contrast to most iron coordination complexes. The cyanide complexes form colored salts, including Prussian blue, $KFe_2(CN)_6$, made from ferric iron and potassium ferrocyanide. The compound Turnbull's blue, made from ferrous iron and potassium ferricyanide, is considered identical to Prussian blue.

Iron forms a large group of materials known as ferroalloys that are important as addition agents in steelmaking. Iron is also a major constituent of many special-purpose alloys developed for characteristics related to magnetic properties, electrical resistance, heat resistance, corrosion resistance, and thermal expansion.

Among the better-known types of Fe alloys are those with carbon, of which the principal ones are wrought iron, cast iron, and steel. Good wrought iron contains no more than 0.035 percent C, but also contains 0.075 to 0.15 percent Si, 0.1 to 0.25 percent P, less than 0.02 percent S, and 0.06 to 0.1 percent Mn, not all of which are alloyed with the iron.

Cast iron contains 2 to 4 percent C and varying amounts of silicon, phosphorus, sulfur, and manganese, to obtain a wide range of physical and chemical properties. Alloying elements such as silicon, nickel, chromium, molybdenum, copper, and titanium may be added in amounts varying from a few tenths to 30 percent or more.

Steel is a generic name for a large group of Fe–C alloys in which the carbon content is about 2 percent. To this basic steel, other alloying elements may be added, the more common types of which are aluminum, chromium, cobalt, Cr–Ni, Cr–Al, manganese, nickel, silicon, and tungsten, each of which has particular uses arising from its special properties.

The several iron oxide forms are used as paint pigments, polishing compounds, magnetic inks, and coatings for magnetic tapes. The soluble salts are variously used

as dyeing mordants, catalysts, pigments, fertilizer, feeds, and disinfectants, and in tanning, soil conditioning, and treatment of sewage and industrial wastes.

The minimum ignition temperatures for iron dust clouds range from 470 to 780°C; for layered dust, the range is 220 to 520°C (1).

Iron pentacarbonyl, $Fe(CO)_5$, like nickel carbonyl, is insoluble in water and unreactive in dilute acids. It may ignite spontaneously in air. Concentrated reducing acids yield ferrous salts, as do gaseous halogens. Iron pentacarbonyl is a strong reducing agent changing ketones to alcohols, benzil to benzoin, and nitrobenzene to aniline.

Iron pentacarbonyl has an ignition temperature of 320°C; the minimal explosive concentration is 105 oz/ft^3; 10 percent oxygen is the limiting concentration to prevent ignition (547).

Although information on storage and handling has been given specifically for $Fe(CO)_5$ (548), it can be assumed that the information applies in like manner to all industrial metal carbonyls. Because the vapors of $Fe(CO)_5$ form explosive mixtures with air, this chemical should be stored under CO, CO_2, or N_2; and because of its high toxicity, handling of this substance should be done in well-ventilated hoods. The danger of spontaneous ignition can be reduced by the addition of hydrocarbons, their halogen derivatives, or alcohol. Workrooms should be provided with good general ventilation, and only persons trained in handling extrahazardous materials should be employed for this work.

16.3 Monitoring

Collection of a particulate filter and analysis by X-ray fluorescence spectrophotometry is the NIOSH method for iron oxide fume (111).

16.4 Physiological Response

The oral absorption of iron is largely limited by physiological homeostatic mechanisms that regulate the intake based on the need. The intestinal mucosa is the major site at which the absorption is limited, but hepatic and pancreatic secretions may influence the absorption. However, in cases of acute iron poisoning the gastric mucosa is often disrupted. The iron transport system is overloaded, and this results in circulating free iron. In the normal homeostatic mode the divalent iron is absorbed into the gastric mucosa where it is converted to the trivalent form. The toxicokinetics of injectable iron and organo-iron compounds, like ferrocene, are not affected by the homeostatic gastrointestinal control of iron absorption. The trivalent iron attached to ferritin passes into the bloodstream and is converted into transferrin. Transferrin is transported to the spleen or liver where it is stored as ferritin or hemosiderin. Under normal conditions the body burden of iron is about 4 g. Hemoglobin contains the greatest amounts of body iron (67 percent), and this largely in the red blood cells. Twenty-seven percent of the total body iron is in the liver as ferritin or in pathological conditions as hemosiderin. Because iron is so important in physiological function, the body tends to conserve iron. The major

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mechanisms for the excretion of iron are desquamation of the gastrointestinal tract and blood loss. However, the iron-deferoxamine formed as the result of administering the specific iron chelator, deferoxamine, is excreted in the urine (71).

Ingestion of iron-containing tablets by children is a frequent occurrence. The estimated toxic dose for a 10-kg child is 20 mg Fe/kg. According to Ellenhorn and Barceloux (112), 5000 cases of iron poisoning occur in the United States each year. One case of acute industrial iron poisoning has been reported. In this case a worker fell into a vat of $FeCl_3$ (549).

The first phase of acute oral iron intoxication is gastrointestinal irritation and damage. Vomiting may occur at this phase. Central nervous system depression, as well as cardiovascular symptoms, such as pallor, tachycardia, and hypotension, may occur. Following the initial phase, the patients may appear to recover. However, in 12 to 48 hr after the ingestion, life-threatening symptoms can appear. These include gastrointestinal perforation, coma, convulsions, vasomotor collapse, cyanosis, and pulmonary edema. Hepatorenal failure may develop. Most deaths occur during this phase. In the prolonged recovery, pyloric constriction and gastric fibrosis may occur (71).

Chronic oral iron intoxication is relatively rare, but can lead to hemosiderosis or hemochromatosis. Hemosiderosis is a condition in which there is a generalized increase in the iron content in the body tissues, particularly the liver and spleen. Hemochromatosis is marked by the accumulation of iron, as in the Kupffer cells of the liver and in the reticuloendothelial cells of the spleen and bone marrow. This is accompanied by fibrotic changes in the affected organ, most often the liver.

Hemosiderosis has been reported in the Bantu of Africa. This may be due to the use of iron pots for cooking, the nature of the diet, and the use of beer brewed in ironware. "Bantu siderosis" occurs more frequently in men than in women and may be a geographic cluster of primary hemochromatosis (71).

Primary hemochromatosis is a genetically determined autosomal recessive disorder occurring most often in men, characterized by the excessive accumulation of body iron (550). The disorder is determined by a locus closely linked to the HLA loci on the short arm of chromosome 6. There is a recessive mode of transmission. The gene frequency may be as high as 0.05 in some parts of the world. HLA typing makes it possible to identify family members who are homozygous for idiopathic hemochromatosis, and measurement of transferrin saturation and serum ferritin concentration will identify those with iron overload (551). Hypogonadism of either testicular or central origin is a frequent complication (552).

Pulmonary siderosis results from inhalation of iron dust or fumes. It falls into the group of pneumoconioses in which the pulmonary reaction is minimal, despite a heavy dust load. Because fibrosis is not caused by inhalation of iron dust, the clinical course is benign; and pulmonary function tests and blood gases are within normal limits (553).

Marazzini et al. (554) showed an increase of bronchial obstruction due to exposure in an iron foundry. In a 100-subject sample, all working in the iron foundry were affected only by small airway obstruction. Thirty months later, 99 of these subjects were reexamined and the present airway condition determined. In 43

subjects there were abnormal results of the tests, indicating total airway obstruction after 30 months. Even in the subsample of nonsmokers, a deterioration had occurred.

A retrospective cohort mortality study was conducted by Andjelkovich et al. (555) among 8147 men and 627 women employed in a gray iron foundry for at least 6 months between 1950 and 1979. More than 1700 deaths occurred during a 35-year period of observation. Standardized mortality ratios (SMRs) for all causes were close to expected values, based on the U.S. general population as the standard. The mortality of nonwhite men was significantly increased for lung cancer (SMR 132) and ischemic heart disease (SMR 126). Other moderate, but nonsignificant, excesses were noted among nonwhite men for cancers of the stomach, pancreas, and prostate, for diabetes mellitus, and for pulmonary emphysema, and among white men for cancers of the lung and stomach, gastric and duodenal ulcers, pulmonary emphysema, and suicide. Small mortality increases were observed in both racial groups for cerebrovascular disease. The lack of a trend with time since hire and duration of foundry employment suggests that lung cancer mortality may not be associated with exposure to the foundry environment. Utilizing indirect measures of smoking, it appears that virtually all excess lung cancer deaths among whites, and at least some of the excess among nonwhites, could be explained by smoking habits. Similarly, smoking may have been responsible for the mortality excesses from emphysema, cerebrovascular diseases, and ischemic heart disease.

Underground hematite mining has been associated by IARC (152) with cancer among workers. It has been suggested that this may be due to excessive exposure to radon. In a retrospective cohort mortality study of 10,403 Minnesota iron-ore (hematite) miners no excesses of lung cancer mortality were present among either underground (SMR = 100) or aboveground (SMR = 88) miners. Yugoslav-born miners incurred a twofold significant excess mortality for lung cancer that did not appear to be associated with their mining exposures. Significant excesses in mortality due to stomach cancer were found for both underground (SMR = 167) and aboveground (SMR = 181) miners as compared with U.S. white males. However, except among Finnish-born miners, these excesses disappeared when comparisons were made with the appropriate country rate. The authors (556) concluded that the apparent absence of significant radon exposure, a strict smoking prohibition underground, an aggressive silicosis control program, and the absence of underground diesel fuel use may explain why these underground miners did not appear to incur the lung cancer risk reported in other studies.

In contrast, a cohort mortality study was conducted with regard to a pyrite mine located in central Italy, where there was exposure to radon. The concentration of free silica in the dust was less than 2 percent. The cohort was determined from company files and included 1899 subjects. Mortality was studied for the years 1965 to 1983. The loss to follow-up was less than 2 percent. The SMR for all causes and all neoplasms was 97 and 107, respectively. That for lung cancer and for nonmalignant respiratory diseases was 131 and 173, respectively. The investigators (557) estimated that the extra cases of lung cancer attributable to radon daughters numbered 13 per 10^6 person-years and working level month in the whole cohort. The

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extra cases of lung cancer were 21.3 per 10^6 person-years in the subcohort with 10 to 25 years of exposure.

Mortality during the years 1947 to 1983 was studied by Cooper et al. (558) in 3444 men employed during the years 1947 to 1958 for at least 3 months in Minnesota taconite mining operations. Taconite is a low-grade iron ore consisting of iron, quartz, and numerous silicates. Taconite from the eastern part of the Mesabi Iron Range contains the amphibole silicate cummingtonite–grunerite, which is a mineral relative of amosite asbestos. During 86,307 person-years of observation, there were 801 deaths for a standardized mortality ratio (SMR) of 88 (U.S. white male rates) or 98 (Minnesota rates). The 41 deaths from respiratory cancer were fewer than expected, the SMR being 61 (U.S. rates) and 85 (Minnesota rates). There were 25 respiratory cancers 20 or more years after first taconite employment, for an SMR of 57 (U.S. rates). SMRs for colon cancer, kidney cancer, and lymphopoietic cancer were elevated, but below the level of statistical significance. There was one death from pleural mesothelioma 11 years after first taconite employment in a man with a long prior employment as a locomotive operator. The pattern of deaths did not suggest asbestos-related disease in taconite miners and millers.

In 1967, 240 workers in the Kiruna, Sweden iron mine were examined with regard to lung function and respiratory symptoms. Seventeen years later, 167 of these workers were reexamined using a structured interview which covered respiratory symptoms, smoking habits, and workplace conditions; lung function tests, including dynamic spirometry and closing volume, were also analyzed. The prevalence of chronic bronchitis in the latter study was 9.6 percent. There was a strong relationship between chronic bronchitis and smoking, but no relationship between chronic bronchitis and working underground in the mine. Only three persons had chronic obstructive lung disease. In the still active mine workers, dynamic spirometry results showed no difference between smokers and nonsmokers or between underground and surface workers. Thus the authors reported no excess of chronic obstructive lung disease or lung function disturbances in the mine workers studied. This may reflect a self-selection process whereby the workers with airway obstruction due to smoking or underground exposure have left underground work and, also, the company. Underground workers with chronic mucous hypersecretion, on the other hand, have not felt motivated to leave underground work because of this. Some, however, may have stopped smoking, but not necessarily because of the hypersecretion (559).

Both NTP and IARC have determined that iron dextran may reasonably be anticipated to cause cancer in humans. This determination is based on the finding of injection site tumors, particularly in rats after subcutaneous injections of iron dextran. Additionally, a few human cases of injection site tumors arising after treatment with iron dextran have been reported (152). The nature of these reported tumors suggests that they may not have been due to iron dextran. However, the finding of injection site tumors in experimental animals alone cannot be considered indicative of an occupational cancer hazard; there is virtually no information to suggest that exposure to iron or iron compounds by any route except intramuscular or subcutaneous injection poses a cancer hazard. However, further studies with

injectable iron compounds have indicated that high doses given intravenously to pregnant rats may result in teratogenic changes (hydrocephalus, anophthalmia). These teratogenic effects can be reduced by deferoxamine (71).

Signs and symptoms of overexposure to $Fe(CO)_5$ resemble those of $Ni(CO)_4$—immediately upon exposure, giddiness and headache, occasionally accompanied by dyspnea and vomiting. Removal from exposure reverses the symptoms, but dyspnea returns in 12 to 36 hr, accompanied by fever, cyanosis, and cough. Death usually occurs in 4 to 11 days from exposure to lethal concentrations. Pathological changes consist of pulmonary hepatization, vascular injury, and degeneration of the central nervous system (1).

Ferrocene has been suggested as a therapeutic agent for anemia related to malabsorption of iron, as well as a gasoline additive. There are no published data with regard to adverse effects resulting from occupational exposure. However, F344/N rats and B6C3F1 mice were exposed to 0, 2.5, 5.0, 10, 20, and 40 mg ferrocene vapor/m^3, 6 hr/day for 2 weeks. During these exposures, there were no mortalities and no observable clinical signs of ferrocene-related toxicity in any of the animals. At the end of the exposures, male rats exposed to the highest level of ferrocene had decreased body-weight gains relative to the weight gained by control rats. The body-weight gains for all groups of both ferrocene and control female rats were similar. Male mice exposed to the highest level of ferrocene also had decreased body-weight gains, relative to controls. The female mice had relative decreases in body-weight gains at the three highest exposure levels. Male rats had a slight decrease in relative liver weights at the highest level of exposure, whereas no relative differences in organ weights were seen in female rats. Male mice had exposure-related decreases in liver and spleen weights, and an increase in thymus weights, relative to controls. For female mice, decreases in organ weights occurred in the brain, liver, and spleen. No exposure-related gross lesions were seen in any of the rats or mice at necropsy (560).

16.5 Health Standards

Although iron dextran is classified as "reasonably expected to be carcinogenic" by NTP and a B2 carcinogen by IARC, its harmful exposure in workers is limited. The TLV for iron oxide fume (Fe_2O_3) is 5 mg/m^3, and the TLV committee also classifies it as a B2 carcinogen. The OSHA PEL for iron oxide is 10 mg/m^3 as total particulate. The TLV and the PEL for iron salts are both 1 mg Fe/m^3 (69). The TLV was selected to prevent the development of X-ray changes following long-term exposure to iron oxide dust and fume, whereas the TLV for the iron salts was recommended to reduce the likelihood of respiratory irritation and skin irritation (105).

The TLV for iron $Fe(CO)_5$, as Fe, is 0.23 mg/m^3 as an 8-hr TWA with a short-term exposure limit (STEL) of 0.45 mg Fe/m^3, whereas the OSHA PEL is 0.1 mg/m^3 as Fe with a STEL of 0.2 mg Fe/m^3 (69). The TLV is believed to be "more than adequate to protect against acute and chronic systemic effects." A previous

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TLV of 0.01 mg/m³ was recommended because of acute toxicity and suspected carcinogenic potential (105).

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17 THE LANTHANIDES (RARE EARTH METALS)

17.1 Sources, Uses, and Industrial Exposures (1, 3)

The lanthanides (or lanthanons) are a group of 15 elements of atomic numbers from 57 through 71 in which yttrium (atomic number 39) and scandium (atomic number 21) are sometimes included. The lanthanide series is the group of chemical elements that follow lanthanum in Group IIIB of the periodic table. Their distinguishing atomic feature is that they fill the 4*f* electronic subshell. Actually, only those elements with atomic numbers 58 through 71 are lanthanides. Most chemists also include lanthanum itself in the series because, although it does not fill the 4*f* subshell, its properties are very like those of the lanthanides. The IIIB elements, including scandium and yttrium as well, are also known as the rare earths because they were originally discovered together in rare minerals and isolated as oxides, or "earths." In comparison with many other elements, however, the rare earths are not really rare, except for promethium, which has only radioactive isotopes. The relative abundance and atomic numbers are tabulated in Table 27.22.

Scandium is a silvery white metallic chemical element, the first member of the first transition series. The name is derived from Scandinavia, where the element was discovered in the minerals euxenite and gadolinite. In 1876, L. F. Nilson prepared about 2 g of high-purity scandium oxide. It was subsequently established

Table 27.22. Atomic Numbers, Weights, and Concentration of the Rare Earths (Lanthanide Series)

Element	Atomic No.	Atomic Weight	Earth's Crust (ppm)
Scandium (Sc)	21	44.9559	5–6
Yttrium (Y)	39	88.9059	28–70
Lanthanum (La)	57	138.9055	5–18
Cerium (Ce)	58	140.12	46
Praseodymium (Pr)	59	140.9077	6
Neodymium (Nd)	60	144.24	24
Promethium (Pm)	61	145	4.5×10^{-20}
Samarium (Sm)	62	150.4	6
Europium (Eu)	63	151.96	1
Gadolinium (Gd)	64	157.3	6
Terbium (Tb)	65	158.9254	0.9
Dysprosium (Dy)	66	162.50	4
Holmium (Ho)	67	164.9304	1
Erbium (Er)	68	167.26	2
Thulium (Tm)	69	168.9342	0.2
Ytterbium (Yb)	70	173.04	3
Lutetium (Lu)	71	174.97	0.8

that scandium corresponds to the element "ekaboron," predicted by Mendeleyev on the basis of a gap in the periodic table. Scandium occurs in small quantities in more than 800 minerals and causes the blue color of aquamarine beryl. The chemical properties of scandium resemble those of yttrium and the rare earth metals. It has 11 known isotopes, only one of which occurs in nature. Scandium exhibits an oxidation state of exclusively 3+. Because it is difficult to process, scandium has few commercial uses, but shows promise in electronics and high-intensity lighting.

Yttrium is one of four chemical elements (the others being erbium, terbium, and ytterbium) named after Ytterby, a village in Sweden which is rich in unusual minerals and rare earths. Yttrium is a metal with a silvery luster and properties closely resembling those of rare earth metals. Its principal use is as the matrix of europium-activated red phosphors that give the red hue in color television tubes.

Lanthanum is a chemical element, a white, malleable metal, and the first of the rare earths. Lanthanum is found with other lanthanides in monazite, bastnaesite, and other minerals. It was discovered in 1839 by the Swedish chemist Carl G. Mosander. Scientists have created many radioactive isotopes of lanthanum. Because lanthanum increases the refractive index of glass, it is used in manufacturing high-quality lenses. Lanthanum is largely used as a catalyst for cracking crude petroleum. It is also used as a reagent and as a phosphor in fluorescent lamps.

The lanthanides are in many minerals, principally monazite. The only commercially useful ores are massive monazite and monazite sand, a phosphate of the cerium group metals: bastnasite and related fluocarbonate minerals of the cerium group; minerals of the yttrium group—gadolinite, a silicate of yttrium, cerium,

COMPREHENSIVE REVIEW IN TOXICOLOGY

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chapter 39

Iron

Iron is distributed throughout all life forms and is one of the most abundant and important of the biological trace metals. Although written reports of the toxic effects of iron have been known for more than 100 years,[1] iron has been used medicinally for several centuries.[2,3] Iron and its compounds were once widely regarded as relatively harmless, and most adults and some medical personnel still may not be fully aware of iron's serious potential as a poison.[3] Iron poisonings still occur each year in the United States. Although the mortality rate today is less than 5%,[4,5] at one time it was as high as 50% in serious poisonings.[3,6–8] The decline in mortality rate is due in part to the use of the chelating agent deferoxamine (Desferal®), but in addition better supportive medical care has become available.[8]

Ferrous sulfate and ferrous gluconate are two of the most common preparations of iron. The accidental ingestion of preparations containing iron is still relatively common in children because of the multitude of such preparations (Table 39-1)[9]; intentional overdose from iron is occasionally seen in adults.[6,10] Many iron preparations are sugar-coated and brightly colored, which increases their attractiveness to children.[2] Iron tablets may also be confused with similar-appearing sugar-coated candies.[11] In addition, in homes with young children containers may be kept on the dining room table or the kitchen counter rather than in the medicine cabinet.[12–14] The failure to dispense iron in child-resistant containers also may contribute to the problem.[15] Because of such factors, the incidence of iron

Table 39-1 Selected Iron Preparations by Trade Name

Ferrous Sulfate	*Ferrous Gluconate*	*Ferrous Fumarate*
Feosol	Fergon	Feco-T
Fer-In-Sol	Ferralet	Femiron
Fero-Gradumet	Ferrous-G	Feostat
Ferralyn		Fumasorb
Mol-Iron		Fumerin
		Ircon
		Laud-Iron
		Manlron
		Toleron

poisonings in children younger than 5 years of age appears to be greater than in adults.

Iron is capable of producing chronic poisoning as a result of dietary or medicinal overload, from various types of iron storage diseases, or secondary to occupational exposure. The emergency department physician, however, is most commonly confronted with the acute ingestion of iron.

ABSORPTION

Iron crosses cell membranes only in the ferrous state; ferric ions in food are liberated in the stomach by acid digestion, reduced to the ferrous state, and absorbed. Typical daily intake of iron is approximately 15 to 40 mg,[16] but because of an intestinal mucosal block only 10% of ingested iron is absorbed.[12,17] In the routine daily absorption of dietary iron, the transport of ferrous compounds is energy dependent. This saturable, carrier-mediated uptake process is dependent on binding of iron in the lumen of the gastrointestinal tract and is the rate-limiting step for iron absorption. Absorption occurs mostly in the duodenum and upper jejunum, although the entire intestinal tract, including the colon, is able to absorb iron.[11,18] The divalent (ferrous) iron is absorbed into the gastrointestinal mucosa and converted to the trivalent (ferric) form, which attaches to ferritin in the intestinal mucosal cell wall.[2] The ferritin-ferric complex then passes into the bloodstream and is attached to transferrin.[12] Iron is then carried to the reticuloendothelial cells of the bone marrow for hemoglobin synthesis or to the liver or spleen for storage as ferritin or hemosiderin (Fig. 39-1).[17]

Toxic amounts of iron in solution are rapidly absorbed in the large and small bowel in a concentration-dependent fashion. With toxic amounts the capacity of the normal mechanisms of absorption is exceeded, and absorption becomes a passive, first-order process.[12]

DISTRIBUTION

The body contains approximately 4 to 5 g of iron, of which approximately 60% is contained in hemoglobin, 25% is stored as ferritin and hemosiderin (mainly in the liver), 3% is in myoglobin, and 1% is distributed among various heme-containing enzymes such as cytochrome oxidase, xanthine oxidase, and catalase.[16,18]

EXCRETION

Once iron is absorbed, its removal from the body is difficult. Although iron is lost through sweat, bile, and the desquamation of skin and mucosal surfaces, this loss only totals roughly 1.5 mg/day. In women an additional 0.5 mg/day may be lost in the menses.[12] There is no effective physiologic mechanism for iron excretion,[16,18] which is a fact of great importance in iron intoxication.

TOXICITY

When estimating toxicity of an acute ingestion of iron, the amount of elemental iron should be used in the calculation rather than the milligrams of a particular iron preparation.[2] Ferrous sulfate contains approximately 20% elemental iron, ferrous gluconate 12%, ferrous fumarate 33%, and ferrocholinate 13%.[2,19] Conversion factors for calculating the amount of elemental iron in an iron preparation are given in Table 39-2. For example, there is 60 mg of elemental iron in 300 mg of ferrous sulfate (the total milligrams of prepared iron [300] divided by 5).

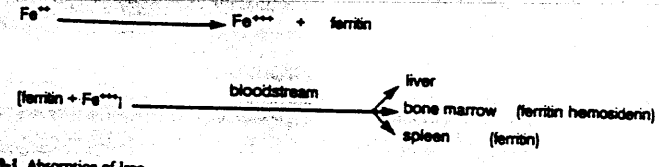

Figure 39-1 Absorption of Iron

Table 39-2 Amounts of Elemental Iron in Various Iron Preparations

Preparation	Percentage of Iron	Conversion Factor*
Ferrous Sulfate	20	5
Ferrous Gluconate	12	8.7
Ferrous Fumarate	33	3
Ferrocholinate	13	7.7

* Conversion factor to calculate amount of elemental iron from milligrams of prepared iron.

Reduced or metallic iron in powder form is nontoxic unless it is oxidized and enters the metabolic cycles.[20] A dose of 20 to 60 mg/kg of elemental iron is considered toxic, and a lethal dose is within the range of 60 to 180 mg/kg.[5,18,21]

The basic pathophysiologic effects of iron in toxic doses are of five types: (1) metabolic disorders, (2) hepatic dysfunctions, (3) CNS dysfunctions, (4) cardiovascular system dysfunctions, and (5) gastrointestinal tract disturbances.[12]

The symptoms of iron poisoning are due to both local and systemic effects and may be influenced by factors such as the chemical and physical forms of the iron, dose, route of administration, and duration of exposure.[22] In general, the ferrous salts are more toxic than the ferric salts. Although a mucosal block or barrier to the absorption of iron exists with normal intake of iron, in overdose situations the mucosal barrier ceases to exist and great amounts of iron may be absorbed.[14] In this event, absorbed iron exceeds the binding capacity of transferrin and passes into various tissues, causing toxicity.

There are five phases of intoxication associated with the acute significant ingestion of iron (Table 39-3). These phases represent a rough guideline for the evolution of various toxic effects.

Table 39-3 Phases of Iron Intoxication

Phase 1: gastrointestinal (30 minutes to 2 hours)
- Vomiting
- Hematemesis
- Abdominal pain
- Diarrhea
- Lethargy
- Shock
- Hypotension
- Metabolic acidosis

Phase 2: "recovery" (2 to 24 hours)
- Apparent response to therapy

Phase 3: metabolic acidosis (12 to 48 hours)
- Shock
- Coma

Phase 4: hepatic (2 to 4 days)
- Hepatic necrosis
- Bleeding diathesis

Phase 5: gastrointestinal (2 to 4 weeks)
- Gastric scarring
- Pyloric stenosis
- Achlorhydria
- Hepatic cirrhosis
- CNS abnormalities

Phase 1

Phase 1 may begin 30 minutes to 2 hours after an acute ingestion. The first obvious signs of toxicity are gastrointestinal; this symptomatology not only is predominant but is considered the *sine qua non* of iron poisoning. Vomiting is invariably the first manifestation of toxicity and usually occurs in the first hour after ingestion.[5] This may possibly proceed to hematemesis as a result of acute hemorrhagic gastritis, which may occasionally be life threatening.[1] Other symptoms include colicky abdominal pain and diarrhea (which sometimes may be bloody and explosive). Lethargy (a common early symptom), coma, hypotension, and metabolic acidosis may ensue during this early phase.[23]

Iron is a corrosive agent and, on direct contact, may produce lesions similar to those caused by acids, although generally they are more superficial in nature.[24] Because iron is a solid, it

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spares the mouth, pharynx, and upper esophagus. Liquid preparations and tablets primarily affect the pyloric region of the stomach and the duodenum. Enteric-coated tablets may also involve the lower small intestine.[14] Chewable tablets are associated with more proximal lesions.

Phase 2

Phase 2 may occur 2 to 24 hours after an ingestion; at this time the patient appears to recover. This phase may be quite deceptive because the patient may seem to have responded to therapy or the condition may continue to go undiagnosed.[24] The course of the intoxication proceeds directly to the next phase, however.

Phase 3

Phase 3 usually begins 12 to 48 hours after ingestion. A metabolic acidosis that may be particularly resistant to bicarbonate therapy, as well as shock and coma, may ensue. Metabolic acidosis from iron may be due to the hydrogen ion produced during conversion of ferrous to ferric iron in the blood, with the formation of ferric hydroxide complexes in the circulatory system.[6,16,25] In addition, however, there is an interference with the Krebs cycle enzymes in the liver and other tissues, which causes a block in organic acid metabolism and a buildup of lactic and citric acids.

Shock is a cardinal feature of fatal acute iron poisoning in children. It may be diphasic, occurring within the first 6 to 8 hours and again approximately 36 hours after ingestion.[26] The shock is thought to be due to peripheral circulatory failure induced by absorbed iron as well as to other factors such as ferritin, which may be acting as a vasodepressant. In addition, serotonin or histamine release may act to cause hypotension. The most likely explanation for shock is a combination of these factors in addition to the direct vasodilation effect of iron on blood vessels, which leads to shock. After acute ingestion of a large dose of iron there is a dramatic decrease in circulating plasma volume, as reflected in increases in the hematocrit. Cardiac output is lowered on the basis of a decreased filling pressure.

Phase 4

Phase 4 may begin 2 to 4 days after an ingestion. The liver may rarely be a target organ for damage by direct uptake of iron, leading to hepatic necrosis. This may be evidenced by elevation of bilirubin, serum glutamic-oxaloacetic transaminase, and alkaline phosphatase concentrations and possibly manifested clinically by jaundice.[27] In severe cases, hepatic coma with behavioral changes and elevated blood ammonia values have been reported. Damage is thought to be due to cellular injury from the direct action of iron on the mitochondrial cells of the liver. Another theory suggests that hepatic necrosis may be caused by depletion of sulfhydryl enzymes secondary to iron, which then allows another unknown toxin to produce necrotic changes.[27,28]

A bleeding diathesis may also be noted during this phase.[5] These changes, if present, are due to a direct effect of iron on the various proteins involved in blood coagulation and are not a consequence of acidosis, shock, or liver damage.[20] Interference with these clotting mechanisms may contribute to severe hemorrhagic manifestations, which may include prolongation of the prothrombin time, reduction in thromboplastin generation, poor to absent clot retraction, and thrombocytopenia.[5] All three stages of clotting may be involved: the generation of thromboplastin becomes impaired (first stage), the prothrombin time is prolonged (second stage), and the conversion of fibrinogen to fibrin becomes defective (third stage).

Phase 5

Phase 5 may occur 2 to 4 weeks after ingestion as a result of the early corrosive effect of iron on the gastrointestinal tract. It may be manifested by intractable nausea and vomiting secondary to gastric scarring as well as fibrosis leading to pyloric obstruction or stenosis.[24] One report described a severe corrosive gastroduodenitis with subsequent fibrosis and scarring of the stomach and duodenum, necessitating abdominal surgery.[29] Also, perforation and stricture formation are not uncommon. These lesions can be demonstrated by barium contrast studies. Because of this destruction, achlorhydria may supervene together with other nutritional problems caused by the destruction of the mucosa.[18]

DIAGNOSIS AND LABORATORY ANALYSIS

History and Physical Examination

The diagnosis of acute iron poisoning in a young child is frequently complicated by an unreliable history and by the diphasic nature of the symptoms. Patients may present without a definite history of iron ingestion, but it should be suspected in any patient who is vomiting, has bloody diarrhea, or is lethargic, comatose, or in shock. If iron poisoning is suspected an examination of the patient's emesis may reveal iron tablets, and the stool should then be examined for a black color secondary to iron ingestion (Table 39-4).[30]

Table 39-4 Diagnostic Workup of Iron Poisoning

Unknown poisoning
Historical clues
Lethargy
Vomiting
Hematemesis
Shock
Bloody diarrhea
(If positive, proceed to suspected or confirmed poisoning)
Suspected poisoning
Plain roentgenogram of abdomen
Examination of emesis for iron
Examination of stool for black color
Provocative deferoxamine test of gastric aspirate
(If positive, proceed to confirmed poisoning)
Confirmed poisoning
Plain roentgenogram of abdomen
Iron and total iron-binding capacity
Fischer test (unreliable)
Clotting studies
Complete blood cell count
Blood type and crossmatch
Electrolyte studies
Arterial blood gas analysis

Plain Roentgenography

Plain roentgenography of the abdomen can be a useful diagnostic procedure in the management of iron overdose (Fig. 39-2).[13,31] Depending on the time after ingestion of iron-containing tablets, the preparation's solubility, and the degree of prior emesis or gastric lavage, the film can be a guide to the number of tablets taken and can indicate whether removal is necessary. A normal roentgenogram, however, does not rule out an ingestion because iron in solution is no longer radiopaque[29] and because iron-containing vitamins can be imaged for only a brief period and appear with low density. Ferrous sulfate, gluconate, and fumarate all have a high content of elemental iron, which results in a slower dissolution of the tablets and thereby renders the preparations radiopaque for a longer period of time.

Figure 39-2 Plain abdominal radiograph showing concretion of iron tablets in the stomach. *Source:* Reprinted with permission from *Medical Toxicology* (1986;1:89). Copyright © 1986, Adis Press International Inc.

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Colorimetric Tests

Colormetric testing has serious limitations, and the results should not be relied on to make a diagnosis or to determine extent of injury.[32] Two tests that have been employed in a suspected iron overdose involve the chelating agent deferoxamine. One test involves the oral administration of deferoxamine and is an attempt at diagnosis. The other involves intravenous administration of deferoxamine and is an attempt at determining whether free iron is in the blood, which is an indication for chelation therapy.

In the first test, a small amount of deferoxamine is mixed with gastric aspirate. If a red color is produced, the presence of iron in the gastrointestinal tract is confirmed.[32] The major limitation of this test is that gastrointestinal bleeding is usually associated with a moderate to severe iron intoxication.[31]

The second test is provocative and is not suggested for routine use; however, it may be helpful in the occasional situation where no laboratory analysis is available. This test involves the administration of deferoxamine intravenously (10 to 15 mg/kg). Production of a reddish-brown urine indicates that there is free iron circulating in the body that has been chelated with the deferoxamine. The value of this test may be limited because the characteristic color may not always develop despite the presence of chelated iron in the urine.[31]

Serum Iron and Total Iron-Binding Capacity

Further workup for suspected iron overdose should include a definitive test of the serum iron and iron-binding capacity, the results of which are crucial when deciding whether chelation treatment is to be instituted. As mentioned earlier, iron is considered toxic when the plasma concentration exceeds the total iron-binding capacity of transferrin because, once plasma transferrin has been saturated, the iron is distributed into cells and causes damage. Many hospitals do not perform serum iron and total iron-binding capacity tests as a "stat" procedure, but the importance of this test requires that there be some backup facility that can do so. Emergency serum iron measurements should be available around the clock to obviate the use of indirect methods.[31]

The serum iron concentration must be measured after absorption is complete and before distribution and protein binding in the tissues have contributed to a significant decrease in the initial peak concentration.[14] Although the kinetics of iron after overdose have not been thoroughly investigated, the limited evidence available indicates that serum iron concentration usually peaks 3 to 5 hours after ingestion and decreases rapidly thereafter[22,33,35]; it is therefore advisable to obtain measurements during that time.[31] Because of the rapid clearance of free iron, severely toxic conditions may be associated with only minimally elevated plasma iron concentrations if values are obtained after the peak period.[35] Once the initial serum iron concentration has been determined to be in the toxic range, there is little value to continued measurements of the serum iron or total iron-binding capacity.

The normal serum iron concentration is 50 to 150 μg/dL in adults and children older than 5 years of age and 40 to 100 μg/dL for children younger than 5 years of age (Table 39-5). Total iron-binding capacity or plasma transferrin is roughly one-third saturated under normal conditions, with the total iron-binding capacity ranging from 300 to 450 μg/dL.[18] Serum iron concentrations less than 350 μg/dL have rarely been associated with significant illness.

Most commonly used methods for the measurement of serum iron concentrations involve the liberation of ferric iron bound to transferrin by weak reducing agents followed by the formation of a colored complex with ferrous iron and a chromogenic agent such as ferrozine. If chelation therapy is instituted these methods may reveal spuriously low serum iron concentrations because of the chelation of some of the iron liberated from transferrin.[31]

Miscellaneous Laboratory Procedures

The Fischer test[34] or variations of the colorimetric test[21] that attempt to determine free iron are unreliable, and their results should not be substituted for serum iron and total iron-binding

Table 39-5 ...ns and Toxicity

Iron Concentration (micrograms per deciliter)	...ne of Toxicity
100	No... (normal value)
100-300	Minimal
350-500	Moderate
500-1000	Serious
1000	Potentially lethal

capacity.[31,32] Clotting studies as well as a complete blood cell count, ...ectrolyte studies, arterial blood gas analys... and li... function tests should be obtained for b... blood type and hold should be performed because patients sometimes need blood transfusions. There is little value in obtaining indicators of hepatic function early in the course of iron intoxication other than for baseline values.[36] It is reasonable to obtain transaminase values after the first 24 hours to assess baseline hepatic function. Prognosis is correlated with the presence of severe symptoms (shock, coma, or vasomotor instability) as well as the serum iron concentration in relation to the total iron-binding capacity within the first 3 to 5 hours after ingestion.[31,37]

TREATMENT

Treatment must be vigorous and prompt and must consist of supportive measures, prevention of absorption of iron in the gastrointestinal tract, and chelation therapy (Table 39-6). Diuresis and dialysis have been shown to be ineffective. Although phlebotomy has been tried, the use of chelating agents is the preferred method of increasing excretion of iron.

Prevention of Absorption

Iron is notorious for its resistance to traditional stomach-emptying procedures probably because of its ability to clump together and form large aggregates. Initial treatment, however, should still consist of emesis or lavage. Gastric lavage in this instance may be preferable because agents can be administered down the lavage tube that form a poorly soluble complex with iron and so limit its absorption.

Table 39-6 Treatment of Iron Poisoning

Indication	Treatment
Acute ingestion	Emesis or lavage
Fluid loss	Normal saline
Metabolic acidosis	Bicarbonate instillation
Shock	Sodium bicarbonate Military antishock trousers ... Vasopressors
Severe ...	Deferoxamine IV: 1 g not to exceed 10 to 15 mg/kg/hour (or 6 g per 24 hours or 80 mg/kg per 24 hours) IM: 40 to 90 mg/kg every 8 hours

Intragastric Complexation

The use of intragastric complexation in iron intoxication is controversial,[37] but phosphates, deferoxamine, bicarbonate, and magnesium hydroxide have been suggested as complexing agents to decrease absorption of iron remaining in the gastrointestinal tract.

Phosphates. Sodium biphosphate (Fleet® enema) solution combines with the ingested iron to form ferrous phosphate and ferric phosphate. Because maximum phosphate absorption occurs in the midgut, even if a small amount of the lavage solution is not retrieved it could present a significant phosphate load for absorption.[14,31] In addition, the absorption of phosphate may be enhanced across an intestinal mucosal barrier that is disrupted by the direct irritant action of ingested iron. Because of reports of toxicity after the administration of phosphate in children, with ensuing hyperphosphatemia, hypocalcemia, and other disturbances (including dysrhythmias), this therapy is not recommended.[38,39]

Deferoxamine. The oral administration of deferoxamine has been suggested to reduce the absorption of iron, but there is evidence that this complex is absorbed and may lead to further iron toxicity. Because deferoxamine is only effective in chelating ferric iron and all medicinal preparations contain ferrous salts, intragastric deferoxamine would seem to be of little value.[31] In addition, deferoxamine is poorly absorbed from

Appendix E
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the gut when the mucosa is intact. Thus its use is not recommended.

Bicarbonate. An alternative lavage solution is sodium bicarbonate, which when administered down the lavage tube forms an insoluble complex of ferrous and ferric carbonate that is not absorbed from the gastrointestinal tract. Because sodium bicarbonate appears to be less dangerous than other intragastric complexing agents, its use is recommended. In addition, absorption of sodium bicarbonate could reduce the metabolic acidosis that occurs in iron intoxication.[38] After gastric emptying, 100 mL of a 5% solution of sodium bicarbonate or sodium bicarbonate ampules can be instilled through the gastric lavage tube and then retrieved. Although the efficacy of this treatment has recently been questioned,[37] there does not appear to be great potential for toxicity from this regimen.

Whole Gut Lavage

Whole gut emptying has been suggested if a slow-release iron formulation was ingested or if an abdominal radiograph after gastric lavage shows persistence of tablets in the stomach or small intestine.[31,40] When a large number of opacities are identified in a single location, it may be reasonable to consider surgical intervention. The clinician must consider the stability of the patient, the number of tablets seen on the radiograph, and the potential for other procedures such as lavage and emesis successfully to remove these tablets.

Other Therapeutic Measures

An important part of therapy consists of adequately correcting any third-space fluid losses with appropriate crystalloid. Military antishock trousers may also be applied in an effort to increase venous return. An indwelling urinary catheter should be placed to measure the urine output and to observe the color of the urine for determining whether the chelating agent should be continued. Sodium bicarbonate should be administered for metabolic acidosis, and vasopressors may be necessary for shock if fluid administration and military antishock trousers are ineffective.

Chelation Therapy with Deferoxamine

Deferoxamine mesylate is a chelating agent that was originally obtained from a species of *Streptomyces*, one of the organisms that produces low–molecular weight chelators as part of its iron-transport system. It was discovered as a result of the investigation of the antibiotic properties of the siderochromes, a class of naturally occurring compounds.[25] Clinical use of deferoxamine mesylate for cases of acute iron poisoning was first reported in the early 1960s.

When deferoxamine chelates with iron, it forms a brownish-red complex with iron bound in the center.[41] This stable ring, unlike free iron, is soluble in water and readily excreted by the kidneys. Theoretically, 100 mg of deferoxamine can bind 8 to 9 mg of elemental iron.[20,35] Deferoxamine has an affinity for iron that is 10 times greater than that of any other known chelator and thus combines more firmly than other chelators, with resultant greater urinary excretion of iron.[23] Deferoxamine also has the advantage of being specific for iron, with virtually no attraction to other metals. It therefore does not cause excretion of calcium, copper, magnesium, or zinc.[14,20,35] Deferoxamine has a volume of distribution of about 60% body weight and a plasma half-life of 10 to 30 minutes. It is metabolized to inactive products by plasma and other tissues.

Indication for Chelation Therapy

Chelation therapy is indicated when iron concentrations exceed the total iron-binding capacity or if the serum iron concentration is greater than 350 μg/dL,[1,33] or in any patient who exhibits serious systemic toxicity when no measurements can be obtained.[31] Chelation is not indicated if the patient is asymptomatic or has minor symptoms with no evidence of gastrointestinal bleeding or if the total iron-binding capacity is greater than the serum iron concentration and the patient has ingested approximately 150 to 300 mg/kg of elemental iron.

Method of Action

It is believed that the efficacy of deferoxamine involves the enhancement of iron elimination through the formation of water-soluble, renally excreted ferrioxamine.[42] Several reports suggest that deferoxamine also exerts a protective effect at the cellular level by chelation of iron in the extracellular space.[23] Another possibility is that deferoxamine enters cells and chelates extramitochondrial iron.[31]

Route of Administration and Dosage

Various regimens and routes of administration of deferoxamine have been recommended. Deferoxamine is poorly absorbed from the gut if the mucosa is intact and therefore should be administered parenterally. Intravenous administration is preferred,[1,35] but intramuscular administration was at one time suggested because of reports of hypotension from intravenous administration. It has been shown, however, that hypotension is a consequence of too rapid an intravenous administration. As long as deferoxamine is administered properly, there should be no significant side effects noted.

It has been shown that a dose of deferoxamine given by slow infusion results in more effective chelation and iron excretion than when the same dose is given as a single injection.[25,43] In addition, maximal iron mobilization may require constant exposure of labile iron pools to deferoxamine.[35] The pharmacodynamics of deferoxamine appear to support its use as a continuous infusion in acute iron overdosage to maximize net iron excretions. One gram should be administered in normal saline, with infusion rates not to exceed 10 to 15 mg/kg/hour.[31] This rate can then be reduced to 5 mg/kg/hour after 4 to 6 hours. In severe cases this therapy may be required for 48 to 72 hours.[44] In view of the possible intracellular action of deferoxamine, it appears reasonable to continue treatment until after the pink color of the urine has disappeared and the patient is without signs and symptoms of iron poisoning for at least 24 hours.[4] The total amount of deferoxamine should not exceed 6 g in any 24-hour period in an adult or 80 mg/kg in a child, whichever is lower.[35] In the absence of toxicity, larger doses may be administered.[31,42]

Although deferoxamine may be administered intramuscularly, the quantities required may cause pain at the site of injection, sterile necrosis, and local discoloration.[41] The dose for intramuscular administration in a child ranges from 40 to 90 mg/kg, not to exceed 1 g every 8 hours.[14,18,44] In an adult, 1 g is administered initially and is followed by 500 mg every 4 hours.[33]

Toxicity

The toxicity of deferoxamine is minimal, but symptoms may include gastrointestinal discomfort after oral administration and hypotension after excessively rapid intravenous administration of a large dose, which is probably a result of venous dilation.[24,35] If hypotension develops, the infusion should be temporarily stopped and begun again at a lower infusion rate.[31] In addition, tachycardia as a result of the hypotension and urticaria as an allergic response may occur. Lens opacification has been reported in animals after long-term administration of deferoxamine, but this is not a problem in the acute overdose situation.[25]

Dialysis

Although dialysis can be effective in removing the ferrioxamine complex or chelated iron, it is not as effective as renal excretion in iron removal. Dialysis is indicated only if renal shutdown occurs after chelation therapy has been instituted.[31]

Miscellaneous Methods

Exchange transfusion has been employed, but in view of the rapid intracellular movement of iron it is not an efficient therapeutic modality.[45] Surgical intervention may be necessary for the patient who develops signs of perforation and peritonitis in the early stages of intoxication or subsequent stricture formation,[24,46] and some investigators have recommended early laparotomy in patients with massive iron ingestion to resect potentially gangrenous bowel.[29] Individuals who recover from significant iron overdose should have adequate followup for potential long-term complications.

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MEDICAL TOXICOLOGY

DIAGNOSIS AND TREATMENT OF HUMAN POISONING

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who developed hemolytic anemia, renal failure, arrhythmias, and central nervous system depression during which an *E. coli* septicemia from intestinal wall invasion developed.[9]

TREATMENT

Vomiting usually makes emesis/lavage unnecessary. Activated charcoal/cathartic may be used but its role is unproven. Chelating agents are recommended in severe poisoning, but few pharmacokinetic data on humans exist to guide their use. Either intravenous $CaNa_2EDTA$ or intramuscular BAL is the agent of choice in severe ingestion. D-Penicillamine may be administered orally, if tolerated, to non-penicillin-allergic patients. Exchange transfusion has been used in a 2-year-old boy together with albumin-enriched peritoneal dialysis.[9]

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GOLD

In the form of gold sodium thiomalate, gold therapy is an acceptable treatment for rheumatoid arthritis. Adverse reactions occurring during therapy include interstitial pneumonitis,[1] dermatitis, stomatitis, bone marrow suppression (leukopenia, thrombocytopenia, anemia), nephrotic syndrome, nephritis, and hepatitis. An encephalopathy also has been associated with gold therapy.[2] Most overdoses to date involve the inadvertent administration of 500 mg gold salt as an intramuscular injection (10 times the therapeutic dose). Usually the patient remains asymptomatic but may develop mild elevations in serum hepatic transaminase levels[3] and thrombocytopenia.[4] A 32-year-old patient developed ventricular tachycardia 3 hours after the intramuscular injection of 500 mg of aurothiomalate.[5]

Studies in animals indicate that high gold concentrations produce acute renal failure.[6] The weekly administration of 50 mg of soluble gold salt produces steady-state serum gold concentrations of 400 to 800 μg/dL by the eighth week; toxicity, however, cannot be predicted by blood levels alone. Peak serum gold level was 5 mg/dL after an injection of 500 mg gold aurothiomalate.[4] Treatment includes the use of steroids for pneumonitis,[7] BAL chelation,[8] and supportive care. (A patient who received two 500-mg gold aurothioglucose injections within 1 week remained asymptomatic without chelation therapy.)[3]

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IRON

INTRODUCTION

Epidemiology

Approximately 5,000 cases of poisoning with iron preparations occur every year in the United States. In contrast to other heavy-metal poisonings, which commonly are associated with work exposures, most iron toxicity results from the ingestion of iron-containing products by children. There has been a dramatic increase in iron poisonings over the last four decades. The introduction of the antidote deferoxamine has reduced the mortality in hospitalized patients from 50% to less than 2%. According to American Association of Poison Control Centers data, iron exposures are less frequent than exposures to calcium salts and fluoride, but fatalities have occurred after iron exposure.[1]

Product Fo ations

The relative toxicity of iron lts from the amount of elemental iron ingested. This in rn depends on the type of iron salt involved. The large m ority of poisonings result from ferrous sulfate ingestion.

The percentages of elemer tal iron contained within specific salts are as follows:

Ferrous sulfate	
Anhydrous salt	36.8%
Crystalline salt	20.1%
Ferrous chloride	
Anhydrous salt	44.1%
Crystalline salt	28.1%
Ferrous gluconate	
Anhydrous salt	12.5%
Dihydrate salt	11.6%
Ferrous fumarate	33%
Ferric chloride	
Anhydrous salt	34.3%
Hexahydrous salt	20.7%
Ferric ammonium citrate	14%–18%

Estimation of Toxic Dosage

Remember that the reliability of estimating the number of tablets ingested is only as good as the history, which itself is often unreliable. Always treat symptoms rather than history. Based on the quantity ingested, the following amounts of elemental iron indicate the severity of toxicity:

Nontoxic Dose. <10 to 20 mg of elemental iron ingested per kilogram (e.g., 3 tablets of ferrous sulfate in a 10-kg child = 3 × (0.20) (325 mg)/10 kg = 19.5 mg/kg).

Toxic Range. >20 mg/kg (4 ferrous sulfate tablets in a 10-kg child). Decontamination is recommended at this level and referral to a physician above 60 mg/kg.

Lethal Range. 180 to 300 mg/kg (30–45 tablets in a 10-kg child). Death has been reported from the ingestion of 2.7 g (542 mg elemental iron) and survival from the ingestion of 19.5 g of ferrous sulfate (3.9 g elemental iron).

PHARMACOKINETICS

Absorption

Iron is absorbed through the mucosal barrier in the ferrous (2+) state where it oxidizes to the ferric (3+) state and attaches to the storage protein, ferritin. Control of iron stores depends on variation in absorption rather than excretion. A fatal case of iron toxicity developed in a worker who fell into a vat of ferrous chloride. Absorption has occurred through aspiration, ingestion, and burned skin.[2]

Distribution

Iron is released from the ferritin to the globulin transferrin in the plasma and then transported to the blood-forming sites.

Excretion

No good mechanism for iron excretion exists. Consequently, the natural elimination of iron by the body is extremely limited and occurs by blood loss or desquamation of gastrointestinal mucosa. Adults lose up to 2 mg of iron daily.

PATHOPHYSIOLOGY

Toxic doses of iron overwhelm the normal gastrointestinal regulatory mechanism (suggesting that saturable transport systems are not involved at high concentrations); this results in massive iron absorption.[3] Major toxicity occurs when serum iron levels exceed the iron-binding capacity of transferrin. Free circulating iron damages systemic blood vessels. The release of the potent vasodilator ferritin and, possibly, the release of serotonin and histamine potentiate the vascular damage caused by free serum iron. In severe iron overdose, the coagulative necrosis with platelet aggregation appears similar to the damage caused by corrosive agents.

Gastrointestinal Tract

The corrosive effect of iron results in stomach and intestinal erosions and ulceration (i.e., hemorrhagic gastritis and enteritis with blood loss); however, there is a lack of correlation between the severity of intestinal damage and death. Pyloric obstruction and intestinal scarring are rare, late complications.

Liver

Circulating free iron initially accumulates in the Kupffer cells and later the hepatocytes. The effects on the liver are highly variable and range from no abnormalities to cloudy swelling of the hepatocytes, portal iron disposition, fatty metamorphosis, and massive periportal necrosis.[4,5]

Hepatic damage may progress to hepatic failure with hypoprothrombinemia and hypoglycemia. Hepatorenal syndrome may occur. Free iron inhibits the thrombin-induced conversion of fibrinogen to fibrin and, therefore, directly affects coagulation.[6]

Cardiovascular System

Fatty degeneration of the myocardium occurs in iron intoxification. Iron acts on the vascular system to increase venous pooling (increased capillary permeability) and decrease cardiac output (reduced postarteriolar and venous tone) and, subsequently, produces hypotension. Proposed etiologies for postarteriolar dilation include a direct iron effect, ferritin release, and serotonin/histamine release.

Kidney

Masses of iron-containing granules accumulate in the capsular space and tubule lumen; however, tubular degeneration is rare.

Acidosis

Interference with oxidative enzymes, the release of hydrogen with formation of ferric hydroxides, and the accumulation of lactic acid from anaerobic metabolism may all result in severe metabolic acidosis.[7] Ferrous ions catalyze lipid peroxidation which can cause disruption of mitochondrial membranes and the Krebs cycle. Iron also shunts electrons from the electron transport system by acting as an electron sink.[8] The result is the production of a metabolic acidosis.

Brain

Iron can produce cerebral edema by an unknown mechanism.

CLINICAL PRESENTATION

Classically, severe iron toxicity presents in four distinct phases.[9] Symptoms in the first phase involve gastrointestinal tract irritation and metabolic abnormalities (e.g., acidosis).

Initial Period

A severe hemorrhagic gastritis characterizes the initial period (½–2 hours postingestion). Vomiting is the most sensitive indicator of serious ingestion, with a 94% sensitivity but only a 25% specificity.[10] Diarrhea is a less sensitive but more specific indicator of serious iron ingestions. Central nervous system (lethargy and coma) and cardiovascular (pallor, tachycardia, hypotension) symptoms may be manifested early in severe ingestions.

Quiescent Period

During this period (variable, up to 12 hours) a deceptive improvement and stabilization occur, which frequently result in premature discharge from health care facilities. Alternating periods of lethargy may appear during this stage. In severe overdoses this quiescent period may be brief.

Recurrent Period

Systemic symptoms that are life threatening predominate during this phase (12–48 hours).

Gastrointestinal Tract. Hematemesis, melena, gastrointestinal perforation.

Central Nervous System. Increasing lethargy, coma, convulsions.

Cardiovascular System. Vasomotor collapse, cyanosis, pulmonary edema.

Liver/Kidney. Hepatorenal failure with coagulation defects and hypoglycemia.[11] These effects developed toward the end of this phase. Some authors consider the hepatic necrosis a distinct phase separate from the recurrent phase.

Metabolic. Severe metabolic acidosis, hypoglycemia.

Late Period

Gastric scarring and pyloric obstruction appear during the late recovery phase (4–6 weeks).

LABORATORY

Serum Levels

Reliability

Although serum iron levels cannot always be correlated with the severity of intoxication, patients are at risk if free iron exists in the plasma (i.e., serum iron level exceeds the total iron-binding capacity [TIBC]). Peak serum iron levels occur 2 to 4 hours after ingestion and correlate best with potential toxicity. Serum iron levels drawn more than 4 to 6 hours postingestion may underestimate toxicity because of the binding of iron to ferritin and the distribution of iron into the tissues. The administration of deferoxamine interferes with chromogenic methods of iron determination but not with atomic absorption spectrophotometry.[12]

Indications

All symptomatic patients and those patients with a history of ingestion of more than 40 mg of elemental iron per kilogram should have blood drawn for serum iron and TIBC tests.

Interpretation

Heparinized samples of whole blood should be drawn 3 to 5 hours postingestion. Because of rapid iron clearance, low blood levels after this period may be misleading.

If TIBC levels are not available to determine the presence of free iron, serum iron levels may be used to predict toxicity. At high serum iron levels, high iron levels may falsely increase serum TIBC concentrations. Fewer than 10% of patients with serum iron levels below 500 μg/dL will develop cardiovascular collapse or coma. Between 500 and 700 μg/dL, the percentage increases to 25%. Above 700 μg/dL, approximately 50% of the patients have severe symptoms.[13] Correlation of serum iron levels (2–4 hours postingestion) with probable toxicity is as follows:

0–100 μg/dl	Normal range
100–350 μg/dl	Definite poisoning, questionable toxicity
350–500 μg/dl	Potentially serious toxicity
500–1000 μg/dl	Definite serious toxicity
Over 1000 μg/dl	Potentially fatal

Abnormalities

Abdominal X-Rays

Radio-opacity depends on several variables, including time since ingestion, content of elemental iron, and type of formulation (e.g., vitamins with iron and sugar-coated candy tablets are not radio-opaque). Negative radiographs, especially 2 hours after ingestion, do not exclude iron overdose.[14] Although chewable vitamins with iron are radio-opaque, visualization of these tablets clinically is unlikely (E. P. Krenzelok, personal communication). Within 2 hours the abdominal x-ray is useful as a measure of the efficiency of gastric emptying in all except minor ingestions.

Blood

Specific indicators of elevated serum iron levels include the white blood cell count and blood glucose levels. A leukocytosis over 15,000/mm^3 and a hyperglycemia exceeding 150 mg/dL correlated with elevated serum iron levels (over 300 μg/dL) in a retrospective study.[10] These measures are *not* sensitive and are *not* predictive if there are fewer than 15,000 WBC or the serum glucose is below 150 mg/dL. When serum iron levels are not immediately available, these levels may help predict potential toxicity *if* elevated.

Ancillary Tests

Supportive studies in patients with serious ingestions (serum iron levels over 350 μg/dL) include guaiac tests of the stool and gastric aspirate, serum hepatic transaminase levels, coagulation studies, complete blood count, hemoglobin, hematocrit, electrolytes, glucose, arterial blood gases, blood type, and antibody screen.

Rapid Screening Tests

Fischer developed a rapid serum detection method for iron using the chromogen 2,4,6-tripyridyl-*s*-triazine (TPTZ).[15] McGuigan et al described a qualitative deferoxamine color test for gastric aspirate as an adjunctive screening method for iron within 2 hours of ingestion.[16]

Two milligrams of gastric fluid and two drops of 30% H_2O_2 are placed in each of two plastic tubes. One-half milliliter of a deferoxamine solution (composed of one 500-mg ampule of deferoxamine and 4 mL of distilled water) is added to one tube. An immediate change of color (light orange to dark red) in that tube compared with the control indicates the presence of iron. Negative results more than 2 hours postingestion do not reliably exclude iron poisoning because of the possibility of absorption.

TREATMENT

Decontamination

Emesis

Emesis should be induced, unless there is a definite risk of aspiration, when the history indicates an iron ingestion exceeding 20 mg/kg or symptoms suggest significant iron ingestion.

Lavage

Gastric lavage is the alternative method of decontamination for obtunded patients who do not have a gag reflex. Mechanical removal may be difficult because of tablet size and cohesiveness. The type of lavage fluid used to complex iron is controversial. A 1% to 4% sodium bicarbonate solution (add 50-mEq ampule to 1 L D_5W/0.45% NaCl) complexes some of the free ferrous ion into the relatively nonsoluble ferrous carbonate form. The actual amount of ferrous carbonate formed has not been well studied in vivo and depends on gastric pH, contact time, and relative concentrations. The role of oral deferoxamine solution is unclear because of the controversy over whether or not the iron–deferoxamine complex is absorbed. This complex requires an alkaline solution and hence bicarbonate must be added. A major problem is the large amount (and high cost) of deferoxamine required to complex the iron (100 mg deferoxamine complexes 8.5 mg iron).

Oral Solutions

The standard bicarbonate solution (1 mL [1 mEq/mL]/kg administered after lavage or emesis) may be the only oral solution necessary in most cases. Whether this solution significantly decreases iron absorption remains controversial; conventional antacids may be an equally safe alternative.[17] However, in severe ingestions the addition of 5 to 10 g of deferoxamine may be theoretically helpful at the end of lavage. All potentially serious iron ingestions should receive an abdominal x-ray, and the decontamination procedures should be repeated if the upright abdominal film shows retained tablets. The use of undiluted sodium dihydrogen phosphate solution (Fleets Phosphasoda Enema) has caused severe hypernatremia and hypocalcemia.[18] This solution appears less efficacious in vitro than bicarbonate in complexing free iron. Even after lavage with either phosphate or bicarbonate, large amounts of iron remain free in solution based on in vitro studies.[19]

Bezoar Formation

Iron tablets may form concretions or adherent masses that are resistant to decontamination measures and endoscopic removal. Continuing release of iron from large bezoars may produce delayed elevation of iron levels, gastrointestinal inflammation, hemorrhage, and scarring.[20] In situations in which serum iron levels rose and the concretions failed to progress down the gastrointestinal tract, gastrotomy has reduced toxic effects and prevented perforations.[21,22]

Activated Charcoal

This compound does not effectively bind iron; however, the iron–deferoxamine complex does adsorb onto charcoal with an affinity similar to that of salicylates.[23]

Cathartics

Sodium sulfate or magnesium sulfate may be used unless the patient already has diarrhea.

Elimination Enhancement

Exchange transfusion offers the greatest potential for iron removal and in experiments in animals this procedure has removed more iron than intravenous deferoxamine. However, the clinical efficacy of such removal is uncertain, since deferoxamine chelates only the important toxic component (i.e., *free* iron), whereas exchange transfusion removes both free and bound iron. Hemodialysis removes the iron–deferoxamine complex but not the iron itself. Hence, its use is limited to those patients with impaired renal function. Methods to enhance elimination probably do not alter clinical outcome because only a small amount of absorbed iron is removed.

Antidotes (Deferoxamine [Desferal])[24]

Mechanism of Action

Deferoxamine is a specific chelator of ferric iron produced by the bacteria *Streptomyces pilosus*; it is currently the chelator of choice. Other chelating iron agents (e.g., ethylenediamine-*N*,*N*′-bis(2-hydroxyphenylacetic acid) appear more effective in animals, but clinical testing has not been started.[25] Although 100 mg of deferoxamine will bind about 9 mg of free circulating elemental iron, deferoxamine does not remove iron from transferrin or hemoglobin. Deferoxamine may operate on the labile iron pool in the intracellular portion of hepatocytes where it preferentially removes ferritin iron over hemosiderin iron.[26]

Increasing the elimination of iron is not necessarily the main mechanism by which deferoxamine reduces iron toxicity.[27] Since the volume of distribution of the iron–deferoxamine (ferrioxamine) is relatively small, free iron is kept in the extracellular space. Furthermore, the binding of cytoplasmic free iron reduces the free iron–induced disruption of mitochondrial cell membranes and enzyme systems. The iron–deferoxamine complex, ferrioxamine, is highly stable at physiological pH.[28]

Pharmacokinetics

Deferoxamine is poorly absorbed from the gastrointestinal tract and, therefore, should be given parenterally for maximum effect. Deferoxamine has a volume of distribution of about 60% of body weight and a plasma half-life slightly over 1 hour. The liver detoxifies deferoxamine. Unlike elemental iron, the deferoxamine iron–complex is excreted from the kidney.

Adverse Effects

Thalassemia patients have received deferoxamine, 425 mg/kg intravenously over 24 hours (i.e., 16 g), without complications.[29] Intravenous doses of 125 mg/kg each day for a number of days caused night blindness and visual field defects which improved on withdrawal.[30] Long-term deferoxamine therapy may cause cataracts, cone and rod dysfunction, and dyschromatopsia, particularly in patients with renal dysfunction.[31] Rheumatoid arthritis patients treated with deferoxamine doses as low as 15 g over a week have developed retinal damage.[32] Flushing, urticaria, and rarely cases of anaphylactic reactions may occur possibly because of histamine release. The most common toxic reactions include gastrointestinal distress and hypotension. Doses of 0.75 mg/kg/min produce hypotension which usually responds to reduced infusion rates and fluid challenges. Vasopressors may be necessary. Rapid desensitization protocols have been developed for sensitized patients with serious iron toxicity.[33] Since the ferrioxamine complex is renally excreted, deferoxamine should be used cautiously in patients with compromised renal function. Hemodialysis may be considered when high deferoxamine doses are needed. Deferoxamine has been administered to pregnant women without adverse effects to the developing child,[34] and, conversely, a pregnant mother died of iron poisoning (serum iron, 1700 mg/dL) after deferoxamine was withheld.[35]

Indications

Therapy can be based on the severity of symptoms and serum iron levels (Fig. 37-1).

Peak Serum Iron Levels below 350 μg/dl. The value of deferoxamine at this level is minimal, if any, since significant toxicity usually does not occur. However, should the TIBC fall significantly below serum iron levels, a deferoxamine intramuscular challenge may be used to detect elevated free iron levels.

Peak Serum Iron Levels between 350 and 500 μg/dl. Any symptomatic patient with these levels should be given deferoxamine. No clear, well-documented guidelines exist to decide which asymptomatic patients in this range will develop subsequent toxicity. Hence, the use of deferoxamine in this range requires clinical judgment. Again, a deferoxamine challenge can be used to identify those patients with free serum iron who may need further chelation therapy.

Peak Serum Iron Levels above 500 μg/dl. All patients should have prompt intravenous deferoxamine therapy.

Significantly Symptomatic Patients. All patients with altered mental status (be sure to check glucose level and give intravenous glucose), hypotension, bleeding, or protracted vomiting should receive prompt intravenous deferoxamine therapy. Do not wait for serum iron levels to return from laboratory.

Dose Recommendations

Deferoxamine Challenge. This procedure helps identify those patients with free, circulating iron who may need

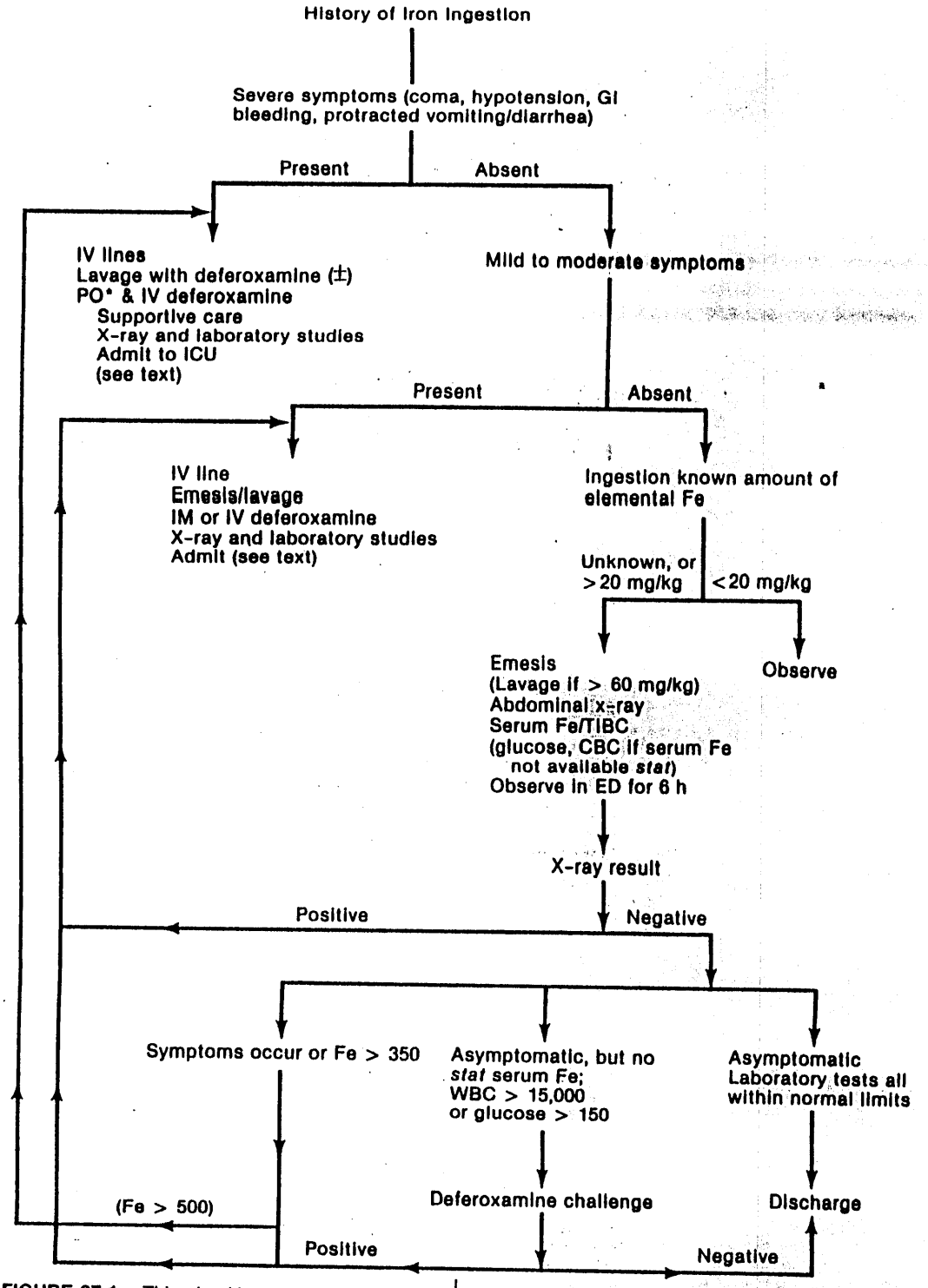

FIGURE 37-1. This algorithm outlines the initial approach to iron ingestion. *Oral use of deferoxamine is controversial; see text for discussion. Adapted from Henretig FM, Temple AR: Acute iron poisoning in children. Emerg Med Clin North Am 1984;2:127. Used with permission from W. B. Saunders Co.

further chelation therapy when serum iron is unavailable or the history suggests a toxic ingestion. The appearance of the iron–deferoxamine complex turns the urine a vin-rose color. Since chelation occurs optimally at a urine pH of 7 to 8, check urine pH periodically. Rarely, high iron levels occur in the absence of colored urine. Dosage of deferoxamine is 40 mg/kg as a deep intramuscular injection (may dilute 500 mg deferoxamine in 2 mL sterile water).

Parenteral Deferoxamine. Intramuscular deferoxamine may be used for patients not showing signs of hypotension. The intravenous route is probably more effective because of the short half-life of deferoxamine (about 1 hour) and the constant exposure to free circulating iron during the redistribution phase.[26] The intramuscular dose is 40 to 90 mg/kg as a deep intramuscular injection, up to a maximum of 2 g per injection. Daily doses should not exceed 6 g.

Intravenous deferoxamine is preferred for any serious iron ingestion and probably is more efficacious for all other patients requiring iron chelation. Although the minimal effective dose has not been calculated, a dose of 15 mg/kg/h usually does not produce hypotension and probably chelates all free circulating iron.[28]

Duration of Treatment

Subsequent doses of intravenous deferoxamine can be reduced when the serum iron level falls below the TIBC. Remember that ferrioxamine interferes with the colorimetric assay of iron. Some authors recommend that deferoxamine treatment continue 24 hours after the urine returns to normal color.[24] However, the exact length of therapy of iron required awaits the clarification of mitochondrial toxicity of iron and the effects of deferoxamine at these sites.[20]

Supportive Care

1. Watch vital signs carefully for signs of hypovolemia.
2. Replace fluid loss aggressively.
3. Watch for signs of blood loss (guaiac-positive stool) and type and cross-match blood.
4. Follow creatinine and prothrombin time/transaminase levels as measures of renal and hepatic function, respectively.

Admission Criteria

1. All patients who require chelation.
2. All positive provocative chelation tests.
3. Patients who remain asymptomatic 6 hours after ingestion (e.g., no vomiting/diarrhea/epigastric pain/lethargy) and who have no leukocytosis (less than 15,000), hyperglycemia (< 150 mg/dL), or positive upright abdomen film for pills may be discharged.[7] Questionable cases should receive a provocative chelation test. Symptomatic cases should receive chelation.

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LEAD

INTRODUCTION

Epidemiology

Lead has been smelted, ingested as a homeopathic medicine, applied as a cosmetic, painted on buildings, and glazed on ceramic pots since the earliest recorded times. By the time of the fall of the Roman Empire, an estimated 40 million tons of lead were produced, primarily as a by-product of silver mining.[1] Lead may also be the oldest recognized chemical toxin.[2] A Greek poet–physician first described occupational lead poisoning in the 2nd century BC. Lead use and environmental pollution have increased dramatically over the last 50 years, as demonstrated in sequential layers of ice in Greenland. At the beginning of the Industrial Revolution in 1780, 1 g of ice contained 10 pg of lead. Two hundred years later, the lead concentration of 1 g reached a level 20 times greater (200 pg), with the greatest increases occurring since 1940.[3] Each year, the United States consumes 1.3 million tons of lead and releases an estimated 100,000 tons into the air and water.[4]

Lead serves no known useful purpose in the body. Throughout life, humans accumulate lead in their bodies based on their exposure. Urban residents have the highest blood lead levels (20–25 μg/dL); suburban (15–20 μg/dL) and rural populations (10–14 μg/dL) have lower levels.[5] These levels correlate with air lead levels and *perhaps* leaded gasoline use. The average US blood lead level declined 37% from 1976 to 1980 as leaded gasoline consumption declined 55%.[6] In the women of Wales, blood lead levels dropped 30% between 1972 and 1982 despite little change in the total amount of lead used in gasoline.[7] Vehicle exhaust contributes up to 24% to 27% of total blood lead.[8]

Recent research work on the clinical effects of lead has focused on the subtle neuropsychiatric, reproductive, and renal effects of chronic low-dose lead exposure. Children are particularly susceptible to lead-induced impairment of neuropsychological development because of their reduced ability to excrete lead and their enhanced absorption of lead compared with adults. Death in children from undetected lead poisoning may be greater than heretofore suspected.[9]

The effect of low-level lead exposure on adults is less clear. Because the body stores over 90% of the total lead body burden in bones, the blood lead concentration reflects recent rather than cumulative absorption.[10] This inability to detect directly the extent of exposure confounds epidemiological studies. To date, studies correlating elevated blood lead levels to hypertension are conflicting.[11] Concern exists over the possibility that soft acid water increases the solubility of lead and that elevated lead levels account for the increased incidence of hypertension and cardiovascular mortality in areas with soft-water supplies. The contribution of increased lead absorption to gout, hypertension, nephropathy, and neurotoxicity remains to be determined.

TABLE 37-3
MAJOR OCCUPATIONS ASSOCIATED WITH RISK OF LEAD POISONING

Battery makers	Metal grinders/burners/refiners
Brass worker	Painters
Bronzers	Pigment makers
Cable makers/splicers	Pipe cutters
Chemical operators	Pottery workers
Foundrymen	Printers (linotype/electrotype)
Glass makers/polishers	Solderers
Gunshot/gun barrel makers	Stained glass makers
Jewelers	Welders
Lead burners/smelters	

Adapted from Cullen MR, Robins JM, Eskenazi B: Adult inorganic lead intoxication: Presentation of 31 new cases and a review of recent advances in the literature. Medicine 1983;62:231. Copyright 1983 Williams & Wilkins. Used with permission.

Sources[12]

Adults

Lead toxicity in adults results primarily from workplace exposure via inhalation. Lead exposure can occur by ingestion as a result of the lack of proper hygiene in lead-contaminated environments (e.g., eating or smoking in areas of lead work).[13] Table 37-3 lists some occupations at risk. Over 92% of all elevated adult blood levels in one series resulted from occupational exposure.[14] Lead toxicity has resulted from the subdermal injection of lead paint.[15] Nonoccupational sources of exposure include hobbies, lead-lined containers, lead bullets near joints,[16] and home-distilled whiskey (Table 37-4). Acid foods such as fruit and vegetable juice can release lead from improperly fired ceramic glazes leading to increased lead consumption.

TABLE 37-4
NONOCCUPATIONAL SOURCES OF LEAD POISONING

Battery burning	Home abortifacients
Bullet retention	Target shooting
Ceramic making	Ingestion of lead-containing herbal medicines
Eating from unfired pottery	Use of lead-containing cosmetics
Cooking in leaden pots	Soldering
Home-distilled wine/whiskey	

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GOODMAN and GILMAN's The Pharmacological Basis of Therapeutics

S E V E N T H E D I T I O N

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In this textbook, reference to proprietary names of drugs is ordinarily made only in chapter sections dealing with preparations. Such names are given in SMALL-CAP TYPE, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in the Index.

PREFACE TO THE SEVENTH EDITION

THE first edition of this textbook, published nearly 45 years ago, was written when basic pharmacology was not fully accepted as a meaningful or relevant biomedical discipline. The appearance of that book did much to change the picture. An eminent pharmacologist, commenting on the first edition many years after its publication, stated that it provided a renaissance or perhaps more properly the *naissance* of the teaching and practice of pharmacology. The second edition, published in the mid-1950s, reflected the immense impact of the post–World War II burgeoning of biomedical research. Subsequent editions have been written as multiauthored works—a reflection of the enormous change in the content, stature, and function of pharmacology; its role in the biomedical sciences; and its impact on the clinical sciences and rational therapeutics. The Preface to the First Edition is reprinted herein, because it clearly states the three primary objectives that have guided the writing of all subsequent editions. Adherence to these objectives has encouraged widespread and successful use of *Goodman and Gilman's The Pharmacological Basis of Therapeutics* by students and practitioners of medicine and other health professions, both in the United States and abroad.

Those familiar with previous editions of this textbook will immediately recognize the organization of the present volume, which remains largely intact from the sixth edition. Nevertheless, the revision of the text has been extensive. This is a reflection not only of the dozens of new therapeutic agents that have become available to the clinician during the past 5 years but also of tremendous advances in both basic pharmacology and the application of that knowledge to medical practice. It is increasingly necessary for the pharmacologist to be a complete biologist, versed in biochemistry, physiology, biophysics, cell biology, and molecular genetics. Technics developed by molecular biologists are now having a profound impact in pharmacology. Molecular cloning of DNA and biosynthesis of the encoded products permit large-scale production of agents such as human insulin and growth hormone. Of even greater significance, detailed information on the primary structure of important macromolecules has become available as a result. These proteins include receptors for acetylcholine and insulin, the voltage-sensitive sodium channel, the receptor for low-density lipoprotein, and many others. While this could not have been anticipated a decade ago, the next few years will see an explosion of such information. To follow will be the capability to predict the tertiary structure of such proteins and, ultimately, to design drugs to alter their functions selectively and predictably. Coupled with these advances have been similarly impressive strides in such areas as mechanisms of receptor function, transmembrane signaling events, regulation of second-messenger synthesis, and so forth. Discussion of such topics appears throughout the textbook. Increased knowledge of pharmacokinetics and its practical application have kept pace with advances in pharmacodynamics. One indication of this growth is the near doubling of the drugs for which detailed pharmacokinetic data are presented in Appendix II. These are just a few of the major trends that are emphasized in the seventh edition.

Most of the contributors to the sixth edition were able and anxious to participate in the current undertaking, and we are pleased with this loyalty. We also welcome several outstanding new authors. Two of us are delighted with the efforts of the two new editors of this volume, Theodore W. Rall and Ferid Murad.

In addition to paying tribute to our collaborators, we gratefully acknowledge the advice and help received from scores of individuals, too numerous to mention by name. However, special note is made of certain extraordinary efforts. Michele Ferguson reviewed all sections of the text on pharmaceutical preparations and dosage with skill and exceptional

Appendix E
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CHAPTER

56 DRUGS EFFECTIVE IN IRON-DEFICIENCY AND OTHER HYPOCHROMIC ANEMIAS

Robert S. Hillman and Clement A. Finch

IRON AND IRON SALTS

Iron deficiency is the most common cause of nutritional anemia in man. When severe, it results in a characteristic microcytic, hypochromic anemia secondary to a reduction in the synthesis of hemoglobin. Since more than 80% of the iron present in the body is involved in the support of red-cell production, this is not surprising. However, the impact of iron deficiency is not limited to the erythron (Dallman, 1982). Iron is also an essential component of myoglobin; heme enzymes such as the cytochromes, catalase, and peroxidase; and the metalloflavoprotein enzymes, including xanthine oxidase and the mitochondrial enzyme alpha-glycerophosphate oxidase. Iron deficiency can affect metabolism in muscle independently of the effect of anemia on oxygen delivery. This may well reflect a reduction in the activity of iron-dependent mitochondrial enzymes. Iron deficiency has also been associated with behavioral and learning problems in children and with abnormalities in catecholamine metabolism and, possibly, heat production (Pollitt and Leibel, 1982; Martinez-Torres *et al.*, 1984). Awareness of this ubiquitous role of iron has stimulated considerable interest in the early and accurate detection of iron deficiency and also in its prevention.

History. Early in civilization, man learned to mine iron and to forge tools of great strength. This entry into the *iron age* carried with it a belief in the special powers of the metal. Legends and early writings described the many medicinal uses to which this "metal from heaven" could be put (Fairbanks *et al.*, 1971). Iron was used extensively by European physicians through the Middle Ages and the Renaissance, but with little rationale. In the sixteenth century, the causative role of iron deficiency in the then-prevalent "green sickness" or chlorosis of adolescent women began to be recognized. It may be that the treatment of this disorder with iron had already enjoyed some vogue in Europe, but Sydenham is properly credited with identifying iron as a specific remedy to take the place of bleedings and purgings. In 1681, he wrote (*see* Latham, 1850): ". . . I comfort the blood and the spirit belonging to it by giving a chalybeate [containing or charged with iron] 30 days running. This is sure to do good. To the worn out or languid blood it gives a spur or fillip, whereby the animal spirits which before lay prostrate and sunken under their own weight are raised and excited. Clear proof of this is found in the effect of steel in chlorosis. The pulse gains strength, the face (no longer pale and deathlike) a fresh ruddy color." In 1713, Lemery and Geoffry provided more direct evidence of the relationship by showing that iron was present in blood (ash) (*see* Christian, 1903). In 1832, the French physician Pierre Blaud wrote that the malady chlorosis ". . . arises from a faulty formation of blood as a result of which the blood is an imperfect fluid or the coloring matter is so defective that it is no longer suitable for stimulating the organism and maintaining the regular exercise of its functions." Blaud recognized that failure in the treatment of chlorosis had been due to the use of too small doses of iron and reported the rapid cure of 30 patients given a mixture of equal parts of ferrous sulfate and potassium carbonate in dosage increasing to as much as 770 mg of elemental iron daily. For many years Blaud's nephew distributed the "veritable pills of Blaud" throughout the world (Neuroth and Lee, 1941). The treatment of anemia with iron followed the principles enunciated by Sydenham and Blaud until the last decade of the nineteenth century and was comparable to modern practice in the amount of iron available for absorption that was prescribed. At that time, however, the teachings of Bunge, Quincke, von Noorden, and others cast doubt on this straightforward approach to the treatment of chlorosis. The dose of iron employed was reduced, and the resulting inefficacy of smaller doses brought discredit on the therapy. It was not until the third and fourth decades of the present century, through the efforts of Faber and Gram, Bloomfield, Heath and associates, and Reimann and coworkers, that the lessons taught by the earlier physicians were relearned (*see* Haden, 1939).

The past half century has brought a clearer understanding of many aspects of iron metabolism in man. In 1937, McCance and Widdowson reported on studies of iron balance that suggested a limited daily absorption and excretion of the element. At the same time, Heilmeyer and Plotner (1937) made quantitative measurements of the concentration of iron in plasma and discussed its function in transport. Laurell in 1947 presented similar information concerning the plasma iron transport protein, which he called *transferrin*. In the early 1940s, Hahn (Hahn *et al.*, 1943) introduced the use of radioactive isotopes of iron as a means to quantitate absorption and demonstrated the capacity of the intestinal mucosa to regulate this function. In the next decade, Huff and associates (1950) initiated isotopic studies of internal iron exchange. In the past 25 years practical clinical measurements of the degree of saturation of transferrin and red-cell protoporphyrin have been developed to a point that permits the accurate detection of iron-deficient erythropoiesis, while quantitation of iron in plasma ferritin and in marrow reveals the status of the body's stores (*see* Bothwell *et al.*, 1979). Even more recently, quantitative methods have been developed for evaluation of the absorption of iron in food, and these have explained the high prevalence of iron deficiency in man as a function of the limited availability of iron in the contemporary diet (Cook and Finch, 1975).

Iron and the Environment. Iron is one of the most abundant elements in the earth's crust; only oxygen, silicon, and aluminum are more common. It exists largely in its trivalent form as ferric oxide or hydroxide or as polymers. In this state, its biological availability is limited unless solubilized by acid or chelates. For example, to meet their needs, bacteria produce high-affinity chelating agents that can extract iron from the surrounding environment (Neilands, 1974). Some plants also have an unique ability to secrete substances that mobilize iron from soils for transport and incorporation into both nonheme and heme-containing enzymes or for storage as phytoferritin. The need for such adaptive mechanisms reflects the poor availability of most environmental iron. In alkaline or high-phosphate soils, plants can, in fact, develop an iron-deficiency disease, chlorosis, manifest by yellowness or blanching of normally green parts. While it might be expected that higher vertebrates would have the greatest problem meeting their requirements because of the high demand for iron to produce hemoglobin, most mammals have little difficulty in acquiring iron. This is probably explained by a more ample iron intake and perhaps also by their greater efficiency in absorbing iron. Man, however, appears to be an exception. While total dietary intake of elemental iron exceeds requirements, the bioavailability of the iron in the diet is limited.

Iron Metabolism in Man. The body store of iron is divided between iron-containing compounds that are essential and those in which excess iron is held in storage. From a quantitative standpoint, *hemoglobin* dominates the essential fraction (Table 56–1). This protein, with a molecular weight of 64,500, contains four atoms of iron per molecule, amounting to 1.1 mg of iron per milliliter of red blood cells. Other forms of essential iron include myoglobin and a variety of heme and nonheme iron-dependent enzymes (Sigel, 1977). *Ferritin* is the protein of iron storage, and it exists as individual molecules or in an aggregated form. Apoferritin has a molecular weight of about 450,000 and is composed of some 24 polypeptide subunits; these form an outer shell within which there is a storage cavity for polynuclear hydrous ferric oxide phosphate (Harrison, 1977). Over 30% of the weight of ferritin may be iron. Aggregated ferritin, referred to as *hemosiderin* and visible by light microscopy, constitutes about one third of normal stores, a fraction that increases as stores enlarge (Wixom *et al.*, 1979). The two predominant sites of iron storage are the reticuloendothelial system and the hepatocytes, although some storage also occurs in muscle (Bothwell *et al.*, 1979).

Table 56–1. THE BODY CONTENT OF IRON

	MALE	FEMALE
	mg/kg of body weight	
Essential iron		
Hemoglobin	31	28
Myoglobin and enzymes	6	5
Storage iron	13	4
Total	50	37

Internal exchange of iron is accomplished by the plasma protein *transferrin* (Aisen and Brown, 1977). This β_1-glycoprotein has a molecular weight of about 76,000 and two binding sites for ferric iron. Iron is delivered from transferrin to intracellular sites by means of specific receptors in the plasma membrane. The iron-transferrin complex binds to the receptor and is taken up by receptor-mediated endocytosis. Iron subsequently dissociates in a pH-dependent fashion in an acidic, intracellular vesicular compartment, and the receptor returns the ferritin to the cell surface to function again (*see* Brown *et al.*, 1983). The concentration of these receptors for transferrin on a given cell is related to the widely disparate requirement of different tissues for iron. The essential role of transferrin is illustrated by the maldistribution of iron

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that occurs in congenital atransferrinemia. These patients have iron-deficiency anemia despite excessive concentrations of iron in nonerythroid tissues (Goya *et al.*, 1972).

The flow of iron through the plasma amounts to a total of 30 to 40 mg per day in the adult (about 0.46 mg/kg of body weight) (Finch *et al.*, 1970). The major internal circulation of iron involves the erythron and the reticuloendothelial cell (Figure 56–1). About 80% of the iron in plasma goes to the erythroid marrow to be packaged into new erythrocytes; these normally circulate for about 120 days before being catabolized by the reticuloendothelium. At that time a portion of the iron is immediately returned to the plasma bound to transferrin, while another portion is incorporated into the ferritin stores of the reticuloendothelial cell and is returned to the circulation more gradually. Isotopic studies indicate some degree of iron wastage in this process, wherein defective cells or unused portions of their iron are transferred to the reticuloendothelial cell during maturation, bypassing the circulating blood. In hemolytic anemia the uptake of iron by the erythron may increase five to tenfold, with a corresponding increase in red-cell breakdown. When there are abnormalities in maturation of red cells, the predominant portion of iron assimilated by the erythroid marrow may be rapidly localized in the reticuloendothelial cell as defective red-cell precursors are broken down: this is termed *ineffective erythropoiesis*. With red-cell aplasia, the rate of turnover of iron in plasma may be reduced by one half or more, with all of the iron now going to the hepatocyte for storage. It should be noted that nonerythroid tissues do not have the ability of erythropoietic cells to increase their number of membrane receptors for transferrin; their capacity to take up iron is thus always limited.

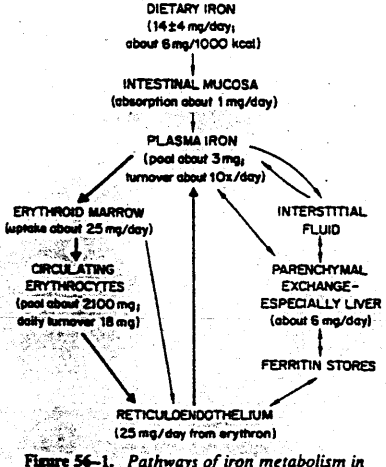

Figure 56–1. *Pathways of iron metabolism in man (excretion omitted).* (*See* text for explanation.)

The most remarkable feature of iron metabolism in man is the degree to which the body store is conserved. Only 10% of the total is lost per year from normal men, that is, about 1 mg per day (Green *et al.*, 1968). Two thirds of this iron is excreted from the gastrointestinal tract as extravasated red cells, iron in bile, and iron in exfoliated mucosal cells. The other third is accounted for by small amounts of iron in desquamated skin and in the urine. Physiological losses of iron in the male vary over a relatively narrow range, decreasing to about 0.5 mg in the iron-deficient individual and increasing to as much as 1.5 or possibly 2 mg per day when excessive iron is consumed. Additional losses of iron occur in the female due to menstruation (Hallberg *et al.*, 1966a). While this averages about 0.5 mg per day, 10% of normal menstruating females lose over 2 mg per day. Menstrual losses may be influenced by various types of contraceptive therapy. Loss can be reduced by about one half when estrogen-containing oral contraceptives are used and is increased by intrauterine devices. Pregnancy imposes a requirement for iron of even greater magnitude (Table 56–2). In addition to these physiological losses, there is a great variety of other causes of iron loss. Examples include the donation of blood, the use of anti-inflammatory drugs that cause bleeding from the gastric mucosa, gastrointestinal disease with associated bleeding, and so forth (Fairbanks *et al.*, 1971). Much rarer is the hemosiderinuria that follows intravascular hemolysis, which may result in urinary losses of iron of as much as 20 mg per day; still rarer is pulmonary siderosis, wherein iron is deposited in the lungs and becomes unavailable to the rest of the body.

The limited physiological losses of iron point to the primary importance of absorption as the determinant of the body's content of iron. Unfortunately, the biochemical nature of the absorptive process is understood only in general terms (Bothwell *et al.*, 1979). After acidification and partial digestion of food in the stomach, its content of iron is presented to the intestinal mucosa as either inorganic or heme iron. These fractions are taken up by the absorptive cells of the duodenum and upper small intestine, and the iron is either transported directly into the plasma or is stored as mucosal ferritin (Figure 56–2). Absorption is regulated by the relative activity of these two pathways, which is in some manner determined by the internal state of iron metabolism. Recent work suggests that the amount of a specific transferrin-like mucosal protein influences absorption (Huebers *et al.*, 1983). Normal absorption is about 1 mg per day in the adult male and 1.4 mg per day in the adult female. Increased uptake and delivery of iron into the circulation occur when there is iron deficiency, when iron stores are depleted, or when erythropoiesis is increased (Heinrich, 1983). However, there is a ceiling of 3 to 4 mg on the amount of dietary iron that may be absorbed, and this is set not only by the absorptive processes of the intestinal mucosa but also by the amount of available iron in the diet.

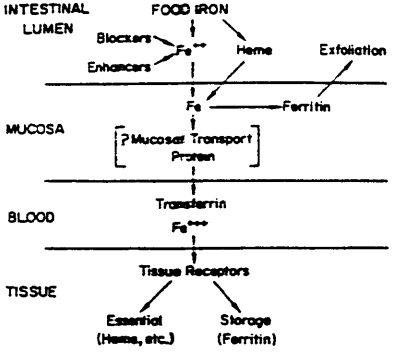

Figure 56–2. *Pathway of iron absorption.* (*See* text for explanation.)

Table 56–2. IRON REQUIREMENTS FOR PREGNANCY

	AVERAGE	RANGE
	mg	*mg*
External iron loss	170	150–200
Expansion of red-blood-cell mass	450	200–600
Fetal iron	270	200–370
Iron in placenta and cord	90	30–170
Blood loss at delivery	150	90–310
Total requirement *	980	580–1340
Cost of pregnancy †	680	440–1050

* Blood loss at delivery not included.

† Iron lost to the mother: expansion of red-cell mass not included.

(After Council on Foods and Nutrition, 1968. Courtesy of the *Journal of the American Medical Association*.)

Iron Requirements and the Availability of Dietary Iron. Iron requirements are determined by obligatory physiological losses and the needs imposed by growth. Thus, the adult male has a requirement of only 13 μg/kg per day (about 1 mg), whereas the menstruating female requires about 21 μg/kg per day (about 1.4 mg). In the last two trimesters of pregnancy, requirements increase to about 80 μg/kg per day (5 to 6 mg), and there are similar requirements for the infant due to its rapid growth (Finch, 1976). These requirements (Table 56–3) must be considered in the context of the amount of dietary iron available for absorption.

The dietary content of iron in developed countries is about 6 mg/1000 kcal; this places the average daily iron intake of the adult male between 12 and 20 mg and that of the adult female between 8 and 15 mg. Foods high in iron (greater than 5 mg/100 g) include organ meats such as liver and heart, brewer's yeast, wheat germ, egg yolks, oysters, and certain dried beans and fruits; foods containing intermediate amounts of iron (1 to 5 mg/100 g) include most muscle meats, fish and fowl, most green vegetables, and most cereals; foods low in iron (less than 1 mg/100 g) include milk and milk products and most nongreen vegetables. The general distribution of iron among foods, however, limits the value of manipulation of iron intake by food selection. The content of iron in food is further affected by

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Table 56–3. DAILY IRON INTAKE AND ABSORPTION

SUBJECT	IRON REQUIREMENT (μg/kg)	AVAILABLE IRON IN POOR DIET–GOOD DIET (μg/kg)	SAFETY FACTOR (Available Iron/Requirement)
Infant	67	33–66	0.5–1
Child	22	48–96	2–4
Adolescent (male)	21	30–60	1.5–3
Adolescent (female)	20	30–60	1.5–3
Adult (male)	13	26–52	2–4
Adult (female)	21	18–36	1–2
Mid-to-late pregnancy	80	18–36	0.22–0.45

the manner of its preparation, since iron may be added through contamination with dirt and from cooking in iron pots.

While the iron content of the diet is obviously important, of greater nutritional significance is the bioavailability of iron in food (Hallberg, 1981). Of the two forms of iron that are absorbed, heme iron is by far the more available, and its absorption is independent of the composition of the diet. Its relative absorption is illustrated by the study carried out by Björn-Rasmussen and associates (1974) in which a diet was fed that contained 17.4 mg of iron per day, of which 16.4 mg was nonheme iron and 1 mg was contained in heme; 37% of the heme iron but only 5% of the nonheme iron was absorbed. Thus, heme iron, which constituted only 6% of the dietary iron, represented 30% of that absorbed. Nevertheless, it is the availability of the *nonheme fraction* that deserves the greatest attention, since it represents by far the largest amount of dietary iron and is almost exclusively the form of dietary iron that is ingested by the economically underprivileged. Unfortunately, nonheme iron is usually largely unavailable, and its absorption is profoundly affected by other foods ingested concurrently. In a vegetarian diet, nonheme iron is absorbed very poorly because of the inhibitory action of a variety of components, particularly phosphates (Layrisse and Martinez-Torres, 1971). Two substances are known to facilitate the absorption of nonheme iron—ascorbic acid and meat. Ascorbate forms complexes with and/or reduces ferric to ferrous iron. While meat facilitates the absorption of iron by stimulating production of gastric acid, it is possible that some other effect, not yet identified, is also involved. Either of these substances can increase availability severalfold. Thus, assessments of available dietary iron should include not only the amount of iron ingested but also an estimate of its availability based on the intake of substances that enhance its absorption (Monsen *et al.*, 1978) (Figure 56–3).

A comparison of iron requirements with available dietary iron is made in Table 56–3. Obviously, pregnancy and infancy represent periods of negative balance. The menstruating woman is also at risk, whereas iron balance in the adult male and nonmenstruating female is reasonably secure. The difference between dietary supply and requirements is reflected in the size of iron stores. These will be low or absent when iron balance is precarious and high when iron balance is favorable. Thus, in the

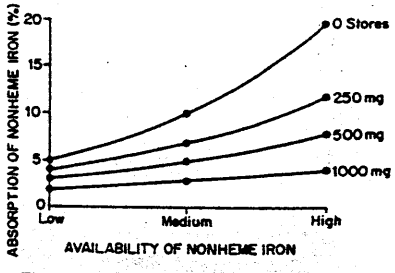

Figure 56–3. *Effect of iron status on the absorption of nonheme iron in food.*

The percentages of iron absorbed from diets of low, medium, and high bioavailability in individuals with iron stores of 0, 250, 500, and 1000 mg are portrayed. (After Monsen, Hallberg, Layrisse, Hegsted, Cook, Mertz, and Finch, 1978. © *American Journal of Clinical Nutrition*. Courtesy of American Society for Clinical Nutrition.)

infant after the third month of life and in the pregnant woman after the first trimester, stores of iron are negligible (Beaton, 1974). Menstruating females have approximately one third the stored iron found in the adult male, indicative of the extent to which the additional average daily loss of about 0.5 mg of iron affects balance (Finch *et al.*, 1977).

Iron Deficiency. Iron deficiency is rampant in human beings, and its victims number in the hundreds of millions (WHO Scientific Group, 1975). The estimate of the prevalence of iron deficiency in the United States and other developed countries depends on the economic status of the population studied and on the methods employed for evaluation. In developing countries as many as 20 to 40% of infants and pregnant women may be affected, while studies in Sweden and the United States suggest that the current prevalence in these countries is 5 to 10% (Hallberg *et al.*, 1979). The difficulty experienced by a substantial proportion of the population in achieving iron balance is recognized by the current practice of fortification of flour with 13 to 16.5 mg of iron per pound, by the use of iron-fortified formulas for infants, and by the prescription of medicinal iron supplements in pregnancy. There have been proposals to increase the current level of fortification of flour in the United States.

Iron-deficiency anemia is due to a dietary intake of iron that is inadequate to meet normal requirements (nutritional iron deficiency), to some condition that produces an increased requirement for iron because of blood loss, or to interference with iron absorption. Most nutritional iron deficiency in the United States is mild. Moderate-to-severe iron deficiency is usually the result of blood loss, either from the gastrointestinal tract or, in the female, from the uterus. *In such patients, no effort should be spared in determining the cause of the bleeding.* Infrequently, impaired absorption of the iron in food results from partial gastrectomy or sprue.

The recognition of iron deficiency rests on an appreciation of the sequence of events that occur with iron depletion. A negative balance first results in a reduction of iron stores and, eventually, a parallel decrease in red-cell iron and iron-related enzymes (Figure 56–4). In adults, *depleted stores* may be recognized by a plasma ferritin of less than 12 μg per liter and the absence of reticuloendothelial hemosiderin in the marrow aspirate. *Iron-deficient erythropoiesis*, defined as a suboptimal supply of iron to the erythron, is identified by a decreased saturation of transferrin to less than 16% and/or by an increase above normal in red-cell protoporphyrin. *Iron-deficiency anemia* represents that stage where the depletion of essential body iron is associated with a recognizable decrease in the concentration of hemoglobin in blood. However, the physiological variation in the concentration of hemoglobin is so great that only about half of the individuals with iron-deficient erythropoiesis are identified by recognizable anemia (Cook *et al.*, 1976). Critical values in infancy and childhood are different, due to the more restricted supply of iron normally present in plasma at that age (Dallman *et al.*, 1980).

The importance of mild iron deficiency lies more in identifying the underlying cause of the deficiency than in any symptoms related to the deficient state. Because of the frequency of iron deficiency in infancy and in the menstruating or pregnant woman, the need for exhaustive evaluation of such individuals is usually determined by the severity of the anemia. However, in the male and the postmenopausal female, in whom iron balance should be favorable, it becomes important to pursue the search for a site of bleeding whenever iron deficiency is present.

A definite diagnosis of iron deficiency can be more accurately established by laboratory tests than by therapeutic trial, particularly when the deficiency is mild. The presence of *microcytic anemia* is the most commonly recognized indicator of iron deficiency. Other laboratory tests, such as quantitation of *transferrin saturation*, *red-cell protoporphyrin*, or *plasma ferritin*, are required to distinguish iron deficiency from other causes of microcytosis. Such measurements are particularly useful when circulating red cells are not yet microcytic due to the recent nature of blood loss, but iron supply is nonetheless limiting erythropoie-

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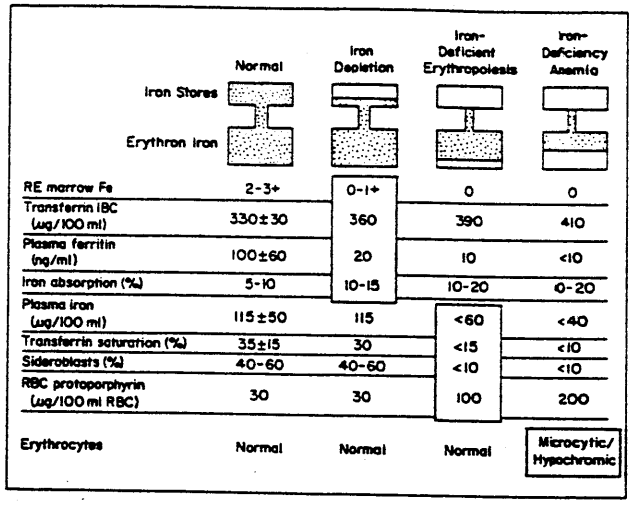

Figure 56–4. *Sequential changes (from left to right) in the development of iron deficiency in the adult.*

Rectangles enclose the first appearance of the indicated abnormal test results. IBC = iron-binding capacity. (After Hillman and Finch, 1974, as modified from Bothwell and Finch, 1962. Courtesy of F. A. Davis Co.)

sis. More difficult is the differentiation of true iron deficiency from iron-deficient erythropoiesis due to inflammation (Finch, 1978). In the latter condition, the stores of iron are actually increased, but the release of iron from the reticuloendothelial cell is blocked; the concentration of iron in plasma is decreased, and the supply of iron to the erythroid marrow becomes inadequate. The increased stores of iron in this condition may be demonstrated directly by examination of an aspirate of marrow or may be inferred from determination of an elevated concentration of ferritin in plasma (Lipschitz *et al.*, 1974).

TREATMENT OF IRON DEFICIENCY

General Therapeutic Principles. The response of iron-deficiency anemia to treatment is influenced by several factors, including the cause and severity of the iron-deficient state, the presence of other complicating illness, and the ability of the patient to tolerate and absorb medicinal iron. Effective therapy is followed by an increased rate of production of red cells, and the increase is proportional to the severity of the anemia and the amount of iron made available to the marrow. Some idea of the importance of the relationship of iron delivery to marrow production is found in the studies of Hillman and Henderson (1969). When normal subjects were phlebotomized, erythropoiesis was reduced to less than one third of the normal rate when the concentration of iron in plasma was below 70 μg/dl. In contrast, production increased to more than three times the basal rate when the plasma iron concentration was between 75 and 150 μg/dl. The highest rates of erythropoiesis occurred in subjects with increased destruction of red cells and elevated concentrations of iron in plasma; this situation is observed in patients with ineffective erythropoiesis (*see* above) and/or hemolysis of mature red cells (Hillman and Giblett, 1965).

The level of response of the marrow is also a reflection of the severity of the anemia, and, by inference, the degree of stimulation of marrow precursors by erythropoietin. This assumes, of course, that the marrow can respond normally. An intrinsic disease of the marrow or, more commonly, a complicating illness, such as an inflammatory disorder, can blunt the response to therapy. Continued bleeding will also interfere with the response in terms of hemoglobin, although reticulocytes will increase in number. The ability of the patient to tolerate and absorb medicinal iron is another important factor in determining the rate of response. There are clear limits to the gastrointestinal tolerance for medicinal iron. In addition, the small intestine regulates absorption and prevents the entry of overwhelming amounts of iron into the blood stream. This places a ceiling on how much iron can be provided by oral therapy. In the patient with a moderately severe anemia, maximal doses of oral iron will supply 40 to 60 mg of iron per day to the erythroid marrow, which is sufficient for production of red cells at a rate that is two to three times normal.

The response to iron therapy can be evaluated from the reticulocyte production index and the rate of rise in the level of hemoglobin or the hematocrit. A modest increase in the reticulocyte index may be observed as early as 4 to 7 days after beginning therapy. A measurable increase in the hemoglobin or hematocrit should be evident after 1 week of therapy. If the concentration of hemoglobin before treatment is reduced by more than 3 g/dl, an average increment of hemoglobin of 0.2 g/dl per day is observed with the usual therapeutic doses of iron, administered either orally or parenterally. It should be noted that this is less than the 0.6 g/dl per day (three times basal) that the erythroid marrow can achieve when the supply of iron is optimal. This simply indicates that neither route of administration can provide sufficient iron for maximal erythropoiesis. A decision about the effectiveness of the treatment should not be made for 3 to 4 weeks. An increase of 2 g/dl or more in the concentration of hemoglobin by this time should be considered a positive response to iron, assuming there has been no other change in the patient's clinical status to account for the improvement. It also assumes that the patient has not been transfused during this time.

If the response to oral iron is inadequate, the diagnosis must be reconsidered. A full laboratory evaluation should be carried out, and such factors as the presence of a concurrent inflammatory disease or poor compliance by the patient must be assessed. A source of continued bleeding should obviously be sought. If there is no other explanation, an evaluation of the patient's ability to absorb oral iron should be considered. There is no justification for merely continuing oral iron therapy beyond 3 to 4 weeks if a favorable response has not occurred.

Once a response to oral iron is demonstrated, therapy should be continued until the hemoglobin returns to normal. Treatment may then be extended if it is desirable to establish iron stores. This may require a considerable period of time, since the rate of absorption of iron by the intestine will decrease markedly as iron stores are reconstituted. The prophylactic use of oral iron should be reserved for patients at high risk, including pregnant women, women with excessive menstrual blood loss, and infants. Iron supplements may also be of value for rapidly growing infants who are consuming substandard diets and for adults with a recognized cause of chronic blood loss. Except for infants, where supplementation of formulas is routine, the use of "over-the-counter" mixtures of vitamins and minerals to prevent iron deficiency is to be discouraged. Also to be discouraged are multicomponent preparations, since the availability of their iron for absorption may be reduced.

Therapy with Oral Iron: Preparations, Dosage, and Untoward Effects. Orally administered ferrous sulfate, the least expensive of iron preparations, is the treatment of choice for iron deficiency (Fairbanks *et al.*, 1971; Callender, 1974; Bothwell *et al.*, 1979). Ferrous salts are absorbed about three times as well as ferric salts, and the discrepancy becomes even greater at high dosage (Brise and Hallberg, 1962). Variations in the particular ferrous salt have relatively little effect on bioavailability, and the sulfate, lactate, succinate, glutamate, gluconate, and other ferrous salts are absorbed to approximately the same extent.

Preparations and Dosage. Ferrous sulfate (iron sulfate) is the hydrated salt, $FeSO_4 \cdot 7H_2O$, which contains 20% iron. It is available as tablets, capsules, timed-release preparations, syrups, elixirs, and drops. *Ferrous fumarate* contains 33% iron and is moderately soluble in water, stable, and almost tasteless. It is available in tablets and suspensions. *Ferrous gluconate* and *ferrous lactate* have also been successfully employed in the therapy of iron-deficiency anemia. The gluconate contains 12% iron and is available in tablets, capsules, and elixirs. The lactate contains 19% iron. Both are tolerated as well as ferrous sulfate. The effective dose of all of these preparations is the same in terms of iron content.

Other iron compounds have utility in fortification of foods. Reduced iron (metallic iron, elemental iron) is considered as effective as ferrous sulfate, provided that the material employed has a small particle size (Elwood, 1968; Cook *et al.*, 1973).

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Large-particle *ferrum reductum* and iron phosphate salts have a much lower bioavailability (Cook *et al.*, 1973), and their use for the fortification of foods is undoubtedly responsible for some of the confusion concerning effectiveness. Ferric edetate has been shown to have a suitable bioavailability and to have advantages for maintenance of the normal appearance and taste of food (Viteri *et al.*, 1978).

The amount of iron, rather than the mass of the total salt in iron tablets, is important, since the latter is obviously modified by the mass of the anion and by the degree of hydration of the compound. It is also essential that the coating of the tablet dissolves rapidly in the stomach. Enteric-coated tablets are virtually worthless but are still being marketed. Surprisingly, since iron is usually absorbed in the upper small intestine, certain delayed-release preparations have been reported to be effective and have been said to be even more effective than ferrous sulfate when taken with meals. However, reports of absorption from such preparations vary. Because there are a number of different forms of delayed-release preparations on the market and information on their bioavailability is limited, the effectiveness of most such preparations must be considered questionable.

A variety of substances designed to enhance the absorption of iron have been marketed, including surface-acting agents, carbohydrates, inorganic salts, amino acids, and vitamins. One of the more popular of these is ascorbic acid. When present in an amount of 200 mg or more, ascorbic acid increases the absorption of medicinal iron by at least 30% (Brise and Hallberg, 1962). However, the increased uptake is associated with a significant increase in the incidence of side effects (Hallberg *et al.*, 1966b), and, therefore, the addition of ascorbic acid seems to have little advantage over increasing the amount of iron administered. There is no practical benefit in employing these compounded preparations. It is particularly undesirable to use preparations that contain other compounds with therapeutic actions of their own, such as vitamin B_{12}, folate, or cobalt, since the patient's response to the combination cannot be easily interpreted. Despite the straightforward nature of therapy with iron, it is discouraging to see the frequency with which expensive preparations with worthless additives are prescribed.

The usual therapeutic dose of iron is about 200 mg per day (2 to 3 mg/kg), based on the iron content of the preparation. In selecting the optimal dose for adults, allowance should be made for body size. Children weighing 15 to 30 kg can take half the average adult dose, and smaller children and infants can tolerate relatively larger doses of iron, for example, 5 mg/kg. The dose employed is a practical compromise between the therapeutic action desired and the toxic effects. Prophylaxis and mild nutritional iron deficiency may be managed with modest doses. When the object is the prevention of iron deficiency in pregnant patients, for example, doses of 15 to 30 mg of iron per day, if not taken with meals, are adequate to meet the 3- to 6-mg daily requirement of the last two trimesters. When the purpose is to treat iron-deficiency anemia, but the circumstances do not demand haste, a total of about 100 mg (35 mg, three times daily) may be used. The average dose for the treatment of iron-deficiency anemia is about 200 mg of iron per day, given in three equal doses of 65 mg.

The responses expected for different dosage regimens of oral iron are given in Table 56–4. However, these effects are modified by the severity of the iron-deficiency anemia and by the time of ingestion of iron relative to meals. Absorption is optimal when the ferrous salt is taken when fasting. As noted previously, food variably reduces the availability of an iron salt, depending on the composition of the diet. Bioavailability of iron ingested with food is probably one half or one third of that seen in the fasting subject (Grebe *et al.*, 1975; Ekenved, 1976). Antacids also reduce the absorption of iron if given concurrently. It is always preferable to administer iron in the fasting state, even if the dose must be reduced because of gastrointestinal side effects. For patients who require maximal therapy to encourage a rapid response or to counteract continued bleeding, as much as 120 mg of iron may be administered four times a day. The timing of the dose is also important. Sustained high rates of red-cell production require an uninterrupted supply of iron. Oral doses should be spaced equally in order to maintain a continuous high concentration of iron in plasma.

The *duration of treatment* is governed by the recovery of hemoglobin and the desire to create iron stores (Norrby, 1974). The former depends on the severity of the anemia. With a daily rate of repair of 0.2 g of hemoglobin per deciliter of whole blood, the red-cell mass is usually reconstituted within 1 to 2 months. Thus, the individual with 5 g of hemoglobin per deciliter may achieve a normal complement of 15 g/dl in about 50 days, whereas the individual with a hemoglobin of 10 g/dl may take only half that time. The creation of stores of iron is a different matter, requiring many months of oral iron administration. The rate of absorption decreases rapidly after recovery from anemia and, after 3 to 4 months of treatment, stores may be increasing at a rate of not much more than 100 mg per month. Much of the strategy of continued therapy depends on the estimated future iron balance of the individual. The person with an inadequate diet may require continued therapy with low doses of iron. The individual whose bleeding has stopped will require no further therapy after the hemoglobin has returned to normal. For the individual with continued bleeding, chronic therapy is clearly indicated.

Table 56–4. AVERAGE RESPONSE TO ORAL IRON

TOTAL DOSE	ESTIMATED ABSORPTION		INCREASE IN HEMOGLOBIN
mg of iron per day	%	*mg*	*g/dl of blood per day*
35	40	14	0.07
105	24	25	0.14
195	18	35	0.19
390	12	45	0.22

Untoward Effects of Oral Preparations of Iron. Contrary to many advertisements, intolerance to oral preparations of iron is primarily a function of the amount of soluble iron in the upper gastrointestinal tract and of psychological factors. Side effects include heartburn, nausea, upper gastric discomfort, constipation, and diarrhea. A good policy, particularly if there has been previous intolerance to iron, is to initiate therapy at a small dosage in order to demonstrate freedom from symptoms at that level and then gradually to increase the dosage to that desired. With a dose of 200 mg of iron per day divided into three equal portions, symptoms occur in approximately 25% of individuals, compared to an incidence of 13% among those receiving placebos; this increases to approximately 40% when the dosage of iron is doubled. Nausea and upper abdominal pain are increasingly common manifestations at high dosage (Sölvell, 1970). Constipation and diarrhea, perhaps related to iron-induced changes in the intestinal bacterial flora, are not more prevalent at higher dosage, nor is heartburn. If an elixir is given, one can place the iron solution on the back of the tongue with a dropper to prevent transient staining of teeth.

Toxicity due to the long-continued administration of iron with the resultant production of iron overload (hemochromatosis) has been the subject of a number of case reports (*see* Bothwell *et al.*, 1979); this is the result of inappropriate therapy. Available evidence suggests that the normal individual is able to control absorption of iron despite high intake, and it is only individuals with underlying disorders that augment the absorption of iron who run the hazard of hemochromatosis.

Iron Poisoning. Large amounts of ferrous salts of iron are toxic but, in adults, fatalities are rare and almost exclusively suicidal. Most deaths occur in childhood and particularly between the ages of 12 and 24 months (Fairbanks *et al.*, 1971; Bothwell *et al.*, 1979). As little as 1 to 2 g of iron may cause death, but 2 to 10 g is usually ingested in fatal cases. The high frequency of iron poisoning obviously relates to its availability in the household, particularly the supply that remains after pregnancy. The colored sugar coating of many of the commercially available tablets gives them the appearance of candy. All such preparations should be kept in child-proof bottles.

Signs and symptoms of severe poisoning may occur within 30 minutes or may be delayed for several hours after ingestion. They are largely those of abdominal pain, diarrhea, or vomiting brown or bloody stomach contents containing pills. Of particular concern are pallor or cyanosis, lassitude, drowsiness, hyperventilation due to acidosis, and cardiovascular collapse. If death does not occur within 6 hours, there may be a transient period of apparent recovery, followed by death in 12 to 24 hours. The corrosive injury to the stomach may result in subsequent pyloric stenosis or gastric scarring. Hemorrhagic gastroenteritis and hepatic damage are prominent findings at autopsy. In the evaluation of the child who is thought to have ingested iron, a color test for iron in the gastric contents and an emergency determination of the concentration of iron in plasma can be performed. If the latter is less than 500 μg/dl, the child is not in immediate danger. However, vomiting should be induced when there is iron in the stomach, and an x-ray should be taken to evaluate the number of pills remaining in the small bowel. Iron in the upper gastrointestinal tract should be precipitated by lavage with sodium bicarbonate or phosphate solution. When the plasma concentration of iron is over 500 μg/dl, deferoxamine should be administered; dosage and routes of administration are detailed in Chapter 69. Shock, dehydration, and acid-base abnormalities should be treated in the conventional manner. Most important is the speed of diagnosis and therapy. With earlier and more effective treatment, the mortality from iron poisoning has been reduced from as high as 45% to about 1% at the present time.

Therapy with Parenteral Iron: Preparations, Dosage, and Untoward Effects. Parenteral administration of iron is the alternative to the use of oral preparations

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(Fairbanks *et al.*, 1971; Callender, 1974; Bothwell *et al.*, 1979). The rate of response to such parenteral therapy is similar to that which follows usual oral doses (Pritchard, 1966; Strickland *et al.*, 1977). One of the advantages is that iron stores may be rapidly created, something that would take months to achieve by the oral route. Its most important indication is when disease such as sprue prevents absorption of iron from the gastrointestinal tract or in patients who are receiving parenteral nutrition. Parenteral iron may also be indicated when oral administration is thought to have an adverse effect on inflammatory disease of the bowel and, on rare occasions, when intolerance to oral iron prevents effective therapy. It has also been used in chronic inflammatory states, such as rheumatoid arthritis, where there is a partial block to the absorption of iron. However, the utilization of parenteral iron is probably suboptimal in this situation because of the block in reticuloendothelial iron transport due to inflammation. Other indications have been suggested that do not seem to be soundly based. These include the unsubstantiated beliefs that the response to parenteral iron is faster than that to oral iron, and that patients undergoing dialysis (who absorb oral iron perfectly well) are better managed by the parenteral route. In the occasional patient who presents specific diagnostic problems and who is poorly compliant in taking medication, parenteral iron has been given to ensure the administration of a known amount of iron.

Iron dextran injection (IMFERON) is the parenteral preparation in general use in the United States at the present time. It is a complex of ferric hydroxide with dextrans of 5000 to 7000 daltons in a colloidal solution containing 50 mg/ml of iron. Iron dextran is available in 10-ml vials containing 0.5% phenol for intramuscular use and in 2-ml ampuls for intramuscular or intravenous administration. When given intramuscularly, a variable portion (10 to 50%) may become fixed locally for many months. The remainder enters the blood, mostly through the lymphatic circulation, and elevates the concentration of iron in plasma for days or 1 or 2 weeks due to the presence of the iron-dextran complex. During this time determination of plasma iron does not indicate the amount of iron present in transferrin. The iron dextran must first be phagocytized by reticuloendothelial cells, and the iron is then split from the sugar molecule of the dextran before it becomes available to the body. A portion of the processed iron is rapidly returned to the plasma and made available to the erythroid marrow; however, an even greater portion remains temporarily trapped within the reticuloendothelial cell (Henderson and Hillman, 1969). These iron dextran deposits are very gradually converted into a usable form of iron. While all iron is eventually used (Kernoff *et al.*, 1975), many months are required before this is complete, and, in the interim, iron dextran within the reticuloendothelial cell can confuse the physician who attempts to evaluate the iron status of the patient.

Intramuscular injection of iron dextran has been carried out with an initial dose of 1 or 2 ml, followed by the administration of as much as 10 ml at a time, 5 ml in each buttock. However, local reactions, including long-continued discomfort at the site of injection and local discoloration of the skin, and the concern about malignant change at the site of injection (Weinbren *et al.*, 1978) make the intramuscular route inappropriate except when the intravenous route is inaccessible.

Intravenous administration of iron dextran avoids the deposition of iron in muscle and local reactions at the site of injection. The technic of intravenous administration involves first the injection of 1 or 2 drops of iron dextran over a period of 5 minutes to determine whether any signs or symptoms of anaphylaxis appear. If not, 500 mg of iron may then be injected over a period of 5 to 10 minutes. This dose may be repeated to reach the total amount required. Alternately, the total dose needed to reconstitute red-cell mass and tissue stores may be administered in one infusion over several hours, although this technic is not approved in the United States. Such a dose (in milligrams) may be calculated from the following formula: 0.66 × body weight in kilograms × (100 − [patient's hemoglobin in g/dl × 100 ÷ 14.8]). However, such calculations do not take into consideration the delay in the utilization of the material injected or the possibility of continued loss of iron. In practice, more iron needs to be given than might be calculated if an increase in hemoglobin of 0.2 g/dl of whole blood per day is required.

Reactions to intravenous iron include headache, malaise, fever, generalized lymphadenopathy, arthralgias, urticaria, and, in some patients with rheumatoid arthritis, an exacerbation of the disease. Of greatest concern, however, is the rare anaphylactic reaction, which may be fatal in spite of treatment. While only a few such deaths have been reported, it remains a deterrent to the use of iron dextran. Thus, there must be *specific* indications for the parenteral administration of iron.

COPPER

Deficiency of copper is extremely rare in man (Underwood, 1971; Evans, 1973). The amount present in food is more than adequate to provide the needed body complement of slightly over 100 mg. There is no evidence that copper ever needs to be added to a normal diet, either prophylactically or therapeutically. Even in clinical states associated with hypocupremia (sprue, celiac disease, nephrotic syndrome), effects of copper deficiency are usually not demonstrable. However, anemia due to copper deficiency has been described in individuals who have undergone intestinal bypass surgery (Zidar *et al.*, 1977), in those who are receiving parenteral nutrition (Klarpel and Peden, 1972; Dunlap *et al.*, 1974), in malnourished infants (Holtzman *et al.*, 1970), and in infants taking copper-deficient diets (Graham and Cordano, 1976). While an inherited disorder affecting the transport of copper in man (Menkes' disease; steely hair syndrome) is associated with reduced activity of several copper-dependent enzymes, this disease is not associated with hematological abnormalities.

Copper deficiency in experimental animals interferes with the absorption of iron and its release from reticuloendothelial cells (Lee *et al.*, 1976). The associated microcytic anemia is related both to a decrease in the availability of iron to the normoblasts and, perhaps even more importantly, to a decreased mitochondrial production of heme. It may be that the specific defect in the latter case is a decrease in the activity of cytochrome oxidase. There are other pathological effects observed in deficient experimental animals that involve the skeletal, cardiovascular, and nervous systems (O'Dell, 1976). In man, the outstanding findings have been leukopenia, particularly granulocytopenia, and anemia. Concentrations of iron in plasma are variable, and the anemia is not always microcytic. When a low plasma copper concentration is determined in the presence of leukopenia and anemia and in a setting conducive to a deficiency of the element, a therapeutic trial with copper is appropriate. Daily doses up to 0.1 mg/kg of copper sulfate have been given by mouth, or up to half this amount may be added to the solution of nutrients for parenteral administration. Copper deficiency usually occurs concurrently with multiple nutritional deficiencies, so that its specific role in the production of anemia is usually difficult to ascertain.

COBALT

The administration of cobalt can produce polycythemia in experimental animals and in the human subject without metabolic disease (Berk *et al.*, 1949). The same effect may be observed in patients with hematological disorders where the underlying proliferative capacity of the marrow is unimpaired (sickle-cell anemia, thalassemia, chronic infection, and renal disease) (Symposium, 1955). In the 1950s cobalt was employed in doses of up to 200 to 300 mg of cobaltous chloride daily, given in divided doses by mouth to patients with various types of anemia. While beneficial effects did not occur in those with aplastic anemia, a response was observed in two patients with pure red-cell aplasia (Voyce, 1963). Cobalt deficiency has not been reported in man.

Cobalt stimulates the production of erythropoietin (Symposium, 1962). It is thought that cobalt acts by inhibition of enzymes involved in oxidative metabolism and that the response is the result of tissue hypoxia. More specifically, cobalt blocks the conversion of pyruvate to acetyl coenzyme A and of α-ketoglutarate to succinate (Webb, 1962). Large amounts of cobaltous chloride depress the production of erythrocytes. Accidental intoxication in children may produce cyanosis, coma, and death. The only disease in which the clinical use of cobalt is still advocated by some is the normochromic, normocytic anemia associated with severe renal failure (Duckham and Lee, 1976). Unwanted effects, including anorexia, nausea and vomiting, and diarrhea, are frequent in these patients, although such effects are said to be reduced by the use of enteric-coated pills in doses below 50 mg per day. In general, the administration of androgens accomplishes the same end and is considered preferable for those with anemia that is associated with renal disease (*see* Chapter 62).

PYRIDOXINE

The first case of pyridoxine-responsive anemia was described in 1956 by Harris and associates. Subsequent reports suggest that the vitamin might improve hematopoiesis in up to 50% of patients with either hereditary or acquired sideroblastic anemias (Horrigan and Harris, 1968; Harris and Kellermeyer, 1970). Characteristically, these patients show an impairment in hemoglobin synthesis and an accumulation of iron in the perinuclear mitochondria of erythroid precursor cells, so-called ring sideroblasts. Hereditary sideroblastic anemia is an X-linked recessive trait with variable penetrance and expression. Affected males typically show a dual population of normal red cells and microcytic, hypochromic cells in the circulation. In contrast, idiopathic acquired sideroblastic anemia and the sideroblastosis seen in association with a number of drugs, inflammatory states, neoplastic disorders, and preleukemic syndromes show a variable morphological picture. Moreover, erythrokinetic studies demonstrate a spectrum of abnormalities, from a hypoproliferative defect with little tendency to accumulate iron to marked ineffective erythropoiesis with iron overload of the tissues (Solomon and Hillman, 1979a).

Oral therapy with pyridoxine is of proven benefit in correcting the sideroblastic anemias associated with the antituberculosis drugs isoniazid and pyrazinamide, which act as vitamin B_6 antagonists. A daily dose of 50 mg of pyridoxine completely corrects the defect without interfering with treatment, and routine supplementation of pyridoxine is thus recommended (*see* Chapter 53). In contrast, if pyridoxine is given to counteract the sideroblastic abnormality associated with administration of levodopa, the effectiveness of levodopa in controlling Parkinson's disease is decreased. The sideroblastic abnormalities produced by chloramphenicol and lead are not corrected by pyridoxine therapy.

Patients with idiopathic, acquired sideroblastic anemia are generally older and their nutritional status is marginal. However, a response to pyridoxine cannot be explained simply on the basis of a nutritional deficiency. Those individuals who appear to have a pyridoxine-responsive anemia require ther-

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apy with large doses of the vitamin, 50 to 500 mg per day, for prolonged periods. Unfortunately, the early enthusiasm for such treatment with pyridoxine has not been reinforced by more recent studies (Chillar *et al.*, 1976; Solomon and Hillman, 1979a). Moreover, even when a patient responds, the improvement is only partial, since both the ring sideroblasts and the red-cell defect persist and the hematocrit rarely returns to normal. However, in view of the low toxicity of oral pyridoxine, a therapeutic trial with the agent is appropriate.

As shown in studies of normal man, oral pyridoxine in a dose of 100 mg three times daily produces a maximal increase in red-cell pyridoxine kinase and the major pyridoxal phosphate–dependent enzyme, glutamic-aspartic aminotransferase (Solomon and Hillman, 1978). For an adequate therapeutic trial, the drug must be administered for at least 3 months, while monitoring the response by means of the reticulocyte index and the concentration of hemoglobin. It has been suggested that the occasional patient who is refractory to oral pyridoxine will respond to parenteral administration of pyridoxal phosphate (Hines and Love, 1975). However, oral pyridoxine in doses of 200 to 300 mg per day produces intracellular concentrations of pyridoxal phosphate equal to or greater than those generated by therapy with the phosphorylated vitamin (Solomon and Hillman, 1979b). Pyridoxine is further discussed in Chapter 66.

RIBOFLAVIN

A pure red-cell aplasia that responded to the administration of riboflavin was reported in patients with protein depletion and complicating infections (Foy *et al.*, 1961). Lane and associates (1964) induced riboflavin deficiency in man and demonstrated that a hypoproliferative anemia resulted within a month. The spontaneous appearance in man of red-cell aplasia due to riboflavin deficiency is undoubtedly rare, if, in fact, it occurs at all. It has been described in combination with infection and protein deficiency, both of which are capable of producing a hypoproliferative anemia. However, it seems reasonable to include riboflavin in the nutritional management of patients with gross, generalized malnutrition. Riboflavin is further discussed in Chapter 66.

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CHAPTER

57 VITAMIN B_{12}, FOLIC ACID, AND THE TREATMENT OF MEGALOBLASTIC ANEMIAS

Robert S. Hillman

Vitamin B_{12} and folic acid are dietary essentials for man. A deficiency of either vitamin results in defective synthesis of DNA in any cell that attempts chromosomal replication and division. Since tissues with the greatest rate of cell turnover show the most dramatic changes, the hematopoietic system is especially sensitive to deficiencies of these vitamins. Clinically, the earliest sign of deficiency is a megaloblastic anemia, where the derangement in DNA synthesis results in a characteristic morphological abnormality of the precursor cells in the bone marrow. Abnormal macrocytic red blood cells are the product, and the patient becomes severely anemic. Recognition of this pattern of abnormal hematopoiesis, more than 100 years ago, permitted the initial diagnostic classification of such patients as having "pernicious anemia" and the investigations that subsequently led to the discovery of the clinical value of vitamin B_{12} and folic acid. Even today, the characteristic abnormality in morphology is used both for diagnosis and as a therapeutic guide for administration of the vitamins.

History. The discovery of vitamin B_{12} and folic acid is a dramatic story that starts more than 150 years ago and includes two Nobel prize-winning discoveries (*see* Castle, 1961; Kass, 1976). The first descriptions of what must have been megaloblastic anemias are credited to Combe and Addison, who published several case reports between 1824 and 1855. While Combe suggested that the disorder might have some relationship to digestion, it was Austin Flint who, in 1860, first described the severe gastric atrophy and called attention to its possible relationship to the anemia. The name "progressive pernicious anemia" was coined in 1872 by Biermer. This exceptionally colorful term has persisted, for it is still common practice to describe the condition as Addisonian pernicious anemia.

Following the observation by Whipple in 1925 that liver is a source of a potent hematopoietic substance for iron-deficient dogs, Minot and Murphy carried out their Nobel prize-winning experiments that demonstrated the effectiveness of the feeding of liver in pernicious anemia. Within a few years, Castle defined the need for both an *intrinsic* factor, a substance secreted by the parietal cells of the gastric mucosa, and an *extrinsic factor*, the vitamin-like material provided by crude liver extracts. However, nearly 20 years passed before Rickes and coworkers and Smith and Parker isolated and crystallized vitamin B_{12}; Dorothy Hodgkin then determined its crystal structure by x-ray diffraction and subsequently received the Nobel prize for this work.

As attempts were being made to purify extrinsic factor, Wills and her associates described a macrocytic anemia in women in India that responded to a factor present in crude liver extracts but not in the purified fractions known to be effective in pernicious anemia (Wills and Bilimoria, 1932; Wills *et al.*, 1937). This factor, first called Wills' factor and later vitamin M, is now known to be folic acid. The actual term *folic acid* was coined by Mitchell and coworkers in 1941, following its isolation from leafy vegetables (Mitchell *et al.*, 1941).

More recent work has shown that neither vitamin B_{12} nor folic acid as purified from liver or various foodstuffs is the active coenzyme for man. During extraction procedures, active, labile forms are converted to stable congeners of vitamin B_{12} and folic acid, cyanocobalamin and pteroylglutamic acid, respectively. These congeners must then be modified *in vivo* to be effective. While much has been learned of the intracellular metabolic pathways in which these vitamins participate, many questions remain to be answered, especially the relationship of vitamin B_{12} deficiency to the neurological abnormalities that occur with this disorder.

Relationships between Vitamin B_{12} and Folic Acid. The major roles of vitamin B_{12} and folic acid in intracellular metabolism are summarized in Figure 57–1. Intracellular vitamin B_{12} is maintained as two active coenzymes, methylcobalamin and deoxyadenosylcobalamin (Stahlberg, 1967; Linnell *et al.*, 1971). Deoxyadenosylcobalamin is a cofactor for the mitochondrial mutase enzyme that catalyzes the isomerization of L-methylmalonyl CoA to succinyl CoA, an important reaction in both carbohydrate and lipid metabolism (Huennekens, 1968; Weissbach and Taylor, 1968). This reaction

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248 Tetraethyl Lead 248

Motor fuels contain no more than 0.15% (3 cc./gal.) and aviation fuels no more than 0.22% (4.5 cc./gal.). Poisoning may occur through skin absorption, inhalation, or ingestion. The symptoms are referable chiefly to the nervous system: insomnia, irritability, and in severe cases an acute encephalopathy with mania. Other symptoms are visual difficulties, gastrointestinal disturbances, weakness, tremors, muscle pains, and easy fatigability. As formulated in motor fuels, petroleum hydrocarbons are more dangerous than tetraethyl lead or other additives. See Gasoline in the index.

See also: Lead, *Reference Congener in Section III.*
Ref.: Boyd et al., 1957; Schlang, 1961; White, 1955.

249 Thallium 249

e.g., Thallium sulfate, Thallium acetate

Toxicity Rating: 5. Salts of thallium were once used as pesticides against rats, mice, ground squirrels, prairie dogs, moles and some insects, but they are currently outlawed in pesticidal formulations in the U.S.A. Thallium is a slow but persistent systemic poison.

See also: Thallium, *Reference Congener in Section III.*

Ferric and ferrous compounds

250 Iron Salts 250

Ferrous and ferric

Toxicity Rating: 3. In large doses soluble iron salts are corrosive irritants and systemic poisons. See ferric and ferrous salts below.

See also: Ferrous Salts, *Reference Congener in Section III.*

251 Burnt Sienna 251

oxide (Fe_2O_3) plus clay. A common insoluble paint pigment. See Ferric salts below.

252 Burnt Umber 252

Toxicity Rating: 3(?). Iron oxides (Fe_2O_3 plus manganese oxide plus clay.) A common paint pigment. Both iron and manganese oxides are insoluble. See Ferric salts below; also Manganese salts in the index.

253 Ferric Salts 253

e.g., Ferric chloride, Ferric ammonium citrate, Ferric sulfate

Toxicity Rating: 3. Given orally, ferric and ferrous salts induce essentially the same toxic syndrome.

See also: Ferrous Salts, *Reference Congener in Section III.*
Ref.: Hoppe et al., 1955.

254 Ferric Subsulfate 254

Monsel's salt, Basic ferric sulfate

Toxicity Rating: 3. Approximate formula is $Fe_4(SO_4)_5(OH)_2 \cdot H_2O$. Monsel's solution is a nearly saturated aqueous solution of this salt; it is prepared by mixing and boiling ferrous sulfate with sulfuric and nitric acids. This solution, which contains 20 to 22% iron, is used externally as a styptic.

See also: Ferrous Salts, *Reference Congener in Section III.*
Ref.: Osol and Farrar, 1955.

255 Ferrocholinate 255

Iron choline citrate, e.g., Ferrolip

Toxicity Rating: 3. An iron chelate containing 12% elemental iron (by weight), used as a hematinic in an adult dose of 50 mg. three times daily. May cause gastric distress in therapeutic doses. Minimal lethal dose for dogs and rabbits is 500 mg./kg.

See also: Ferrous Salts, *Reference Congener in Section III.*

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FERROUS SALTS

Ferrous salts are widely used in the treatment of iron-deficiency anemias. Ferrous carbonate, chloride, fumarate (32.9% Fe by weight), gluconate (12.5% Fe), lactate (23.9% Fe), and glutamate have all been prescribed, but the sulfate is the most popular iron preparation in the United States. The official U.S.P. tablets contain 300 mg. $FeSO_4 \cdot 7H_2O$ or an equivalent amount of dried (anhydrous) ferrous sulfate containing 60 mg. computed as elemental iron. It is also available as a syrup and as elixirs. Ferric salts (*e.g.*, the ammonium citrate and hydroxide) and even metallic iron powder ("reduced iron") have been employed in the treatment of anemia. The latter, however, is no longer a significant market product. Carbonyl iron is a reduced form of high bioavailability and apparent low toxicity (Sachs and Houchin, 1978).

Chelated forms of iron include iron choline citrate. These preparations when given by mouth are claimed to be less irritating to the gastric mucosa (Franklin *et al.*, 1958), but no convincing evidence exists to prove that they are less hazardous than the inorganic salts when given in equivalent bioavailable doses. Small amounts of soluble copper and manganese salts are often included along with iron compounds in preparations for the treatment of iron-deficiency anemia. These additives do not contribute significantly to the toxicity of ferrous sulfate preparations (Forbes, 1947; Somers, 1947), but the evidence that they improve the therapeutic result has always been suspect.

Toxicology: Iron is potentially toxic in all of its dosage forms, and a single toxic syndrome is common to them all. As tested in several animal species, five different iron compounds proved to lie in toxicity class 3 (Somers, 1947; Hoppe *et al.*, 1955). Elemental iron is significantly less toxic in rats than soluble salts (Boyd and Shanas, 1963a). For the purposes of the discussion below, ferrous sulfate may be taken as representative. In the body, the ferrous ion is believed to be rapidly oxidized to Fe^{3+}.

The incidence of acute accidental intoxication with ferrous sulfate appears to parallel its use in medicine. Very few authenticated case reports of iron poiso ng of any type can be found in the medical literature of the decades prior to 1947, when iron was in disrepute as a therapeutic agent (Forbes, 1947). It was so universally regarded as innocuous when reinstated in the treatment of anemia that such signs as severe shock and hematemesis were often not recognized as consequences of known prior ingestions of excessive amounts of ferrous sulfate (Hertzog *et al.*, 1943; Howard, 1949). The number of such reported cases continues to grow steadily. A 50%

mortality rate was reported in one early selected series of severe cases (Aldrich, 1958; Cann and Verhulst, 1960d), but more recent experience suggests that a considerably lower mortality can be anticipated (Barr and Fraser, 1968; Fischer *et al.*, 1971; Greengard and McEnery, 1968; James, 1970). In a review of 474 cases published in 1971, there was a mortality of about 1% (Westlin, 1971).

Most of the reported deaths from iron poisoning have occurred in infants and young children who ingested ferrous sulfate tablets because of the sweet candy or chocolate coating. In the case of infants and young children it is usually difficult to determine with any degree of certainty the number of tablets swallowed, but in fatal cases the quantities are invariably in gross excess of customary therapeutic doses. Recoveries have occurred following the ingestion of as many as 70 tablets (0.3 gm. each), perhaps because substantial but unknown portions were promptly removed by vomiting (Cann and Verhulst, 1960d); however, serious sequelae and deaths have followed as few as 15 tablets (Amerman *et al.*, 1958; Duffy and Diehl, 1952; Hoppe *et al.*, 1955).

In general the ingestion of up to 10 tablets by a child is associated with mild poisoning, whereas moderate to severe intoxication follows ingestion of 20 tablets or more (James, 1970). On a body weight basis 20 to 60 mg. (computed as elemental iron) per kg. (body weight) is a mildly to moderately toxic dose whereas 200 to 250 mg./kg. is a life-threatening dose (Robotham and Lietman, 1980; Stein *et al.*, 1976a). The latter often results in serum iron levels of 500 μg./100 ml. or higher.

Iron poisoning in adults is very rare (Eriksson *et al.*, 1974; Henriksson *et al.*, 1979; Wallack and Winkelstein, 1974), but adults appear to be as susceptible as infants and children if appropriate amounts are consumed. In one adult female 42 mg. iron/kg. produced only epigastric pain whereas in another 180 mg./kg. produced a severe poisoning (Eriksson *et al.*, 1974). Death has been reported in an adult who ingested at one time ¼ lb. of the sulfate (Foucar *et al.*, 1948). Iron poisoning poses special problems in pregnancy. In one case both fetus and mother died perhaps because of a decision to withhold chelation therapy (Strom *et al.*, 1976).

Acute iron poisoning may occur in a number of distinct phases (Aldrich, 1958). Ferrous sulfate can exert an intensely corrosive action on the gastric mucosa, particularly at the pyloric end. Epigastric pain and vomiting may begin within 10 to 60 minutes, followed over the next 6 to 8 hours by shock, coma and death (Charney, 1961; Curtiss and Kosinski, 1954; Davis and Gibbs, 1956; Duffy and Diehl, 1952; Murphy *et al.*, 1951; Smith *et al.*, 1950; Swift *et al.*, 1952; Thomson, 1947). Vomitus may contain particles of tablets and be brown in color, but blood is also frequently found. Hematemesis may occur even in the absence of ulceration apparently because of capillary dilation and diapedesis (Jacobs *et al.*, 1965). Watery diarrhea sometimes with ribbons of bowel mucosa further contributes to cardiovascular collapse from fluid and electrolyte loss.

If the victim survives this initial phase, a quiescent period usually follows with some clinical improvement. Some victims ultimately progress to complete recovery, but others relapse within 12 hours into fatal secondary shock (Aldrich, 1958; Prain, 1949; Thomson, 1950) or pneumonitis resulting from the aspiration of vomitus (Forbes, 1947).

In relapse a profound metabolic acidosis is often observed (Reissmann and Coleman, 1955). Acidosis has been ascribed to the hydrolysis of ferric ions in blood, but increases in lactic and citric acids also occur. Respiratory changes characteristic of acidosis are frequently noted. Although the severity of symptoms shows some correlation with serum iron levels (Franklin *et al.*, 1958), acidosis is not always reversed when the serum iron concentration is lowered with a chelating agent (Felts *et al.*, 1962a). Undoubtedly acidosis contributes to cardiovascular collapse. Phenylephrine produced no blood pressure response in dogs that were hypotensive because of iron poisoning until their acidosis was controlled with THAM (Felts *et al.*, 1962a).

Other factors that are postulated to contribute to peripheral circulatory collapse include a direct effect of iron in vascular walls (Roberts *et al.*, 1975), the production or release of ferritin, which may be identical with v.d.m. or vasodepressor material (Demulder, 1958; Jacobs *et al.*, 1965; Schafir, 1961; Smith, 1952), hemoconcentration because of increased capillary leakage, decreases in the production of plasma proteins because of liver injury, and possible release of bacterial toxins from the gut (Jacobs *et al.*, 1965; Shafir, 1961).

Postmortem examination usually reveals liver damage consisting of periportal hemorrhagic necrosis (Large, 1961; Luongo and Bjornson, 1954). Among some survivors delicate fibrosis of the liver (mild cirrhosis) has been described. Derangements of liver function such as hypoglycemia, elevated blood ammonia, multiple coagulation defects due to impaired synthesis of clotting factors, etc., are common in iron poisoning (Brown and Gray, 1955; de Castro *et al.*, 1977; Henriksson *et al.*, 1979; Greenblatt *et al.*, 1976; Witzelben and Chaffey, 1962), and occasionally death has been ascribed to acute hepatic failure (Covey, 1964; Gleason *et al.*, 1979).

Late pyloric stenosis, similar to that incurred by survivors of mineral acid ingestion (p. III-8),

and intestinal obstruction secondary to infarction (see below) are well known (Crosskey, 1952; Gandhi and Robarts, 1962; Ross, 1953; Warden *et al.*, 1958; Wilmers and Heriot, 1954). Endoscopy and fluoroscopy are mandatory procedures to assess the extent of the damage once the acute phase has subsided. Changes have been reported as late as 6 years after ingestion. Gastrectomy may be necessary in cases of severe scarring and fibrosis (Gezernik *et al.*, 1980). A single tablet of ferrous sulfate ingested by an elderly woman became lodged in the hypopharynx and produced local ulceration there (Abbarah *et al.*, 1976).

Iron does not appear to impair renal function directly (Enerbäck and Lundin, 1965), and even renal failure secondary to shock appears to be a rare occurrence. Neurologic sequelae (abnormal EEG, hyperkinetic and destructive behavior) have been reported at least once (Barr and Fraser, 1968).

Biochemical and physiological mechanisms underlying iron poisoning are not understood. Perhaps iron can initiate circulatory or respiratory collapse directly. Methemoglobinemia is not responsible for the cyanosis (Swift *et al.*, 1952), even though one patient unresponsive to oxygen was said to show a rapid improvement in color after methylene blue (Smith *et al.*, 1950). Toxic doses of iron can be absorbed through the intact mucosa of both the small and large bowel of rabbits and dogs (Franklin *et al.*, 1958; Reissmann *et al.*, 1955), but preexisting damage to the mucosa is believed to facilitate absorption and promote toxicity (Demulder, 1958; Prain, 1949). Serum iron is strongly bound to a plasma protein known as transferrin, which is normally only 20 to 45% saturated; the binding capacity is equivalent to 3.3 mg. of iron per liter (National Academy of Science, 1979). Signs of systemic iron poisoning appear only after this reserve binding capacity is saturated.

Because many brands of ferrous sulfate tablets are enteric coated and therefore insoluble in gastric juice, gastric lavage may be ineffective in removing them. If emesis can be induced or has already occurred, an examination of the vomitus may reveal the state of the ingested material and indicate the proper course of further therapy. Whether the tablets are enteric coated or not, an X-ray of the abdomen is useful for revealing their presence and for evaluating the success of emesis, gastric lavage, catharsis or enemas (Green, 1971; Hosking, 1969; James, 1970). Positive X-ray evidence for the continued presence of tablets after failure to evacuate the stomach by conventional means led to the performance of a successful gastrotomy in one case (Peterson and Fifield, 1980). Segmental necrosis of the small intestines is common with enteric coated tablets (Smith *et al.*, 1950; Swift *et al.*, 1952). Small bowel resection may be necessary to remove areas of necrosis (Walsh, 1980; Roberts *et al.*, 1975).

Experimental treatment: Rats receiving ferrous sulfate by stomach tube have been shown to tolerate lethal doses if given promptly a soluble phosphate salt (Sisson and Bronson, 1958). This and later work (Bronson and Sisson, 1960) are the basis for the phosphate treatment which has been widely recommended in the past. Not only has its effectiveness not been proved in human victims of iron poisoning, but in at least two cases complications of hypocalcemia and hyperphosphatemia indicated that systemic phosphate poisoning was superimposed on the pre-existing iron intoxication (Bachrach *et al.*, 1979; Geffner and Opas, 1980); see also Phosphates in Section II. Moreover, an *in vitro* study indicated that neither sodium bicarbonate nor phosphate (diluted Fleet Phosphosoda oral solution) was effective in precipitating iron at acidic pH values (Czajka *et al.*, 1981).

Although research on the therapeutic role of chelating agents in iron poisoning has been extensive, no totally satisfactory drug or procedure has been developed. Dimercaprol (BAL, p. III-50) increased the mortality of experimental animals given near mean lethal doses of iron (Edge and Somers, 1948). In spite of this evidence that the BAL-iron complex is more toxic than iron alone, BAL has received a limited clinical trial. Its use has met only indifferent success (Roxburgh, 1949; Shoss, 1954), and it is best avoided in favor of less toxic and more effective agents.

Considerably more experience has accumulated with EDETATE CALCIUM DISODIUM (p. III-163) and chemically related structures, *e.g.*, DTPA or diethylenetriaminepentaacetic acid. In dogs edetate prolonged survival time perhaps by lowering serum iron concentrations, but mortality was not decreased (Bronson and Sisson, 1960). It has been used in a number of clinical cases with ultimate survival of the victims (Barrie and Wilson, 1962; Covey, 1964; Dugdale and Powell, 1964; Piotrowska and Warnecka, 1966; Schafir, 1961; Simpson and Blunt, 1960). Some of these reports indicate decreases in serum iron concentration together with a hastening of urinary excretion. Not all investigators, however, are enthusiastic about the clinical response of the edetate-treated patient. Chelated iron may also be excreted in bile, but the importance of this route has not been defined in man (Haddock *et al.*, 1965). Even early treatment has failed at times to prevent death (Dugdale and Powell, 1964). These polycarboxylic acid-type chelators are probably not as safe or effective as deferoxamine (below).

Deferoxamine (DFOM) is an iron chelating agent introduced for use in primary and secondary hemochromatosis and in acute iron poison-

ing (Moeschlin and Schnider, 1963). DFOM was derived from naturally occurring iron complexes, siderochromes, and its affinity for ferric iron is very high and quite specific. It is absorbed from the gastrointestinal tract to some extent (Whitten *et al.*, 1966). It can be given intravenously if the rate of administration is carefully controlled, but the intramuscular route is preferred. Its antidotal capacity in acute iron poisoning is small but significant. When given by mouth 0.5 to 2 hours after an LD_{50} of ferrous sulfate, all guinea pigs survived; 80% survived an LD_{100} under similar circumstances (Moeschlin and Schnider, 1963). Only 3 of 9 dogs survived when enteral and parenteral DFOM was started 1 hour after an oral LD_{100} of ferrous sulfate (Whitten *et al.*, 1965).

When several chelating agents (including some not available for clinical use) were tested in equimolar doses in mice, DFOM by mouth immediately after ferrous sulfate was much more effective than edetate. Other experimental drugs were even more active than DFOM (Nigrovic and Catsch, 1965). When administration of the chelating agent was delayed for only 30 minutes, however, it was no longer effective by mouth. In contrast intraperitoneal DFOM retained highly significant antidotal activity even when its administration was delayed. Thus, early therapy with DFOM is critical for success, and both oral and parenteral administration appear to be indicated.

Because even the maximal benefits of DFOM are small and rigidly dictated by the circumstances of its employment, the clinical experience is difficult to interpret (Dugdale and Powell, 1964; Henderson *et al.*, 1963; Jacobs *et al.*, 1965; McEnery and Greengard, 1966; Perlmutter and Sanders, 1966; Santos and Pisciotta, 1964; Shapiro and Barbezat, 1964; Whelan *et al.*, 1966). In all of the above reports victims survived and many experienced an abatement of clinical symptoms when DFOM was administered. In a controlled series of mild to moderate poisonings, the combination of oral and parenteral DFOM seemed to have no significant effect on serum iron levels when compared to a control group that received only supportive care or a group that received only oral DFOM. All patients receiving DFOM, however, showed an increased urinary iron excretion (Leikin *et al.*, 1967). Whitten *et al.* (1965) successfully treated 13 children, mostly with a combination of oral and intravenous DFOM, but they remained unconvinced that the DFOM therapy was responsible for the recoveries. In a much larger but uncontrolled study involving 172 patients (Westlin, 1966), DFOM was judged to have produced clinical improvement in most victims, and the overall mortality was only 1.7%.

The recommended dose of deferoxamine (Desferal) mesylate in children (Westlin, 1966) is 5 to 10 gm. by gastric tube at the conclusion of lavage. If the patient is not in shock, also give 1 gm. intramuscularly, followed by 0.5 gm. i.m. every 4 hours for 2 doses and, if indicated, every 4 to 12 hours thereafter. If the patient is in shock, the intravenous route is preferable. By infusion, the rate of administration should not exceed 15 mg./kg. per hour. Overly rapid intravenous administration may produce tachycardia, hypotension, erythema and urticaria.

Exchange transfusion has produced good clinical results (Amerman *et al.*, 1958; Tomlinson, 1964) and compares favorably (Whitten, 1963) or is superior to chelation therapy (Movassaghi *et al.*, 1969) in animal studies. Even without exchange, transfusions of fresh whole blood may be of value (Emmanouilides, 1959) both to treat shock and to provide additional iron-binding capacity. Under ordinary circumstances hemodialysis is probably of little value because of the plasma protein binding of iron (Demulder, 1958). The possible beneficial effects of including protein in the dialysis fluid to trap dialyzed iron does not appear to have been explored. The effect of contemporaneous administration of chelating agents on the efficiency of peritoneal dialysis (Covey, 1964; Lavender and Bell, 1970) or hemodialysis (Felts *et al.*, 1962a) has been disputed.

Symptomatology:

1. Severe gastritis or gastroenteritis with abdominal pain, retching, and prolonged vomiting, beginning 10 to 60 minutes after ingestion. Vomitus may become bloody. Diarrhea is sometimes violent; the feces are watery and later tarry. Dehydration becomes intense.
2. Shock, pallor, cyanosis and coldness. Rapid, weak or imperceptible pulse, low blood pressure, rapid and shallow respirations.
3. Sometimes breathing is deep and rapid, reflecting an accompanying metabolic acidosis.
4. Drowsiness, hyporeflexia, dilated pupils, coma. Vasomotor instability, shock or coma and a serum iron level in great excess of the total iron-binding capacity (see Laboratory below) are poor prognostic signs.
5. Liver injury, consisting of hemorrhagic necrosis which is usually reversible.
6. Death from shock, usually in 4 to 5 hours. Sometimes following apparent recovery, pneumonia with fever or secondary shock may cause death 1 to 3 days later.
7. Among survivors pyloric stenosis and mild hepatic cirrhosis may be encountered as

persistent sequelae, but recovery is usually complete.

Treatment:

1. Induce vomiting by administering promptly syrup of ipecac (p. I-2) if enteric-coated tablets are known to have been ingested. If a readily soluble form of iron was consumed, it may be better to swallow promptly activated charcoal (p. I-4). Although charcoal does not bind ferrous iron tightly, it has a moderately high binding capacity at gastric pH values (Smith *et al.*, 1967a). (Once in the alkalinity of the duodenum, dissolved iron presumably hydrolyzes promptly to form insoluble oxides.) Milk of magnesia may be an effective alternative to activated charcoal. In a recent rat study, milk of magnesia prevented or delayed the absorption of a lethal dose of ferrous sulfate (Chadwick *et al.*, 1982).
2. Gastric lavage with water or 5% sodium bicarbonate solution. We currently believe that neither the safety nor efficacy of the widely recommended phosphate lavage fluid has been adequately established (see text above).
3. An X-ray of the abdomen may show the presence of intact tablets, which can sometimes be removed by further lavage or by administering a saline cathartic.
4. Deferoxamine mesylate (5 to 10 gm.) in water may be left in the stomach. Whereas this procedure is not endorsed by the FDA, the evidence commonly cited against oral deferoxamine (Whitten *et al.*, 1965, 1966) is not so convincing in our opinion as the evidence for its efficacy and safety (see text above).
5. In a patient not in shock, give 1.0 gm. deferoxamine intramuscularly followed by 0.5 gm. every 4 to 12 hours. Do not exceed 6 gm. in 24 hours. For patients in cardiovascular collapse the drug may be given by slow intravenous infusion not to exceed 15 mg./kg. per hour. The initial intravenous dose of 1 gm. may be followed by two 0.5-gm. doses 4 hours apart.
6. Intravenous 5% glucose in saline to correct dehydration. See pp. IV-66–67. Watch for evidence of acidosis and treat vigorously if present (pp. IV-69–72).
7. Transfusion with plasma or whole blood if shock becomes severe (p. IV-18).
8. Oxygen therapy as indicated (p. IV-12).
9. Exchange transfusion or plasmapheresis may be employed particularly in the event of renal shutdown, but hemodialysis is of little or no value for removing iron.
10. For supportive treatment of liver injury see p. IV-59–63.
11. Antibiotics at the first sign of infection. See pp. IV-85–86.
12. Observe the patient carefully for signs of relapse (48 hours) or late stricture formation (several days to weeks).

Laboratory:

1. It is important to differentiate between mild and severe cases when planning therapy. Rapid methods for determining the approximate serum iron level are useful for this purpose (Cooper *et al.*, 1971; Fischer, 1967; Hosking, 1969a). If the serum iron is in excess of the total iron binding capacity or has an absolute value of greater than 400 to 500 μg./dl., the patient should be regarded as severely poisoned (Fischer *et al.*, 1971; Westlin, 1971).
2. Once deferoxamine therapy has been started, the single most useful serum index of the need for additional therapy is the iron binding capacity. Values for total serum iron may be misleading because some methods do and some do not measure that iron complexed with deferoxamine (Gevirtz and Wasserman, 1966).
3. A change in color of the urine from straw to "vin rose" or "port wine" indicates excretion of the DFOM-iron complex. Its persistence indicates the need for continued chelation therapy (Greengard, 1975).
4. Hyperglycemia and leukocytosis frequently accompany high serum iron levels (James, 1970).
5. Multiple blood coagulation defects have been reported, but massive hemorrhage is uncommon.

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FLUORIDE

Sodium fluoride (NaF) and sodium fluosilicate (Na_2SiF_6) were once employed widely as insecticides (ant, roach and beetle powders) and occasionally as rodenticides. Sodium fluoride has been used internally as an anthelminic in swine (*never* in man) and externally as a delousing powder on poultry and cattle. Sodium fluoride preparations for the prevention of dental caries are available in several forms, *e.g.*, tablets (chewable, acidulated phosphate, etc.), liquids, rinses, gels, dentrifices and lozenges. Fluoride concentrations and the total amount of fluoride in a single container are safely limited by law (Hennon *et al.*, 1964; Hodge, 1963); the safety of these preparations in the home has been discussed (Duxbury *et al.*, 1982).

Dentrifices containing stannous fluoride (SnF_2), sodium fluoride or the most widely used sodium monofluorophosphate constitute sources of absorbable fluoride but not ones likely to be hazardous (Desphande and Bester, 1964; Segreto *et al.*, 1961). Cryolite (Na_3AlF_6), an insoluble sodium fluoaluminate, is sometimes dusted on vegetable or fruit crops as an insecticide; thousands of tons are employed in mixtures with bauxite (Al_2O_3) in electrolysis pots to produce aluminum. Although infrequently found outside of laboratories and various industries, HF as a gas (hydrogen fluoride) and as an aqueous solution (hydrofluoric acid) warrants consideration because it is a very hazardous form of fluoride. Some commercially available rust removers contain dangerous quantities of HF in solution (see also Section VI, General Formulations).

Worker errors and malfunctioning of automatic fluoridation equipment have occasionally led to toxic concentrations of fluoride in drinking water; in the resulting mini-epidemics of acute fluoride poisoning, no deaths have occurred, but the potential exists for mass poisonings (Hoffman *et al.*, 1980; Vogt *et al.*, 1982).

Chronic endemic fluorosis due to high concentrations of natural fluoride in local water supplies is characterized by mottling of the teeth, osteosclerotic changes in the skeleton and rarely central nervous system involvement (Dean, 1936; Hodge and Smith, 1965; Kilborn *et al.*, 1950; Linsman and McMurray, 1943; Marier *et*

CASARETT AND DOULL'S TOXICOLOGY

The Basic Science of Poisons

FOURTH EDITION

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Chapter 19

TOXIC EFFECTS OF METALS

Robert A. Goyer

INTRODUCTION

Metals differ from other toxic substances in that they are neither created nor destroyed by humans. Nevertheless, utilization by humans influences the potential for health effects in at least two major ways: first, by environmental transport, that is, by human or anthropogenic contributions to air, water, soil, and food, and second, by altering the speciation or biochemical form of the element (Li, 1981; Beijer and Jernelöv, 1986).

Metals are redistributed naturally in the environment by both geologic and biologic cycles (Figure 19–1). Rainwater dissolves rocks and ores and physically transports material to streams and rivers, adding and deleting from adjacent soil, and eventually to the ocean to be precipitated as sediment or taken up in rainwater to be relocated elsewhere on earth. The biologic cycles include bioconcentration by plants and animals and incorporation into food cycles. These natural cycles may exceed the anthropogenic cycle, as is the case for mercury. Human industrial activity, however, may greatly shorten the residence time of metals in ore, form new compounds, and greatly enhance worldwide distribution. The role of human activity in redistribution of metal is demonstrated by the 200-fold increase in lead content of Greenland ice beginning with a "natural" low level (about 800 B.C.) and a gradual rise in lead content of ice through the evolution of the industrial age, followed by a nearly precipitous rise in lead corresponding to the period when lead was added to gasoline in the 1920s (Ng and Patterson, 1981). Metal contamination of the environment, therefore, reflects both natural sources and contribution from industrial activity.

Metals emitted into the environment from combustion of fossil fuels in the United States are shown in Table 19–1. These include many of the metals most abundant in particulates in ambient air. The only metals or metal-like elements that may be emitted in gaseous discharges in measurable concentrations are mercury or selenium. Metals in raw surface water reflect erosion from natural sources, fallout from the atmosphere, and additions from industrial activities. Lowering pH as occurs with acid precipitation or the acid rain phenomenon may enhance solubilization and mobilization and perhaps change chemical species for many metals (Goyer, 1985). Metals in soil and water may enter the food chain. For persons in the general population, food sources probably represent the largest source of exposure to metals, with an additional contribution from air. Further potential sources of human exposure include consumer products and industrial wastes as well as the working environment.

Occupational exposure to metals is restricted to "safe" levels, defined as the threshold limit value for an eight-hour day, five-day workweek. These levels are intended to provide a margin of safety between maximum exposure and minimum levels that will produce illness. Permissible levels vary widely, and the differences reflect, in a sense, the toxicologic potency of the metal. As a general rule, the metals that are most abundant in the environment have lesser potential for toxicity as evidenced by the prevailing standard for permissible occupational exposure.

Metals are probably the oldest toxins known to humans. Lead usage may have begun prior to 2000 B.C. when abundant supplies were obtained from ores as a by-product of smelting silver. Hippocrates is credited in 370 B.C. with the first description of abdominal colic in a man who extracted metals. Arsenic and mercury are cited by Theophrastus of Erebus (387–372 B.C.) and Pliny the Elder (A.D. 23–79). Arsenic was obtained during the melting of copper and tin, and an early use was for decoration in Egyptian tombs. On the other hand, many of the metals of toxicologic concern today are only recently known to humans. Cadmium was first recognized in ores containing zinc carbonate in 1817. About 80 of the 105 elements in the periodic table are regarded as metals, but less than 30

Appendix E
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Goyer (Casarett & Doull) 4th Ed

Indian childhood cirrhosis has not been noted in the United States, but there are case reports of severe liver disorders resulting from ingestion of 10 mg Cu per 10-kg child per day in contaminated milk.

Iron

The major interest in iron is as an essential metal, but toxicologic considerations are important in terms of accidental acute exposures and chronic iron overload due to idiopathic hemochromatosis or as a consequence of excess dietary iron or frequent blood transfusions. The complex metabolism of iron and mechanisms of toxicity are detailed by Jacobs and Worwood, (1981) and Spivey Fox and Rader (1988).

Disposition. The disposition of iron is regulated by a complex mechanism to maintain homeostasis. Generally, about 2 to 15 percent is absorbed from the gastrointestinal tract, whereas elimination of absorbed iron is only about 0.01 percent per day (percent body burden or amount absorbed). During periods of increased iron need (childhood, pregnancy, blood loss), absorption of iron is greatly increased. Absorption occurs in two steps: (1) absorption of ferrous ions from the intestinal lumen into the mucosal cells and (2) transfer from the mocusal cell to plasma where it is bound to transferrin for transfer to storage sites. Transferrin is a β_1-globulin with a molecular weight of 75,000 and is produced in the liver. As ferrous ion is released into plasma, it becomes oxidized by oxygen in the presence of ferroxidase I, which is identical to ceruloplasmin. There are 3 to 5 g of iron in the body. About two-thirds is bound to hemoglobin, 10 percent is bound to myoglobin and iron-containing enzymes, and the remainder is bound to the iron storage proteins ferritin and hemosiderin. Exposure to iron induces synthesis of apoferritin, which then binds ferrous ions. The ferrous ion becomes oxidized, probably by histidine and cysteine residues and carbonyl groups. Iron may be released from ferritin by reducing agents; ascorbic acid, cysteine, and reduced glutathione release iron slowly. Normally, excess ingested iron is excreted, and some is contained within shed intestinal cells and in bile and urine and in even smaller amounts in sweat, nails, and hair. Total iron excretion is usually on the order of 0.5 mg/day.

With excess exposure to iron or iron overload, there may be a further increase in ferritin synthesis in hepatic parenchymal cells. In fact, the ability of the liver to synthesize ferritin exceeds the rate at which lysosomes can process iron for excretion. Lysosomes convert the protein from ferritin to hemosiderin, which then remains *in situ* (Trump *et al.*, 1973). The formation of hemosiderin from ferritin is not well understood but seems to involve denaturation of the apoferritin molecule. With increasing iron loading, ferritin concentration appears to reach a maximum, and a greater portion of iron is found in hemosiderin. Both ferritin and hemosiderin are, in fact, storage sites for intracellular metal and are protective in that they maintain intracellular iron in bound form.

A portion of the iron taken up by cells of the reticuloendothelial system enters a labile iron pool available for erythropoiesis, and part becomes stored as ferritin.

Toxicity. Acute iron toxicity is nearly always due to accidental ingestion of iron-containing medicines, and most often occurs in children. As of 1970, there were about 2000 cases in the United States each year, generally among children aged one to five years, who eat ferrous sulfate tablets with candylike coatings. Decrease of this occurrence should follow use of "child-proof" lids on prescription medicines. Severe toxicity occurs after ingestion of more than 0.5 g of iron or 2.5 g of ferrous sulfate. Toxicity becomes manifest with vomiting, one to six hours after ingestion. The vomitus may be bloody, owing to ulceration of the gastrointestinal tract. Stools may be black. This is followed by signs of shock and metabolic acidosis, liver damage, and coagulation defects within the next couple of days. Late effects may include renal failure and hepatic cirrhosis. The mechanism of the toxicity is thought to begin with acute mucosal cell damage, absorption of ferrous ions directly into the circulation, which cause capillary endothelial cell damage in liver.

Chronic iron toxicity or iron overload in adults is a more common problem. There are three basic ways in which excessive amounts of iron can accumulate in the body. The first circumstance is idiopathic hemochromotosis due to abnormal absorption of iron from the intestinal tract. The condition may be genetic. A second possible cause of iron overload is excess dietary iron. The African Bantu who prepares his daily food and brews fermented beverages in iron pots is the classic example of this form of iron overload. Sporadic other cases occur owing to excessive ingestion of iron-containing tonics or medicines. The third circumstance in which iron overload may occur is from the regular requirement for blood transfusion for some form of refractory anemias and is sometimes referred to as *transfusional siderosis* (Muller-Eberhard *et al.*, 1977).

The pathologic consequences of iron overload are similar regardless of basic cause. The body

iron content is increased to between 20 and 40 g. Most of the extra iron is hemosiderin. Greatest concentrations are in parenchymal cells of liver and pancreas, as well as endocrine organs and heart. Iron in reticuloendothelial cells (spleen) is greatest in transfusional siderosis and in the Bantu. Further clinical effects may include disturbances in liver function, diabetes mellitus, and even endocrine disturbances and cardiovascular effects. At the cell level, increased lipid peroxidation occurs with consequent membrane damage to mitochondria, microsomes, and other cellular organelles (Jacobs, 1977).

Treatment of acute iron poisoning is directed toward removal of the ingested iron from the gastrointestinal tract by inducing vomiting or gastric lavage and providing corrective therapy for systemic effects such as acidosis and shock. Deferrioxamine is the chelating agent of choice for treatment of iron absorbed from acute exposure as well as for removal of tissue iron in hemosiderosis. Repeated phlebotomy can remove as much as 20 g of iron per year. Ascorbic acid will also increase iron excretion as much as twofold normal (E. B. Brown, 1983).

Inhalation of iron oxide fumes or dust by workers in metal industries may result in deposition of iron particles in lungs, producing an X-ray appearance resembling silicosis. These effects are seen in hematite miners, iron and steel workers, and arc welders. Hematite is the most important iron ore (mainly Fe_2O_3). A report of autopsies of hematite miners noted an increase in lung cancer, as well as tuberculosis and interstitial fibrosis (Boyd *et al.*, 1970). The etiology of the lung cancer may be related to concomitant factors such as cigarettes or other workplace carcinogens. Hematite miners are also exposed to silica and other minerals, as well as radioactive materials; other iron workers have exposures to polycyclic hydrocarbons (A. I. G. McLaughlin, 1956). Dose levels of iron among iron workers developing pneumoconiosis have been reported to exceed 10 mg Fe/m^3.

Manganese

Manganese is an essential element and is a cofactor for a number of enzymatic reactions, particularly those involved in phosphorylation, cholesterol, and fatty acids synthesis. Manganese is present in all living organisms. While it is present in urban air and in most water supplies, the principal portion of the intake is derived from food. Vegetables, the germinal portions of grains, fruits, nuts, tea, and some spices are rich in manganese (NAS, 1973; Underwood, 1977; Keen and Leach, 1988).

Daily manganese intake ranges from 2 to 9 mg. Gastrointestinal absorption is less than 5 percent. It is transported in plasma bound to a β_1-globulin, thought to be transferrin, and is widely distributed in the body. Manganese concentrates in mitochondria, so that tissues rich in these organelles have the highest concentrations of manganese including pancreas, liver, kidney, and intestines. Biologic half-life in the body is 37 days. It readily crosses the blood-brain barrier, and half-time in the brain is longer than in the whole body.

Manganese is eliminated in the bile and is reabsorbed in the intestine, but the principal route of excretion is with feces. This system apparently involves the liver, auxiliary gastrointestinal mechanisms for excreting excess manganese, and perhaps the adrenal cortex. This regulating mechanism, plus the tendency for extremely large doses of manganese salts to cause gastrointestinal irritation, accounts for the lack of systemic toxicity following oral administration or dermal application.

Manganese and its compounds are used in making steel alloys, dry-cell batteries, electrical coils, ceramics, matches, glass, dyes; in fertilizers, welding rods; as oxidizing agents; and as animal food additives.

Industrial toxicity from inhalation exposure, generally to manganese dioxide in mining or manufacturing, is of two types: The first, manganese pneumonitis, is the result of acute exposure. Men working in plants with high concentrations of manganese dust show an incidence of respiratory disease 30 times greater than normal. Pathologic changes include epithelial necrosis followed by mononuclear proliferation.

The second and more serious type of disease resulting from chronic inhalation exposure to manganese dioxide, generally over a period of more than two years, involves the central nervous system. In iron-deficiency anemia, the oral absorption of manganese is increased, and it may be that variations in manganese transport related to iron deficiency account for individual susceptibility (Mena *et al.*, 1969). Those who develop chronic manganese poisoning (manganism) exhibit a psychiatric disorder characterized by irritability, difficulty in walking, speech disturbances, and compulsive behavior that may include running, fighting, and singing. If the condition persists, a masklike face, retropulsion or propulsion, and a Parkinson-like syndrome develop (Mena *et al.*, 1967). The outstanding feature of manganese encephalopathy has been classified as severe selective damage to the subthalamic nucleus and pallidum (Pentschew *et al.*, 1963). These symptoms and the pathologic lesions, degenerative changes in the basal ganglia, make the analogy to Parkinson's disease feasible. In addition to the central nervous

ferric phosphate

+3

Synonyms: *iron phosphate*

CAS: 10045-86-0.

MF: $FePO_4=2H_2O$

Properties: Yellowish-white powder, insoluble in water, soluble in acids, density 2.87.

Derivation: By adding a solution of sodium phosphate to a solution of ferric chloride. The product is filtered and then dried.

Uses: Fertilizers, feed and food additive.

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Downloaded from NLM: 27-Nov-95

1 - HSDB
NAME - FERRIC PHOSPHATE
RN - 10045-86-0
HSN - 453
DATE - 950823
RVDT - NO DATA
UPDT - 08/23/95, 1 field
UPDT - 05/26/95, 1 field
UPDT - 04/20/95, 1 field
UPDT - 04/20/95, 1 field
UPDT - 01/26/95, 1 field
UPDT - 12/21/94, 1 field
UPDT - 08/17/94, 1 field
UPDT - 03/25/94, 1 field
UPDT - 08/07/93, 1 field
UPDT - 02/05/93, 1 field
RLEN - 12283
RELT - NO DATA
SY - FERRIC ORTHOPHOSPHATE **PEER REVIEWED**
SY - IRON PHOSPHATE [FEPO4] **PEER REVIEWED**
SY - PHOSPHORIC ACID, IRON(3+) SALT (1:1) **PEER REVIEWED**
MF - FE.H3-O4-P **PEER REVIEWED**
WLN - NO DATA
RTEC - NO DATA
OHMN - NO DATA
SHPN - NO DATA
STCC - NO DATA
HAZN - NO DATA
ASCH - NO DATA
MMFG - ...FROM FE(H2PO4)3: REMY, BOULLE, COMPT REND 253, 2699 (1961); FROM FE(CO)5 & H3PO4: CATE ET AL, SOIL SCI 88(3), 130 (1959); FROM PHOSPHATE ROCK: VICKERY, US PATENT 2,914,380 (1959 TO HORIZONS INC); FROM MILL SCALE & H3PO4: ALEXANDER, MATHES, US PATENT 3,070,423 (1962 TO CHEMETRON CORP). [MERCK INDEX 9TH ED 1976 , p. 525] **PEER REVIEWED**
IMP - NO DATA
FORM - NO DATA
MFS - NO DATA
OMIN - CONTAINS 37% IRON. [ROSSOFF. HDBK VET DRUGS 1974 , p. 218] **PEER REVIEWED**
OMIN - A NUTRIENT AND/OR DIETARY SUPPLEMENT FOOD ADDITIVE. ALSO USED AS TRACE MINERAL ADDED TO ANIMAL FEEDS. [SAX. DANGER PROPS INDUS MATER 5TH ED 1979 , p. 685] **PEER REVIEWED**
OMIN - AS FEED SOURCE OF IRON (EVEN IN BREAD FOR MAN), PARTICULARLY IN MINERAL MIXES. [ROSSOFF. HDBK VET DRUGS 1974 , p. 218] **PEER REVIEWED**
OMIN - SMALL QUANTITIES...USED AS IRON-ENRICHMENT COMPD IN FOOD APPLICATIONS. ...ALTHOUGH IT IS INSOL IN WATER, IT IS SOL TO VARYING DEGREES IN DIL HYDROCHLORIC-ACID SOLN, SUCH AS THOSE IN THE STOMACH. THE DEGREE OF SOLUBILITY CAN BE CONTROLLED BY THE METHOD OF MFR. [FURIA. HDBK FOOD ADD 2ND ED 1972 , p. 624] **PEER REVIEWED**
OMIN - ADDN OF FERRIC ORTHOPHOSPHATE TO SUPPLY NUTRITIONAL LEVELS OF IRON DOES NOT AFFECT ASCORBIC ACID STABILITY IN FROZEN ORANGE DRINK CONCENTRATE. [FURIA. HDBK FOOD ADD 2ND ED 1972 , p. 107] **PEER REVIEWED**
USE - FOOD AND FEED SUPPLEMENT, PARTICULARLY IN BREAD ENRICHMENT; AS FERTILIZER /DIHYDRATE/ [MERCK INDEX 9TH ED 1976 , p. 525] **PEER REVIEWED**
CPAT - NO DATA
PROD - NO DATA
IMPT - NO DATA
EXPT - NO DATA
COFO - NO DATA
ODOR - NO DATA
TAST - NO DATA
BP - NO DATA
MP - NO DATA
MW - 150.83 **PEER REVIEWED**
CORR - NO DATA
CTP - NO DATA
DEN - NO DATA
DSC - NO DATA
HTC - NO DATA
HTV - NO DATA
OWPC - NO DATA
PH - NO DATA
SOL - NO DATA
SPEC - NO DATA
SURF - NO DATA
VAPD - NO DATA
VAP - NO DATA
EVAP - NO DATA
VISC - NO DATA
OCPP - LOSES WATER ABOVE 140 DEG C; DENSITY: 2.87 /DIHYDRATE/ [MERCK INDEX 9TH ED 1976 , p. 525] **PEER REVIEWED**
OCPP - WHITE, GRAYISH-WHITE, OR LIGHT PINK, ORTHORHOMBIC OR MONOCLINIC CRYSTALS OR AMORPHOUS POWDER /DIHYDRATE/ [MERCK INDEX 9TH ED 1976 , p. 525] **PEER REVIEWED**
OCPP - PRACTICALLY INSOL IN WATER; READILY SOL IN HYDROCHLORIC ACID; SLOWLY SOL IN NITRIC ACID /DIHYDRATE/ [MERCK INDEX 9TH ED 1976 , p. 525] **PEER REVIEWED**
OCPP - SOL IN SULFURIC ACID /DIHYDRATE/ [WEAST. HDBK CHEM & PHYS 60TH ED 1979 B-87] **PEER REVIEWED**
HAZS - NO DATA
DOT - NO DATA
FPOT - NO DATA
NFPA - NO DATA
FLMT - NO DATA
FLPT - NO DATA
AUTO - NO DATA
FIRP - NO DATA
TOXC - NO DATA
OFHZ - NO DATA
EXPL - NO DATA
REAC - NO DATA
DCMP - NO DATA
POLY - NO DATA
OHAZ - NO DATA
ODRT - NO DATA
SERI - NO DATA
EQUP - NO DATA
OPRM - NO DATA

SSL - NO DATA
SHIP - NO DATA
STRG - NO DATA
CLUP - NO DATA
DISP - NO DATA
RADL - NO DATA
TOXS - NO DATA
CAREV- NO DATA

THE FOLLOWING OVERVIEW IS A SUMMARY. CONSULT THE COMPLETE POISINDEX (R) DATABASE FOR TREATMENT PURPOSES. COPYRIGHT 1974-YEAR MICROMEDEX, INC. ALL RIGHTS RESERVED. DUPLICATION PROHIBITED.

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The following Overview, *** IRON ***,
is relevant for this HSDB record chemical.

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EMT -
o EMLS - LIFE SUPPORT :

This overview assumes that basic life support measures have been instituted.

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o EMCE - CLINICAL EFFECTS :

SUMMARY OF EXPOSURE
0.2.1.1 ACUTE EXPOSURE
o CLINICAL FINDINGS
1. MAJOR: Stupor, shock, acidosis, hematemesis, bloody diarrhea or coma
2. MINOR: Vomiting, diarrhea, mild lethargy, leukocytosis (WBC greater than 15,000), and hyperglycemia.

o CLINICAL COURSE (May Not Occur In All Cases)
1. PHASE I (0.5 to 2 h) includes vomiting, hematemesis, abdominal pain, diarrhea, hematochezia, lethargy, shock, acidosis, and coagulopathy. Necrosis to the GI tract occurs from the direct effect of iron on GI mucosa.
a. Severe gastrointestinal hemorrhagic necrosis with large losses of fluid and blood contribute to shock. Free iron and ferritin produce vasodilatation that may also contribute to shock.
2. PHASE II (after phase I) includes apparent recovery may contribute to a false sense of security. Observe closely.
3. PHASE III (2 to 12 hours after phase I) includes profound shock, severe acidosis, cyanosis and fever.
a. Increased total peripheral resistance, decreased plasma volume, hemoconcentration, decrease in total blood volume, hypotension and metabolic acidosis have been demonstrated.
4. PHASE IV (2 to 4 days) includes possible hepatotoxicity. Thought to be a direct action of iron on mitochondria. Monitor liver function tests and bilirubin.
5. Phase V (days to weeks) includes GI scarring and strictures.
a. GI obstruction secondary to gastric or pyloric scarring may occur due to corrosive effects of iron. Evaluate with barium contrast studies.
b. Sustained-release preparations have resulted in small intestinal necrosis with resultant scarring and obstruction.
6. The phases of iron poisoning do not occur in all patients. After massive overdose, patients may present in shock. With less serious overdoses, the initial gastrointestinal symptoms may be the only findings to develop even without treatment.
7. Although serious iron poisoning in adults is rare, deaths have been reported.

VITAL SIGNS
0.2.3.1 ACUTE EXPOSURE
o Blood pressure may be decreased following an iron overdose.

CARDIOVASCULAR
0.2.5.1 ACUTE EXPOSURE
o Hypotension may develop secondary to vomiting, diarrhea, blood loss or vasodilation with severe overdose. Cardiac failure has been rarely reported.

RESPIRATORY
0.2.6.1 ACUTE EXPOSURE
o Noncardiogenic pulmonary edema may develop with severe intoxication.

NEUROLOGIC
0.2.7.1 ACUTE EXPOSURE
o Lethargy, restlessness or confusion may be seen early in the poisoning. Convulsions and coma may occur in later phases.

GASTROINTESTINAL
0.2.8.1 ACUTE EXPOSURE
o Nausea, vomiting, diarrhea and gastrointestinal hemorrhage may develop.

HEPATIC
0.2.9.1 ACUTE EXPOSURE
o Hepatic necrosis may develop after severe poisoning.

GENITOURINARY
0.2.10.1 ACUTE EXPOSURE
o Acute renal failure may develop.

ACID-BASE
0.2.11.1 ACUTE EXPOSURE
o Anion gap metabolic acidosis is a common early finding.

DERMATOLOGIC
0.2.14.1 ACUTE EXPOSURE
o Severe thermal burn with ferrous sulfate slurry has caused classical symptoms of ingested iron poisoning.

ENDOCRINE
0.2.16.1 ACUTE EXPOSURE
o Hyperglycemia is seen in the early phases of iron poisoning. Hypoglycemia may be seen in late phases.

REPRODU[illegible] HAZARDS

- o Case rep[illegible] of pregnant women who have received early aggressive treatment (decontamination and/or deforoxamine) have described good fetal outcomes.

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o EMLAB- LABORATORY :

- o Obtain CBC, electrolytes, blood sugar, serum iron and abdominal radiograph. Baseline PT, PTT, and LFT's should be obtained in severe overdoses.

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o EMTR - TREATMENT OVERVIEW :

SUMMARY EXPOSURE

- o Decontamination is recommended with syrup of ipecac (at home, if recent ingestion) or gastric lavage (in health care facility) if greater than 20 mg/Kg or unknown amount of ingestion OR symptomatic. Decontamination efficacy should be monitored by following serial KUBS until no pills are seen.
- o Deferoxamine chelation is indicated in symptomatic patients or those with a peak serum iron greater than 350 micrograms/deciliter. As iron absorption can be erratic after overdose, particularly after ingestion of enteric coated tablets, relying on peak serum iron level alone to determine need for chelation is unwise.
  1. Clinical signs and symptoms, persistence of tablets in the GI tract, presence of metabolic acidosis and assessment of the ingestion will all influence this decision.
- o Treatment is directed at:
  1. Removal of iron from the gastrointestinal tract.
  2. Maintaining electrolytes, treating shock, hypotension, and hyperglycemia.
  3. Removal of iron from the patient's system.
  4. Repairing damage caused by the iron component.

ORAL EXPOSURE

- o EMESIS: May be indicated in recent substantial ingestion unless the patient is or could rapidly become obtunded, comatose or convulsing. Is most effective if initiated within 30 minutes. (Dose of Ipecac Syrup: ADULT: 30 mL; CHILD 1 to 12 years: 15 mL).
- o GASTRIC LAVAGE: May be indicated if performed soon after ingestion, or in patients who are comatose or at risk of convulsing. Protect airway by placement in Trendelenburg and left lateral decubitus position or by cuffed endotracheal intubation.
  1. After control of any seizures present, perform gastric lavage. Volume of lavage return should approximate fluid given.
- o Lavage with bicarbonate solutions or deferoxamine is NOT recommended.
- o Administer a cathartic such as magnesium citrate N.F. (ADULT and CHILD: 4 mL/kg up to 300 mL/dose). A cathartic may not be necessary.
- o Whole bowel irrigation with polyethylene glycol is indicated when there is radiographic evidence of iron tablets past the pylorus or if tablets persist in the gastrointestinal tract after other attempts at decontamination.
  1. DOSE (PEG): ADULTS: 1.5 to 2 L/hr. CHILD: 25 mL/Kg/hr. ENDPOINT: clear rectal effluent and/or disappearance of radiopacities when present.
- o MAJOR CLINICAL FINDINGS PRESENT
  1. Monitor electrolytes carefully, treat shock. Blood products may be necessary.
  2. HYPOTENSION: Administer IV fluids and place in Trendelenburg position. If unresponsive to these measures, administer dopamine (2 to 5 mcg/kg/min) (first choice) or norepinephrine (0.1 to 0.2 mcg/kg/min) and titrate as needed to desired response.
  3. INSTITUTE DEFEROXAMINE THERAPY as outlined below.
  4. CONSIDER EXCHANGE TRANSFUSION in severely symptomatic patients with a serum iron exceeding 1,000 mcg/dL.
- o MINOR OR NO CLINICAL FINDINGS PRESENT
  1. ASYMPTOMATIC PATIENT
     a. Decontamination is recommended with syrup of ipecac (at home, if recent ingestion) or gastric lavage (in health care facility) if greater than 20 mg/Kg or unknown amount of ingestion. Decontamination efficacy should be monitored by following serial KUBS until no pills are seen.
     b. Whole bowel irrigation with polyethylene glycol is indicated when there is radiographic evidence of iron tablets past the pylorus or if tablets persist in the gastrointestinal tract after other attempts at decontamination.
     (1) DOSE (PEG): ADULTS: 1.5 to 2 L/hr. CHILD: 25 mL/Kg/hr. ENDPOINT: clear rectal effluent and/or disappearance of radiopacities when present.
     c. Obtain CBC, blood sugar, and serum iron (SI). Institute deferoxamine therapy if SI exceeds the TIBC (if obtained), peak SI is more than 350 to 500 mcg/dL, or patient is symptomatic.
  2. SYMPTOMATIC PATIENT
     a. Evacuate stomach; obtain abdominal and chest x-ray. If iron tablets are present in the gastrointestinal tract begin whole bowel irrigation.
     b. Determine serum iron (SI), CBC, electrolytes and blood sugar. SI may be most useful 3 to 4 hours postingestion for liquids/tablets. An additional level 3 to 4 hours later may be helpful with sustained-release/enteric-coated products.
     c. Begin deferoxamine therapy if SI exceeds the TIBC (if obtained), peak SI is more than 350 mcg/dL or SI cannot be obtained in a reasonable time in a symptomatic patient.
- o DEFEROXAMINE THERAPY
  1. INTRAVENOUS DOSE: Administer by continuous infusion at a rate of up to 15 milligram/kilogram/hour. Faster rates or IV boluses may cause hypotension in some individuals, but infusion rates up to 35

milligram/k...gram/hour have been used in children with severe overdoses.

a. Duration of infusion is guided by the patient's clinical condition. Patients with moderate toxicity are generally treated for 8 to 12 hours, those with severe toxicity may require deferoxamine for 24 hours or longer. Patients should be reevaluated for evidence of recurrent toxicity (hypotension, metabolic acidosis) several hours after the infusion is discontinued. Infusion duration of greater than 24 hours has been associated with the development of ARDS.

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o EMTOX- RANGE OF TOXICITY :

o Toxicity is likely following 60 mg/kg elemental iron. Twenty to 60 mg/kg is possibly toxic.

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o REFERENCE :

[Rumack BH: POISINDEX(R) Information System. Micromedex Inc., Englewood, CO, 1995; CCIS CD-ROM Volume 87, edition exp Feb, 1996. Hall AH & Rumack BH (Eds): TOMES(R) Information System. Micromedex, Inc., Englewood, CO, 1995; CCIS CD-ROM Volume 87, edition exp Feb, 1996.] **PEER REVIEWED**

ANTR - NO DATA

MEDS - NO DATA

HTOX - ...SYMPTOMS OF IRON INTOXICATION INCL VOMITING, HEMATEMESIS, DIARRHEA, LETHARGY, COMA, IRRITABILITY, SEIZURES, & ABDOMINAL PAIN. ...INCR CARDIAC & RESP RATE...MARKED INCR IN TOTAL PERIPHERAL VASCULAR RESISTANCE MAY MAINTAIN ARTERIAL BLOOD PRESSURE FOR VARIABLE PERIODS BEFORE MANIFESTATIONS OF LOW OUTPUT SHOCK... /IRON/ [PATTY. INDUS HYG & TOX 3RD ED VOL2A,2B,2C 1981-82 , p. 1665] **PEER REVIEWED**

HTOX - ...CONSEQUENCES OF ACUTE IRON INTOXICATION INCL METABOLIC ACIDOSIS, DUE IN PART TO ACCUM OF LACTIC & CITRIC ACIDS, & HYPOGLYCEMIA. /IRON/ [PATTY. INDUS HYG & TOX 3RD ED VOL2A,2B,2C 1981-82 , p. 1666] **PEER REVIEWED**

HTOX - ORALLY, IRON SALTS OF BOTH VALENCE FORMS ARE NOT STRIKINGLY TOXIC; ON THE OTHER HAND, WHEN INTRODUCED DIRECTLY INTO THE BLOODSTREAM IRON SALTS ARE INSTANTANEOUSLY TOXIC, PARTICULARLY FERRIC SALTS. /IRON SALTS/ [PATTY. INDUS HYG & TOX 3RD ED VOL2A,2B,2C 1981-82 , p. 1665] **PEER REVIEWED**

NTOX - IMMEDIATE CAUSE OF DEATH FROM /PARENTERAL ADMIN OF/...INORG COMPD OF IRON IN ANIMALS IS RESP FAILURE. CLINICAL SIGNS PRECEDING DEATH ARE ANOREXIA, OLIGODIPSIA, OLIGURIA, ALKALOSIS, DIARRHEA, LOSS OF BODY WT, HYPOTHERMIA, & ALTERNATING IRRITABILITY & DEPRESSION. /INORG IRON COMPD/ [PATTY. INDUS HYG & TOX 3RD ED VOL2A,2B,2C 1981-82 , p. 1665] **PEER REVIEWED**

NTOX - /IN ANIMALS AFTER PARENTERAL ADMIN/...THERE IS LOSS OF WT IN MOST ORGANS, ACCOMPANIED BY DEHYDRATION WHEN DEATH OCCURRED EARLY, & EDEMA WHEN DEATH WAS DELAYED. VASCULAR CONGESTION OF GI TRACT, LIVER, KIDNEYS, HEART, LUNGS, BRAIN, SPLEEN, ADRENALS, & THYMUS GLAND IS DOMINANT HISTOPATHOLOGICAL SIGN. /INORG IRON COMPD/ [PATTY. INDUS HYG & TOX 3RD ED VOL2A,2B,2C 1981-82 , p. 1665] **PEER REVIEWED**

NTOX - ...UPTAKE BY EXOGENOUS, EXCESS IRON OF ELECTRONS DONATED BY FERRIC REDUCTASE IN MITOCHONDRIAL MEMBRANE THAT NORMALLY CATALYZES ENDOGENOUS FERRIC IRON TO FERROUS IRON, RESULTING IN IMMEDIATE CESSATION OF AEROBIC SYNTHESIS OF ADENOSINE TRIPHOSPHATE, INITIATING CELLULAR ENERGY CRISIS & CELL DEATH. /IRON/ [PATTY. INDUS HYG & TOX 3RD ED VOL2A,2B,2C 1981-82 , p. 1670] **PEER REVIEWED**

HTXV - NO DATA

NTXV - NO DATA

ETXV - NO DATA

NTP - NO DATA

IARC - NO DATA

TCAT - NO DATA

POPL - NO DATA

ADE - FERROUS IRON IS GENERALLY ABSORBED FROM GI TRACT MORE READILY THAN FERRIC IRON, PRESUMABLY BECAUSE OF GREATER SOLUBILITY OF FERROUS COMPD. AMT OF IRON ABSORBED IS INVERSELY PROPORTIONAL TO THE INTAKE. /IRON COMPD/ [PATTY. INDUS HYG & TOX 3RD ED VOL2A,2B,2C 1981-82 , p. 1667] **PEER REVIEWED**

ADE - NORMAL HUMAN BODY CONTAINS 4.5 G IRON; OF THIS, HEMOGLOBIN, WHICH IS ALMOST ENTIRELY IN BLOOD, COMPRISES 72.9% OF TOTAL IRON; MYOGLOBIN, 3.3%; PARENCHYMAL IRON (OXIDATIVE ENZYMES) 0.2%; & STORAGE IRON (FERRITIN, HEMOSIDERIN, & UNACCOUNTED IRON) 23.5%. MOST OF STORAGE IRON IS FOUND IN LIVER, BONE MARROW, & SPLEEN. /IRON/ [PATTY. INDUS HYG & TOX 3RD ED VOL2A,2B,2C 1981-82 , p. 1669] **PEER REVIEWED**

METB - NO DATA

BHL - NO DATA

ACTN - NO DATA

INTC - NO DATA

BION - NO DATA

THER - NO DATA

MINF - NO DATA

WARN - NO DATA

IDIO - NO DATA

TOLR - NO DATA

MXDD - NO DATA

ENVS - NO DATA

NATS - OCCURS IN NATURE AS MINERALS: BERAUNITE, CACOXENITE, DUFRENITE, KONINCKITE, PHOSPHOSIDERITE, STRENGITE. [MERCK INDEX 9TH ED 1976 , p. 525] **PEER REVIEWED**

NATS - ...IN SMALL QUANTITIES IN PRACTICALLY ALL PHOSPHATE ROCK & IN RATHER LARGE QUANTITIES IN SOME OF LOWER GRADES OF ROCK. [FARM CHEM HDBK 1981 B-40] **PEER REVIEWED**

ARTS - NO DATA

FATE - NO DATA

BIOD - NO DATA

ABIO - NO DATA

BIOC - NO DATA

KOC - NO DATA

VWS - NO DATA

WATC - NO DATA

EFFL - NO DATA

SEDS - NO DATA

ATMC - NO DATA

FOOD - NO DATA

PLNT - NO DATA

FISH - NO DATA

ANML - NO DATA

MILK - NO DATA
OEVC - NO DATA
RTEX - NO DATA
AVDI - NO DATA
BODY - NO DATA
IDLH - NO DATA
ADI - NO DATA
ATOL - NO DATA
OSHA - NO DATA
NREC - NO DATA
TLV - 8 hr Time Weighted Avg (TWA) 1 mg/cu m (1986) /Iron salts, soluble, as Fe/ [ACGIH. TLV'S CHEM SUBSTS & PHYSICAL AGENTS & BIOLOGICAL EXP INDICES 1994-1995 , p. 24] **QC REVIEWED**
TLV - Excursion Limit Recommendation: Excursions in worker exposure levels may exceed three times the TLV-TWA for no more than a total of 30 min during a work day, and under no circumstances should they exceed five times the TLV-TWA, provided that the TLV-TWA is not exceeded. /Iron salts, soluble, as Fe/ [ACGIH. TLV'S CHEM SUBSTS & PHYSICAL AGENTS & BIOLOGICAL EXP INDICES 1994-1995 , p. 5] **QC REVIEWED**
OOPL - NO DATA
ASTD - NO DATA
SSTD - NO DATA
FDWS - NO DATA
FDWG - EPA 300 ug/l /Iron/ [USEPA. SUM STATE FED DRINK WATER STDS GUIDE 1993] **QC REVIEWED**
SDWS - (IL) ILLINOIS 1000 ug/l /Iron/ [USEPA. SUM STATE FED DRINK WATER STDS GUIDE 1993] **QC REVIEWED**
SDWS - (NC) NORTH CAROLINA 300 ug/l /Iron/ [USEPA. SUM STATE FED DRINK WATER STDS GUIDE 1993] **QC REVIEWED**
SDWG - (MD) MARYLAND 300 ug/l /Iron/ [USEPA. SUM STATE FED DRINK WATER STDS GUIDE 1993] **QC REVIEWED**
SDWG - (ME) MAINE 340 ug/l /Iron/ [USEPA. SUM STATE FED DRINK WATER STDS GUIDE 1993] **QC REVIEWED**
CWA - NO DATA
CERC - NO DATA
TSCA - NO DATA
RCRA - NO DATA
FIFR - NO DATA
FDA - 121.101; LIMITATIONS: GRAS, NUTRIENT &/OR DIETARY SUPPLEMENT. [FURIA. HDBK FOOD ADD 2ND ED 1972 , p. 852] **PEER REVIEWED**
SAMP - NO DATA
ALAB - ANALYTE: IRON; MATRIX: AIR; PROCEDURE: FILTER COLLECTION, ACID DIGESTION, AAS. /IRON/ [NIOSH MANUAL ANALY METH. VOL1-7 1977-PRESENT V5 173-1] **PEER REVIEWED**
CLAB - NO DATA
RPTS - NO DATA
TEST - NO DATA
HIST - NO DATA

[HSDB,RTECS] SS 2 /cf?
USER:

N I O S H T I C(R)

Produced by : US National Institute for Occupational Safety and Health
Provided by : Canadian Centre for Occupational Health and Safety
Issue : 95-3 (August, 1995)

NIOSHTIC RECORD NUMBER : 119212

TITLE :

A Study Of Dust Toxicity Using A Quantitative Tissue Culture Technique

NIOSHTIC CONTROL NUMBER : NIOSH-00157377

AUTHOR(S) :

Marks, J., M. A. Mason, and G. Nagelschmidt

SOURCE :

British Journal of Industrial Medicine, Vol. 13, No. 3, pages 187-191, 25 references

PUBLICATION DATE : 1956-07-00

ABSTRACT :

The toxicity of a number of dusts was compared using an in-vitro technique. Guinea-pig exudate cells were cultured with varying concentrations of the dusts of interest. The end point was defined as the smallest concentration of dust required to reduce the number of cells to less than 10 percent of the inoculum within 3 days. Effects of vitreous silica (60676860) and tridymite (15468323), cristobalite (14464461), and quartz (14808607) of different particle sizes were examined. Feldspar, mica, and kaolin dusts were studied. Anthracite (8029105), bituminous, and steam coal samples were tested. Ferric-phosphate (10045860), calcium-fluoride (7789755), aluminum-phosphate (7784307), and alumina (1344281) dusts were tested at concentrations up to 120 micrograms (microg)/1,000,000 cells. Protective effects of potassium-aluminum-sulfate (10043671) against damage by tridymite were also examined. Tridymite and cristobalite produced the standard degree of cell damage at a concentration of 7.5microg/1,000,000 cells. Quartz and vitreous silica were 8 times less toxic. Toxicity increased with the specific surface of the dust sample. The effect of kaolin and feldspar was equivalent to that of quartz. Mica was the least toxic of the silicates. Cells seemed to suffer no harm from coal unless burdened with very large amounts. The standard degree of cell damage was produced by anthracite samples administered in Ringers solution in a dose of 240microg/1,000,000 cells. Effects of bituminous and steam coal samples were similar when particle dispersion was improved by initial suspension in serum or lecithin. Ferric-phosphate and alumina had negligible effects on cultures. Aluminum-phosphate showed some toxicity, insufficient to produce standard cell damage. Calcium-fluoride produced standard cell damage in a concentration of 60microg/1,000,000 cells. Potassium-aluminum-sulfate protected cells against the toxic effects of tridymite, presumably by formation of aluminum-hydroxide. The authors conclude that the rapidity and sensitivity of this quantitative dust culture technique makes it useful for screening dust for toxicity.

DESCRIPTOR(S) :

BJIMAG / Quantitative analysis / Lung / Dust exposure / Air sampling / Lung irritants / Analytical models / Inhalants / Pulmonary clearance / Pulmonary function / Metabolites / Respiration

N I O S H T I C(R)

Produced by : US National Institute for Occupational Safety and Health
Provided by : Canadian Centre for Occupational Health and Safety
Issue : 95-3 (August, 1995)

NIOSHTIC RECORD NUMBER : 12359

TITLE :

Preliminary Air Pollution Survey of Iron and Its Compounds A Literature Review

NIOSHTIC CONTROL NUMBER : NIOSH-00020389

AUTHOR(S) :

Sullivan, R. J.

SOURCE :

National Air Pollution Control Administration, Consumer Protection and Environmental Health Service, Public Health Service, DHEW, Report No. APTD 69-38, 94 pages, 225 references

PUBLICATION DATE : 1969-10-00

ABSTRACT :

Review of iron and iron compounds as harmful atmospheric pollutants, including characteristics, sources, distribution, effects, and control technology for abatement, iron and iron oxide being cited as causing siderosis and iron oxides as potentiating vehicles for transporting carcinogens and sulfur dioxide deep into the lungs. Topics include pathogenic and toxic effects on humans, including carcinogenesis, synergism, nutrition, and iron pentacarbonyl; effects on animals, plants, and materials; environmental air standards and concentrations; natural occurrence; production sources, including coal, fuel oil, and the iron and steel industry (as the biggest source of emission, including sintering plants, blast furnaces, ferromanganese blast furnaces, open-hearth furnaces, ferromanganese blast furnaces, open-hearth furnaces, electric-arc furnaces, basic oxygen furnaces, and gray iron cupolas); product sources, including incineration, welding rods, and antiknock compounds; economics; and sampling and quantitative methods of analysis. Data are given for composition, consumption, emission, uses, and toxic properties of compounds including dextran iron complex, oxides, acetates, fluorides, chlorides, bromides, ferrichromes, hydroxides, formates, nitrates, cyanides, hematite, phosphates, sulfates, carbonates, magnetite, ferrite, ferrocene, iodides, oxalates, thiocyanates, phosphides, and sulfides.

DESCRIPTOR(S) :

Toxic substances / Heavy metals / Ores / Ironmaking / Steelmaking / Lung cancer / Cancerogens / Air contaminants / Pathogens / Organo iron compounds / Respiratory system disorders / Dust control / Physical properties / Chemical properties / Analytical techniques / Airborne dusts / TLV / Environment control / Air quality control / 7439896 / 10031262 / 7705080 / 7783508 / 555760 / 1309337 / 7782618 / 10421484 / 1309371 / 7782629 / 10045860 / 1310458 / 10028225 / 1317540 / 102545 / 1317619 / 7789460 / MX8030351 / 7758943 / 7785220 / 7783860 / 516030 / 1345251 / 10028236 / 1310436 / 7720787 / 5978563 / MX8050939 / 13463406

N I O S H T I C(R)

Produced by : US National Institute for Occupational Safety and Health
Provided by : Canadian Centre for Occupational Health and Safety
Issue : 95-3 (August, 1995)

NIOSHTIC RECORD NUMBER : 168435

TITLE :

An Epidemic of Dermatitis at a Large Construction Site

NIOSHTIC CONTROL NUMBER : NIOSH-00199020

AUTHOR(S) :

Sinks, T., M. O'Malley, R. Hartle, T. R. Hales, and R. Ruhe

SOURCE :

Journal of Occupational Medicine, Vol. 33, No. 4, pages 462-467, 12 references

PUBLICATION DATE : 1991-04-00

ABSTRACT :

An outbreak of dermatitis at one of the largest construction sites in the United States was evaluated. The evaluation started as a result of a request from one of the workers at the site for a Health Hazard Evaluation to be conducted by NIOSH in August of 1986. Two nuclear power facilities were under construction at the site, employing more than 5000 workers. The wood that was used for scaffolding and other temporary structures was treated with free retardant made by mixing dicyandiamide (461585), phosphorus-acid (13598362), and formaldehyde (50000) in water and applying it to the wood by a vacuum pressure process. Pruritic, maculopapular lesions were noted on the arms of some workers. Other parts of the body affected included the shoulders and flank. Workers reported the rashes began at work and lasted from days to weeks. Between February 2 and October 19, 1986 there was a total of 445 visits from 407 workers to the medical facility for skin related problems. Only 122 visits were made during the same time period the year before. Carpenters had the highest rate of skin related visits to the medical facility, following by laborers and then iron workers. Of all the carpenters who completed a questionnaires (92% of those eligible), 54% reported skin conditions, and 29% met the case definition of possible contact dermatitis. Total phosphate concentrations for the extracts of the fire retardant treated lumber ranged from 4.7 to 7.1 milligrams/gram of wood. Results indicated that no specific agent could be identified, nor was it conclusive that a causal role for the fire retardant lumber existed. The large number of workers afflicted suggested that the offending agent was more likely to have been an irritant than an allergen. The authors state that phosphates can leach from treated lumber by both water and sweat. The increased temperatures during the summer season suggests this possible course of events. Construction workers have been advised to handle this lumber with caution, particularly in high temperature and humidity conditions.

DESCRIPTOR(S) :

JOCMA7 / NIOSH Publication / NIOSH Author / Skin irritants / Woodworkers / Skin exposure / Construction industry / Construction materials / Preservatives / Contact dermatitis / Occupational exposure

* Produced by : US National Institute for Occupational Safety and Health *
* Provided by : Canadian Centre for Occupational Health and Safety *
* Issue : 95-3 (August, 1995) *

NIOSHTIC RECORD NUMBER : 24293
TITLE :
Tissue Changes in Rats' Lungs Caused by Hydroxides, Oxides and Phosphates of Aluminium and Iron
NIOSHTIC CONTROL NUMBER : NIOSH-00032729
AUTHOR(S) :
Stacy, B. D., E. J. King, C. V. Harrison, G. Nagelschmidt, and S. Nelson
SOURCE :
Journal of Pathology and Bacteriology, Vol. 77, pages 417-426, 6 references
PUBLICATION DATE : 1959-00-00
ABSTRACT :
The fibrogenic activity of several hydroxides, oxides, and phosphates of aluminum and iron was tested by intratracheal injection into rats, with histological observation up to one year after injection. Gamma-alumina was found to be the most fibrogenic material: this was followed by the quartz-like and tridymite-like modification of aluminum phosphate which acted equally--in contrast to the differing fibrogenicity of the corresponding silica forms. A poorly crystallized sample of gamma-AlOOH of very small size was fairly fibrogenic, but a well-crystallized sample of gamma-AlOOH was inert. Alpha-alumina was almost inert, and all iron compounds tested were completely so. There was a positive correlation for the aluminum oxides and hydroxides between alumina solubility and fibrogenic activity, but the alumina phosphates were more fibrogenic than their solubility suggested.
DESCRIPTOR(S) :
Metals / Fibrogenicity / Histology / 7439896 / 1344281 / 7784307

* *
* N I O S H T I C(R) *
*
* Produced by : US National Institute for Occupational Safety and Health *
* Provided by : Canadian Centre for Occupational Health and Safety *
* Issue : 95-3 (August, 1995) *

NIOSHTIC RECORD NUMBER : 10579
TITLE :
PATHOGENESIS OF DIETARY SIDEROSIS IN THE RAT
NIOSHTIC CONTROL NUMBER : NIOSH-00007064
AUTHOR(S) :
Anonymous
SOURCE :
Nutrition Reviews, Vol. 22, No. 1, pages 20-22, 5 references
PUBLICATION DATE : 1964-00-00
ABSTRACT :
A review is made of the literature concerning the role of iron overload in producing pathologic changes in hemochromatosis and in siderosis. The pathogenesis as well as the pathology of siderosis in rats is similar to that in man, e.g. in the Bantus. Apparently, high dietary iron intake alone is not sufficient to cause excess iron storage; related factors may be

either a low phosphate intake or ultrastructural changes in the tissues due to nutritionally inadequate diet.

DESCRIPTOR(S) :

Nutrition / Deficiencies / 7439896

Date: 28-Nov-95
Name: iron
Database: Current Contents/Life Sciences <12/05/94 - 11/27/95>

Set	Search	Results
001	iron.ab,ti,kw,kp.	2616
002	phosphate.ab,ti,kw,kp.	4929
003	(iron adj phosphate).ab,ti,kw,kp.	2
004	10045-86-0.ab,ti,kw,kp.	0
005	(inorganic adj iron).ab,ti,kw,kp.	7
006	from 5 keep 4	1

<1>
Accession Number
QZ910-0012
Authors
Ebihara K. Okano J.
Title
COMPARISON OF BIOAVAILABILITY AND HEMOGLOBIN REPLETION OF FERRIC AND FERROUS IRON INFUSED INTO THE CECUM IN ANEMIC RATS
Source
Nutrition Research. 15(6):889-897, 1995 Jun.
Author Keywords
Iron bioavailability. Intracecal infusion. Anemic rats. Hemoglobin regeneration efficiency.
KeyWords Plus
Chain fatty-acids. Absorption.
Abstract
The bioavailability of ferrous and ferric iron following cecal infusion was compared by assessing the hemoglobin regeneration method in ileally fistulated anemic rats. Rats were fed an iron-deficient diet (8 mg Fe/kg diet) for 14 days after recovery from surgery. The anemic rats were then divided into three groups of 11 rats. Group 1 (control) was fed an iron-adequate diet (45 mg Fe/kg diet) and infused with NaCl solution (150 mM). Group 2 and 3 were fed an iron-deficient diet and infused with ferrous sulfate [Fe(II)] suspension or ferric sulfate [Fe(III)] solution (800 ppm as Fe, pH 6.8) to provide the same amount of iron as that consumed one day before by the control group. NaCl, Fe(II) and Fe(III) were infused through the fistula as two times (1000h and 1800h) for 14 days. The volume of NaCl infused was about equal to the volume of Fe(II) suspension and Fe(III) solution infused. Hemoglobin regeneration efficiency, hematocrit, plasma iron concentration, transferrin saturation, total iron-binding capacity, iron contents in organs (liver, spleen and kidney), body weight gain and food intake were almost the same among groups. These results suggest that inorganic iron is absorbed from the large intestine and is not influenced by forms of iron, ferrous iron or ferric iron. [References: 16]
Institution
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JAPAN

Date: 28-Nov-95
Name: iron
Database: Current Contents/Life Sciences <12/05/94 - 11/27/95>

Set	Search	Results
001	iron.ab,ti,kw,kp.	2616
002	phosphate.ab,ti,kw,kp.	4929
003	(iron adj phosphate).ab,ti,kw,kp.	2
004	10045-86-0.ab,ti,kw,kp.	0
005	(inorganic adj iron).ab,ti,kw,kp.	7
006	ferric.ab,ti,kw,kp.	324
007	(ferric adj iron).ab,ti,kw,kp.	55
008	from 7 keep 14,16,21,31,46,51	6

<1>
Accession Number
RL344-0005
Authors
Carpenter CE. Ummadi M.
Title
IRON STATUS ALTERS THE ADSORPTION, UPTAKE, AND ABSORPTION CAPACITIES OF RAT DUODENUM FOR FERROUS AND FERRIC IRON
Source
Nutrition Research. 15(8):1129-1138, 1995 Aug.
Author Keywords
Iron. Absorption. Uptake. Rats. Intestine.
KeyWords Plus
Mouse duodenum. Uptake invitro. Ph gradient. Invivo. Dependence. Mechanisms. Kinetics. Mucosa. Fe-3+. Meat.
Abstract
We employed an in situ technique to determine the duodenal capacity for adsorption, uptake and absorption of free ferrous and ferric iron in both iron-replete and iron-deficient rats. Uptake and absorption capacities were related to luminal iron concentration by a two-component equation representing the simultaneous functioning of two pathways. One component of the equation was analogous to the Michaelis-Menton equation. This component suggested a saturable pathway for uptake of iron bound to mucin in the intestinal mucous layer. The second component of the equation was analogous to second order kinetics. This component suggested non-saturable uptake, perhaps due to the opening of a mucosal barrier, such as the tight junctions between mucosal cells, to diffusion of unbound iron. Iron deficiency caused an increase in the capacity of the saturable components about 5-fold for uptake and about 8-fold for absorption. This change was qualitatively, but not quantitatively, in agreement with the corresponding

20-fold increase in vivo absorption in rats maintained as cohorts.
[References: 31]
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<2>
Accession Number
RK172-0016
Authors
Caraceni P. Vanthiel DH. Borle AB.
Title
DUAL EFFECT OF DEFEROXAMINE ON FREE RADICAL FORMATION AND REOXYGENATION INJURY IN ISOLATED HEPATOCYTES
Source
American Journal of Physiology - Gastrointestinal & Liver Physiology. 32(1):G 132-G 137, 1995 Jul.
Author Keywords
Superoxide formation. Hydroxyl radical formation. Lucigenin chemiluminescence. Lipid peroxidation. Iron chelation. Free radical scavenging.
KeyWords Plus
Haber-weiss reaction. Hydroxyl radicals. Lipid-peroxidation. Ferric iron. Desferrioxamine. Superoxide. Inhibition. Protection.
Abstract
The effects of low concentrations (10 and 100 mu M) and high concentrations (1, 10, and 20 mM) of deferoxamine (DFO) on superoxide (O-2-radical anion) formation, lipid peroxidation, and cell injury were studied in freshly isolated perfused rat hepatocytes during a 2-h reoxygenation period after 2.5 h of anoxia. O-2-radical-anion production was measured by lucigenin-enhanced chemiluminescence, lipid peroxidation by malondialdehyde (MDA) formation, and cell injury by lactate dehydrogenase (LDH) release. On reoxygenation and in the absence of DFO, O-2-radical-anion generation increased 11-fold, MDA increased 3.7-fold, and LDH release practically doubled. Low concentrations of DFO had no effect on O-2-radical-anion generation but decreased MDA and LDH release from 44 to 75%. High concentrations of DFO significantly depressed O-2-radical-anion formation, with very little additional effect on MDA or LDH release. These experiments illustrate in a biological system the dual effect of DFO: 1) at low concentrations, DFO acts as a specific iron chelator and inhibits lipid peroxidation and cell. injury without preventing O-2-radical-anion formation, and 2) at high concentrations, DFO acts as a nonspecific scavenger of oxygen free radicals such as O-2-radical-anion. [References: 19]
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<3>
Accession Number
RD084-0002
Authors
Morris CJ. Earl JR. Trenam CW. Blake DR.
Title
REACTIVE OXYGEN SPECIES AND IRON - A DANGEROUS PARTNERSHIP IN INFLAMMATION [Review]
Source
International Journal of Biochemistry & Cell Biology. 27(2):109-122, 1995 Feb.
Author Keywords
Inflammation. Reactive oxygen species. Iron. Reperfusion injury. Nitric oxide. Transcription factors.
KeyWords Plus
Hydroxyl-radical generation. Porphyria-cutanea-tarda. Nitric-oxide synthesis. Lipid-peroxidation. Oxidative stress. Rheumatoid synovitis. Hydrogen-peroxide. Skin inflammation. Xanthine-oxidase. Transition-metals.
Abstract
Cells of nearly all forms of life require well-defined amounts of iron for survival, replication and expression of differentiated processes. It has a central role in erythropoiesis but is also involved in many other intracellular processes in the tissues of the body. It is the fourth most abundant element in the Earth's crust and the most abundant transition metal in living organisms for which its characteristic chemistry endows it with a series of properties enabling it to fulfil certain biological reactions especially those involving redox mechanisms. It is involved in the transport of oxygen, in electron transfer, in the synthesis of DNA, in oxidations by oxygen (O-2) and hydrogen peroxide (H2O2) and in many other processes maintaining normal structure and function of virtually all mammalian cells. Because an iron atom can exist in two valency states, ferrous and ferric, iron became the primordial partner of oxygen in evolution. However, as de Sousa et al. (1989) state, such long standing partnerships have to use protective devices to ensure that the toxicity of neither partner is expressed in the presence of the other. Here, we discuss this dangerous partnership and its relevance to inflammation. The main themes of this review are the known roles of iron in the generation of reactive oxygen intermediates and new developments, including iron and transcription and the reaction of iron with nitric oxide. We also consider the widening recognition of the importance of oxygen metabolites in hypoxia-reperfusion injury and disease of the skin and joint. [References: 98]

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Accession Number
QV678-0002
Authors
Ahmad S. Singh V. Rao GS.
Title
RELEASE OF IRON FROM FERRITIN BY 1,2,4-BENZENETRIOL
Source
Chemico-Biological Interactions. 96(2):103-111, 1995 May 19.
Author Keywords
1,2,4-benzenetriol. Ferritin. Autooxidation. Iron. Lipid peroxidation.
KeyWords Plus
Dependent lipid-peroxidation. Benzene toxicity. Free-radicals. Copper ions. Metabolites. Transport. Storage. Oxygen. Mobilization. Hydroquinone.
Abstract
Release of iron from ferritin in the presence of polyhydroxy metabolites of benzene i.e,, hydroquinone (HQ) or 1,2,4-benzenetriol (BT) was studied in acetate buffer, pH 5.6. The release of iron from ferritin was quantitated by monitoring the formation of iron-ferrozine complex. The presence of hydroquinone (330 mu M) did not result in the release of iron from ferritin, whereas the same concentration of BT resulted in the release of significant amounts of iron (3.2 mu M/min) from ferritin. BT concentration-dependent increase in iron release from ferritin was observed although the increase was not linear with the concentration of BT. Under a N-2 atmosphere the presence of BT resulted in the release of iron (2.1 mu M/min) from ferritin. The presence of oxyradical scavengers i.e., albumin, catalase or superoxide dismutase significantly inhibited iron release from ferritin by BT. The iron released from ferritin by BT enhanced lipid peroxidation in rat brain homogenate and released aldehydic products from bleomycin-dependent degradation of DNA. Addition of BT to bone marrow lysate resulted in an increase of iron release as a function of time. These studies indicate that BT is a potent reductant of ferric iron of ferritin and also mobilizes and releases iron from ferritin core. The release of iron from bone marrow lysate by BT may be of toxicological significance as this could lead to disruption of intracellular iron homeostasis in bone marrow cells. [References: 32]
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Accession Number
QG033-0003
Authors
Lash A. Saleem A.
Title
IRON METABOLISM AND ITS REGULATION - A REVIEW [Review]
Source
Annals of Clinical & Laboratory Science. 25(1):20-30, 1995 Jan-Feb.
KeyWords Plus
Ferritin messenger-rna. Element-binding-protein. Receptor-mediated endocytosis. Responsive element. Transferrin receptor. Rabbit reticulocytes. Untranslated region. 5-aminolevulinate synthase. Chromosomal localization. Intracellular pathways.
Abstract
Iron metabolism and its molecular regulation are reviewed. Ferric iron is bound to mucin in the stomach and delivered to the duodenum where it can be absorbed. Iron is transported across the apical membrane of the gut mucosa by integrin. Once within the mucosal cell, iron may be stored, utilized in protein synthesis, or exported to the serum. In the serum, iron is carried by transferrin. Diferric transferrin binds to transferrin receptor on the surface of cells and is endocytosed. In the cell, iron is bound to high and low molecular weight ligand and is thought to shuttle iron within the cell. Iron can be stored intracellularly within ferritin, or can be utilized in a number of iron containing proteins synthesized by the mitochondrion, including heme, aconitase, and cytochromes. The first chain of enzymes in the biosynthesis of heme is erythroid 5-aminolevulinate synthase (eALAS). Intracellular iron concentration regulates the synthesis of ferritin, transferrin receptor, and eALAS, thus controlling our iron metabolism. Iron regulates these proteins post-transcriptionally via iron responsive elements (IRE), which are highly conserved stem-loop structures found in messenger ribonucleic acid (mRNA), and an IRE binding protein (IRE-BP), which responds to increased intracellular iron concentrations by binding the IRE and repressing mRNA translation or stabilizing the mRNA, depending on whether the IRE is located in the upstream or downstream untranslated regions of the mRNA. Cellular responses to iron depletion and iron overload can be explained in terms of these regulatory mechanisms. [References: 86]
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Accession Number
QA021-0004
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Title
MECHANISMS OF CELL INJURY BY ACTIVATED OXYGEN SPECIES
Source
Environmental Health Perspectives. 102(Suppl 10):17-24, 1994 Dec.
Author Keywords
Superoxide. Hydrogen peroxide. Hydroxyl radical. Iron. Lipid peroxidation. Mitochondria. Dna. Poly(adp-ribose)polymerase.
KeyWords Plus
Tert-butyl hydroperoxide. Cultured rat hepatocytes. Single-strand breaks. Superoxide-dismutase prevents. Induced lipid-peroxidation. Haber-weiss reaction. Hydrogen-peroxide. Oxidative stress. Dna damage. Ferric iron.
Abstract
Current evidence suggests that O-2(-) and H2O2 injure cells as a result of the generation of a more potent oxidizing species. In addition to O-2(-) and H2O2, the third essential component of the complex that mediates the lethal cell injury is a cellular source of ferric iron. The hypothesis most consistent with all the available data suggests that O-2(-) reduces a cellular source oi ferric to ferrous iron, and the latter then reacts with H2O2 to produce a more potent oxidizing species, like the (OH)-O-. or an equivalently reactive species. In turn, (OH)-O-. initiates the peroxidative decomposition of the phospholipids of cellular membranes. (OH)-O-. also damages the inner mitochondrial membrane. Upon mitochondrial deenergization, a sequence of events is initiated that similarly leads to the loss of viability of the cell. DNA represents a third cellular target of (OH)-O-.. Depending on the cell type, oxidative DNA damage can be coupled to cell killing through a mechanism related to the activation of poly (ADP-ribose) polymerase. [References: 66]
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Date: 28-Nov-95
Name: iron
Database: Current Contents/Life Sciences <1994 Annual>

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003	(ferric adj iron).ab,ti,kw,kp.	35
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005	(iron adj phosphate).ab,ti,kw,kp.	2
006	1 or 2 or 3 or 4 or 5	40
007	6 and (toxicity or health effects).ab,ti,kw,kp.	2
008	from 6 keep 9,20,22,24,34,40	6

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Accession Number
PJ969-0002
Authors
Oestreicher E. Sengstock GJ. Riederer P. Olanow CW. Dunn AJ. Arendash GW.
Title
DEGENERATION OF NIGROSTRIATAL DOPAMINERGIC NEURONS INCREASES IRON WITHIN THE SUBSTANTIA NIGRA - A HISTOCHEMICAL AND NEUROCHEMICAL STUDY
Source
Brain Research. 660(1):8-18, 1994 Oct 10.
Author Keywords
Iron. Substantia nigra. Nigrostriatal degeneration. Dopamine.
KeyWords Plus
Parkinsons-disease. Lipid-peroxidation. Metal-ions. Brain. Glutathione. Ferritin. Rat. Neuromelanin. Stress. Acid.
Abstract
Parkinson's-diseased (PD) brains have increased levels of iron in the zona compacta of the substantia nigra (SNc). To determine whether these elevated nigral iron levels may be caused secondarily by degeneration of nigrostriatal dopaminergic (NS-DA) neurons, the NS-DA pathway was unilaterally lesioned in rats through 6-hydroxydopamine (6-OHDA) infusion and nigral iron levels evaluated three weeks later. A significant increase was observed in both iron concentration (+35%) and iron content (+33) within the substantia nigra (SN) ipsilateral to comprehensive 6-OHDA lesions. Moreover, ferric iron staining was dramatically increased within the SNc following 6-OHDA lesions, primarily due to the appearance of iron-positive SNc neurons and infiltrating reactive glial cells. Iron staining in the SN zona reticularis was modestly increased after 6-OHDA lesions, but staining in the neostriatum and globus pallidus was unaffected. These results indicate that loss of NS-DA neurons is associated with increased iron levels in the SN. This suggests that increased nigral iron levels in PD may be secondary to some neurodegenerative process. Nonetheless, even a secondary increase in nigral iron levels may be of pathogenic importance in PD because of iron's ability to catalyze neurotoxic free radical formation and perpetuate neurodegeneration. [References: 45]
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Accession Number
NQ007-0010

Authors
Conrad ME. Uzel C. Berry M. Latour L.

Title
IRONIC CATASTROPHES - ONES FOOD ANOTHERS POISON [Review]

Source
American Journal of the Medical Sciences. 307(6):434-437, 1994 Jun.

Author Keywords
Integrin. Mobilferrin. Metals. Oxidant. Free radical. Lipid peroxidation. Absorption.

KeyWords Plus
Idiopathic hemochromatosis. Transition-metals. Binding protein. Free-radicals. Absorption. Transferrin. Heme. Disease. Stores. Hemoglobin.

Abstract
Iron deficiency is an important nutritional problem in third world countries because it diminishes work performance. In meat-eating countries, iron excess may be more important than iron deficiency. Heme iron is more efficiently absorbed from the diet than inorganic iron, and iron excess can produce cellular oxidation in association with superoxide dismutase. Metal ion catalysis is linked to aging, coronary artery disease, stroke, carcinogenesis, neurodegenerative disorders, and inflammatory disorders. Prudence is advised in the excessive consumption of meat and iron supplementation of the diet until this process is more thoroughly investigated. [References: 63]

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NP020-0011

Authors
Willis RB. Montgomery ME.

Title
MEASUREMENT OF AMORPHOUS FERRIC PHOSPHATE AS AN ASSESSMENT OF IRON BIOAVAILABILITY

Source
Analytical Chemistry. 66(11):1832-1836, 1994 Jun 1.

KeyWords Plus
Availability.

Abstract
A method for measuring amorphous ferric phosphate in complex salt mixtures and animal diets is described. The procedure uses citrate solutions for extraction of salt mixtures and tartrate solution for extraction of prepared diets. Tron in the solution is then determined colorimetrically. Crystalline ferric phosphate, which has no iron bioavailability, is not extracted by either solution. Thus, the procedure can determine if the amorphous form, which has a high iron bioavailability, is present. The procedure was tested on gypsy moth artificial diet and Wesson salt mixture, which is a salt supplement of the diet. [References: 31]

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NH560-0021

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Palmer C. Roberts RL. Bero C.

Title

DEFEROXAMINE POSTTREATMENT REDUCES ISCHEMIC BRAIN INJURY IN NEONATAL RATS

Source
Stroke. 25(5):1039-1045, 1994 May.

Author Keywords
Cerebral ischemia. Deferoxamine. Neuroprotection. Free radicals. Pharmacokinetics.

KeyWords Plus
Reperfusion-induced edema. Lipid-peroxidation. Nitric-oxide. Cerebral-ischemia. Oxygen radicals. Gerbil brains. Superoxide. Desferrioxamine. Damage. Peroxynitrite.

Abstract
Background and Purpose Iron catalyzes the formation of damaging reactive species during cerebral reperfusion. Brain iron concentration is highest at birth, so the brain of the asphyxiated newborn may be at increased risk of iron-dependent injury. We investigated whether the ferric iron chelator deferoxamine could reduce hypoxic-ischemic brain injury in neonatal rats. Because deferoxamine has concentration-dependent activities other than iron chelation, we measured brain deferoxamine levels and calculated deferoxamine pharmacokinetic parameters.

Methods We produced hypoxic-ischemic injury to the right cerebral hemisphere of 7-day-old rats by right common carotid artery ligation followed by 2.25 hours of hypoxia in 8% oxygen. At 5 minutes of recovery from hypoxia the rats received 100 mg/kg deferoxamine mesylate or saline subcutaneously. Rats (saline, n=33; deferoxamine, n=38) were killed at 42 hours of recovery to assess early acute edema by measurement of hemispheric water content. Other rats (saline, n=31; deferoxamine, n=32) were killed at 30 days of age for morphometric determination of right hemisphere atrophy. In still other rats, we measured deferoxamine levels in blood and brain after hypoxia-ischemia.

Results Deferoxamine significantly reduced right hemisphere injury as measured by early water content (P<.01) and later atrophy (P=.019). Deferoxamine brain levels peaked between 100 and 200 mu mol/L. at 40 to 60 minutes after injection and exceeded serum levels by +/-70%.

Conclusions Deferoxamine administered after induction of cerebral hypoxia-ischemia reduces injury in 7-day-old rats. Deferoxamine concentrates in the brain at levels between 100 and 200 mu mol/L. At the concentrations achieved, deferoxamine might protect the brain through mechanisms unrelated to its ability to chelate iron. [References: 52]

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MW371-0006

Authors
Ebihara K. Okano J. Miyata T.

Title
COMPARISON OF FERROUS AND FERRIC IRON BIOAVAILABILITY FOLLOWING RAT CECAL INFUSION

Source
Nutrition Research. 14(2):221-228, 1994 Feb.

Author Keywords
Iron bioavailability. Ferrous iron. Ferric iron. Intracecal infusion. Rat.

KeyWords Plus
Chain fatty-acids. Absorption. Cecum.

Abstract
The comparison of ferrous and ferric iron bioavailability following cecal infusion was studied in ileally fistulated rats. Rats were divided into four groups of 10 rats after recovery from surgery. Group 1 (control) was given an iron-adequate diet (45 mg Fe/kg diet) and infused with NaCl solution (150 mM). Group 2 was given an iron-deficient diet (8 mg Fe/kg diet) and infused with NaCl solution. Group 3 and 4 were given an iron-deficient diet and infused with ferrous sulfate [Fe(II)] suspension or ferric sulfate [Fe(III)] solution (800 ppm as Fe, pH 6.8) to provide the same amount of iron as that consumed one day before by the control group. NaCl, Fe(II) and Fe(III) were infused through the fistula at two times (1000h and 1800h) for 28 days. The volume of NaCl infused was about equal to the volume of Fe(II) and Fe(III) suspension or solution infused. Compared with the control group, body mass gain and food intake for Group 3 and 4 did not decrease. However, the hematological indices and total iron contents in the liver and spleen for Group 3 and 4 did not decrease. However, the hematological indices and total iron contents in the liver and spleen for Group 3 and 4 showed 20 to 30% and 30 to 40% lower, respectively, compared with those of the control group. There was no significant difference between Group 3 and 4 on iron bioavailability. These results suggest that the lower part of the digestive tract plays an important role in iron absorption. [References: 10]

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Accession Number
MJ601-0001

Authors

Gershoff SN.
Title
VITAMIN-C (ASCORBIC ACID) - NEW ROLES, NEW REQUIREMENTS [Review]
Source
Nutrition Reviews. 51(11):313-326, 1993 Nov.
KeyWords Plus
Ischemic-heart-disease. Bladder carcinogenesis promotion. Sodium l-ascorbate. Epidemiologic evidence. Guinea-pigs. Cardiovascular-disease. Neutrophil chemotaxis. Nitrosamine formation. Antioxidant vitamins. Cataract prevention.
Abstract
There is an enormous amount of literature on vitamin C intake and health in animals, cell cultures, and humans. Beyond its function in collagen formation, ascorbic acid is known to increase absorption of inorganic iron, to have essential roles in the metabolism of folic acid and of some amino acids and hormones, and to act as an antioxidant. In recent years, research has increasingly focused on this latter function, stimulated by suggestions that "oxidative stress" may be a causal factor in the etiology of such diverse and important disorders of aging as cancer, cardiovascular disease, and cataract formations. The present evidence is strong enough to have convinced nutritionists that daily vitamin C intake should be many times higher than the amount needed to protect against scurvy, and this is reflected in the present Recommended Dietary Allowances. Suggestions that the recommended levels should be higher still are largely based on extrapolations from results of animal and tissue culture studies. How much ascorbic acid is necessary to achieve in humans the effects seen in animal studies is not clear. In general, the limited human studies have not been persuasive. The data are incomplete, and many of the studies have serious flaws. There are no toxicity studies of the type done for new compounds being considered for approval as therapy for major disease conditions. Intervention studies will be difficult, but are essential, and methods for tissue saturation measurement must be defined before new recommendations for the public are designed. [References: 113]
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Date: 28-Nov-95
Name: iron
Database: Current Contents/Life Sciences <1993 Annual>

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Accession Number
LB606-0024
Authors
Regan RF. Panter SS.
Title
NEUROTOXICITY OF HEMOGLOBIN IN CORTICAL CELL CULTURE
Source
Neuroscience Letters. 153(2):219-222, 1993 Apr 30.
Author Keywords
Hemoglobin. Neuronal culture. Iron. Antioxidant. Chelator. Toxicity. Deferoxamine. Trolox.
KeyWords Plus
Lipid-peroxidation. Iron. Inhibition. Injury.
Abstract
Hemoglobin (Hb) has been demonstrated to be neurotoxic when injected into the cerebral cortex in vivo. However, associated systemic factors such as ischemia and epileptogenesis have limited investigations of Hb toxicity in the intact central nervous system (CNS). In this study, the neurotoxicity of human Hb was assessed in mixed neuronal and glial neocortical cell cultures derived from fetal mice. Exposure of cultures to Hb for 24-28 h produced widespread and concentration-dependent neuronal death (EC50 1-2.5 muM), without injuring glia. Brief exposures (1-2 h) were not toxic. Neuronal death was completely blocked by the 21-aminosteroid U74500A, the antioxidant Trolox, and the ferric iron chelator deferoxamine. The results of these experiments suggest that, in this system, Hb is a potent neurotoxin, and that Hb neurotoxicity may contribute to secondary injury processes after trauma and intracranial hemorrhage. [References: 26]
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Accession Number
KM797-0004
Authors
Figueiredo MS. Baffa O. Neto JB. Zago MA.
Title
LIVER INJURY AND GENERATION OF HYDROXYL FREE RADICALS IN EXPERIMENTAL SECONDARY HEMOCHROMATOSIS
Source

Research in Experimental Medicine. 193(1):27-37, 1993 Feb.

Author Keywords

Iron overload. Hemochromatosis. Liver. Free radicals. Hydroxyl free radical.

KeyWords Plus

Hepatic iron overload. Lipid-peroxidation. Hemosiderin. Pathology. Rats.

Abstract

An experimental model of secondary hemochromatosis is described. Saccharated iron was administered i.v. to rats for 7 months in total doses in the range 1.0-1.7 g per kg body weight. After the completion of iron loading, the biochemical measurements revealed elevation of alanine aminotransferase (ALT), slight reduction of plasma glucose concentration, and significant reduction of both plasma and liver ascorbic-acid levels. The mean liver iron concentration was 50 times higher in iron-loaded animals than in controls. High concentrations of inorganic iron were also observed in spleen, pancreas, and heart. Histologic analysis revealed marked hepatic fibrosis in most animals in the experimental group. These results demonstrate this animal model presents some pathologic findings observed in human transfusional hemochromatosis. Additionally, hydroxyl free radicals were detected by electron paramagnetic resonance (EPR) spectroscopy in the iron-overloaded liver tissue processed at pH 5.0. No free radicals were detected at pH 7.4. These results suggest the possible participation of hydroxyl free radicals in the cellular toxicity of iron overload. [References: 43]

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Accession Number

KM222-0044

Authors

Zager RA. Schimpf BA. Bredl CR. Gmur DJ.

Title

INORGANIC IRON EFFECTS ON INVITRO HYPOXIC PROXIMAL RENAL TUBULAR CELL INJURY

Source

Journal of Clinical Investigation. 91(2):702-708, 1993 Feb.

Author Keywords

Adenosine triphosphate. Antimycin-a. Hypoxia. Iron. Malondialdehyde.

KeyWords Plus

Oxygen free-radicals. Failure. Mechanisms. Disease. Rat. Peroxidation. Assessments. Mannitol.

Abstract

Iron-dependent free radical reactions and renal ischemia are believed to be critical mediators of myohemoglobinuric acute renal failure. Thus, this study assessed whether catalytic iron exacerbates O2 deprivation-induced proximal tubular injury, thereby providing an insight into this form of renal failure. Isolated rat proximal tubular segments (PTS) were subjected to either hypoxia/reoxygenation (H/R: 27:15 min), "chemical anoxia" (antimycin A; 7.5 muM x 45 min), or continuous oxygenated incubation+/-ferrous (Fe2+) or ferric (Fe3+) iron addition. Cell injury (%lactic dehydrogenase [LDH] release), lipid peroxidation (malondialdehyde, [MDA]), and ATP depletion were assessed. Under oxygenated conditions, Fe2+ and Fe3+ each raised MDA (approximately 7-10X) and decreased ATP (approximately 25%). Fe2+, but not Fe3+, caused LDH release (31+/-2%). During hypoxia, Fe2+ and Fe3+ worsened ATP depletion; however, each decreased LDH release (approximately 31 to approximately 22%; $P < 0.01$). Fe2+-mediated protection was negated during reoxygenation because Fe3+ exerted its intrinsic cytotoxic effect (LDH release: Fe2+ alone, 31+/-2%; H/R 36+/-2%; H/R + Fe2+ 41+/-2%). However, Fe3+-mediated protection persisted throughout reoxygenation because it induced no direct cytotoxicity (H/R, 39+/-2%; H/R +Fe3+, 25+/-2%; $P < 0.002$). Fe3+ also decreased antimycin toxicity (41+/-4 vs. 25+/-3%; $P < 0.001$) despite inducing marked lipid peroxidation and without affecting ATP. These results indicate that catalytic iron can mitigate, rather than exacerbate, O2 deprivation/reoxygenation PTS injury. [References: 34]

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Name: iron
Database: Current Contents/Life Sciences <1993 Annual>

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004	(ferric adj phosphate).ab,ti,kw,kp.	0
005	(iron adj phosphate).ab,ti,kw,kp.	3

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Accession Number
LG146-0038
Authors
Desilva D. Guo JH. Aust SD.
Title
RELATIONSHIP BETWEEN IRON AND PHOSPHATE IN MAMMALIAN FERRITINS
Source
Archives of Biochemistry & Biophysics. 303(2):451-455, 1993 Jun.
KeyWords Plus
Horse spleen. Cores. Apoferritin. Superoxide. Storage. Release.
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TISSUE CHANGES IN RATS' LUNGS CAUSED BY HYDROXIDES, OXIDES AND PHOSPHATES OF ALUMINIUM AND IRON

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(Plates LXXXVI-LXXXIX)

It has been shown (King *et al.*, 1955 and 1958) that aluminium and certain relatively insoluble aluminium compounds, the hydroxide γ-AlOOH and the phosphate berlinite ($AlPO_4$ with a crystal structure similar to quartz), behave as fibrogenic materials when injected into the lungs of rats.

A sample of γ-AlOOH (particle-size a few hundred A.U.) given in a single dose of 100 mg. produced fibrosis of grade 3 (lesions somewhat cellular but made up mostly of collagen) after 4 months and of grade 5 (confluent lesions) after one year. Aluminium powder at 100 mg./rat had given fibrosis of grade 3 after 4 months and of grade 4 after 7 months and up to one year. The fibrosis induced by aluminium phosphate of average particle-size 3 μ, injected in amounts of 50 mg. per rat, had not exceeded grade 3 after 14 months. There had been strong evidence, from aurine-stained sections, that free alumina was lost from the lungs in the course of time and aluminium-protein complexes were suggested as having something to do with causing the fibrosis. These observations had come as a surprise, because previously silica was believed to be unique in having specific fibrogenic properties. It was therefore considered advisable to extend the range of observations.

In parallel studies in experimental silicosis it had been found that size and crystal structure of silica had an effect on fibrogenic activity in rats' lungs. In particular, tridymite had acted more strongly than quartz. As aluminium phosphate exists in the same modifications as silica it was decided to test this compound in its quartz-like and tridymite-like modifications, to test a number of aluminium oxides or hydroxides and to extend the study also to the phosphate and hydroxides of iron.

Materials

Table I lists the samples used, together with relevant details. Figs. 1 and 2 show X-ray diffraction patterns and electron micrographs.

The aluminium hydroxide (γ-AlOOH, Gardner's HX1010) was a poorly crystalline, commercially prepared sample, identical with that used to produce fibrosis grade 5 in our previous experiment (King *et al.*, 1955). To contrast with it, a well-crystallised sample of γ-AlOOH of average size 2 μ was used

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(trade name Cera hydrate). γ-Al_2O_3 was prepared by heating the aluminium hydroxide (HX1010) at 850°C. for 5 hr; there was little evidence of sintering in the sample according to the electron micrographs (fig. 2). α-Al_2O_3 (corundum) was prepared by heating the aluminium hydroxide (HX1010) at 1200° C. for 5 hr; the sample appeared coarser than the original HX1010 and was re-ground in a mortar of sintered alumina.

The crystalline iron hydroxides goethite (α-FeOOH) and lepidocrocite (γ-FeOOH) were synthetic materials obtained from paint manufacturers. Their degree of crystallinity was intermediate between that of the aluminium hydroxide HX1010 and that of Cera hydrate. They consisted of aggregates of lath-like particles, well below 2 μ in size.

TABLE 1

Characteristics of aluminium and iron hydroxides, oxides and phosphates used for injections

Material	X-ray.	Degree of crystallinity	Mean particle diameter (μ) *	Dosage (mg./kg.)	No. of rats
Aluminium hydroxides and oxides					
γ-AlOOH, HX1010	1048	poor	c. 0·02	70†	12
				14	12
γ-AlOOH, Cera hydrate	823	good	3	60†	12
γ-Al_2O_3, HX1010 at 850° C.	1342	poor	c. 0·02	50	12
α-Al_2O_3, HX1010 at 1200° C.	1330	good	< 1	50	12
Iron hydroxides					
α-FeOOH	1418	medium	< 1	100	15
γ-FeOOH	1370	medium	< 1	100	15
Aluminium phosphates					
$AlPO_4$, quartz structure	2518	good	2	50	15
$AlPO_4$, tridymite structure	2507	good	2	50	15
Iron phosphate					
$FePO_4$, quartz structure	2867	good	2	100	15

* assessed from electron photomicrographs.
† equivalent to 50 mg. Al_2O_3.

Aluminium phosphate of quartz structure was prepared from alumina and phosphoric acid. Pure hydrated alumina was ignited at 850° C. in a platinum dish. After cooling, an equivalent amount of phosphoric acid was added, the mixture was slowly heated and stirred with a platinum rod, and finally heated for 4 hr in an electric muffle furnace at 600° C. The material was ground in a mortar of sintered alumina, suspended in water, and a fraction below 2 μ in particle diameter prepared by repeated sedimentation and centrifuging. The sample gave an X-ray diffraction-pattern very similar to that of quartz (see fig. 1) but it may have been slightly contaminated by the cristobalite modification.

Aluminium phosphate of tridymite structure was prepared by heating phosphoric acid with a 10 per cent. excess of aluminium chloride ($AlCl_3.6H_2O$). The mixture was finally heated at 600° C. for 4 hr. It was powdered and a fine fraction separated by sedimentation. X-ray diffraction showed mainly a structure resembling tridymite (fig. 1) but there was a little of the quartz modification present. Table II gives chemical analyses of these samples.

Iron phosphate, which exists only in the quartz structure, was prepared by heating iron chloride with excess phosphoric acid, and finally keeping the temperature at 650° C. for 4 hr. The sample was ground and sedimented, and showed an X-ray pattern resembling that of quartz (fig. 1).

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ALUMINIUM AND IRON EFFECTS IN RAT LUNG

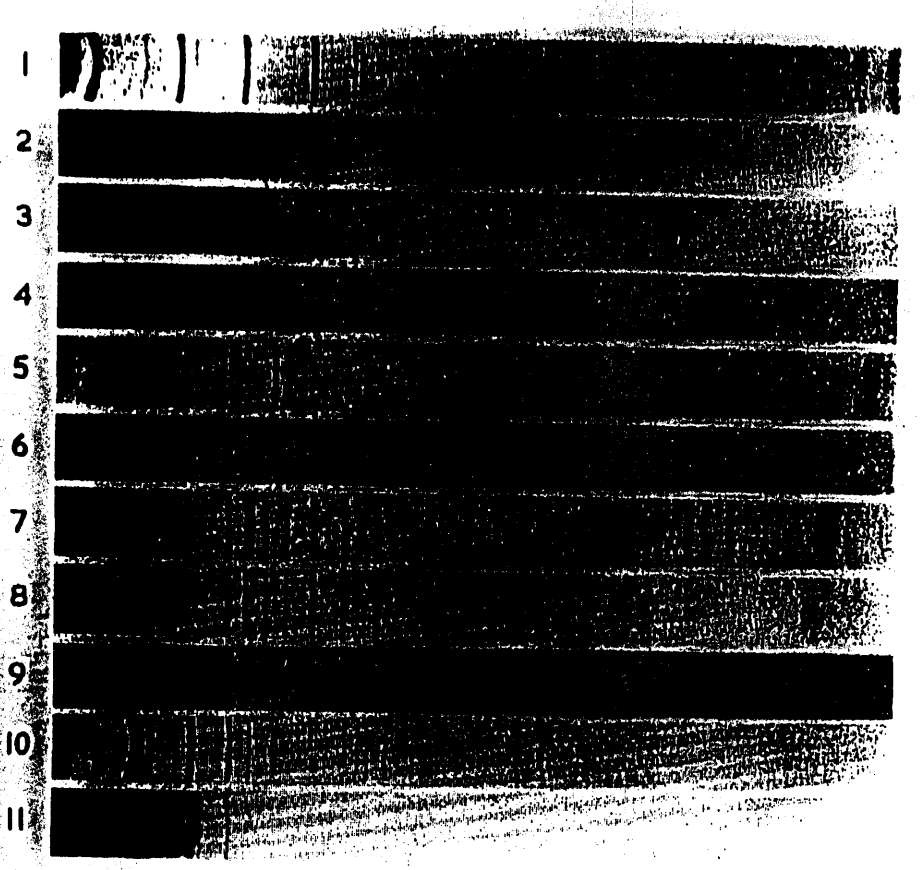

FIG. 1.—X-ray diffraction patterns of minerals used in animal experiments (see table I). 1, γ-AlOOH, Cera hydrate; 2, γ-AlOOH, HX1010; 3, γ-FeOOH; 4, γ-Al_2O_3; 5, α-Al_2O_3; 6, α-FeOOH; 7, quartz; 8, $AlPO_4$, quartz structure; 9, $FePO_4$, quartz structure; 10, tridymite; 11, $AlPO_4$, tridymite structure.

Alumina solubilities

Solubilities of the aluminium compounds were determined at room temperature in sodium acetate buffer of *p*H 4·1 at a concentration of 6 g. sample per 100 ml. buffer. The samples were shaken continuously in plastic tubes for 3, 6, 22, 38, and 73 days. At the end of each period the tubes were centrifuged, the clear supernatant siphoned off, and fresh buffer added. Two samples of each

TABLE II

Chemical analyses of aluminium phosphates

Constituent	Percentage content of constituent in $AlPO_4$		
	according to theory	by chemical analysis of	
		quartz modification	tridymite modification
Al_2O_3	41·8	41·2	42·7
P_2O_5	58·2	62·3	56·8

material were used, and duplicate colorimetric determinations of dissolved aluminium made on each sample. The *p*H of the extracts varied somewhat but did not fall outside the range 4·1-4·7. The dissolved aluminium was complexed with aluminon reagent at *p*H 4·1, and the colour compared with a set of standards prepared from analar $KAl(SO_4)_2 12H_2O$. The results of the solubility determinations are shown in table III.

TABLE III

Cumulative alumina solubilities of different aluminium compounds after repeated extractions with phosphate buffer pH 4·1 at room temperature

Period of extraction (days)	Percentage of total Al_2O_3 originally present in sample dissolved from					
	Gibbsite	$AlPO_4$ modifications		HX1010		
		X2518 (quartz)	X2607 (tridymite)	heated to 1200° C.	original	heated to 920° C.
3	0·0035	0·34	0·57	1·42	2·1	5·09
6	0·014	0·54	0·91	1·95	3·7	7·95
22	0·05	0·84	1·4	2·57	7·6	11·22
38	0·12	1·0	1·7	3·14	12·2	15·4
73	0·18	1·2	1·9	3·5	15·9	19·1

EXPERIMENTAL

Samples of the different powders were weighed and transferred to all-glass tissue-grinders containing normal saline in amounts sufficient to give the final concentration of each powder indicated in table I, the dose administered being contained in 1 ml. of the final suspension. The mixtures were well ground until fine suspensions were obtained. They were then transferred to screw-capped glass bottles and sterilised by autoclaving. Each dust suspension was prepared in this way immediately before injection, before which it was kept continuously shaken in a mechanical shaker.

The dust suspensions were injected intratracheally by the method of Kettle and Hilton as modified by King *et al.* (1958), the dust being introduced into the lung from a syringe through a long blunt needle inserted via the mouth into the trachea. For each animal injected, the dose indicated in table I was given in 1 ml. of saline, an extra 0·1 ml. of suspension being injected (total 1·1 ml.) in order to allow for the small amount lost on the walls of the syringe and needle. There was no regurgitation of the administered suspensions. No post-operative deaths occurred.

The necropsies, removal of the lungs, fixation, embedding, sectioning and staining were according to the descriptions in our previous communications (King *et al.*, 1955, 1958).

The histological grading of fibrosis was according to Belt and King (1945): grade 1, loose reticulin and no collagen; grade 2, compact reticulin with or without a little collagen; grade 3, somewhat cellular but made up mostly of collagen; grade 4, wholly composed of collagen fibres and virtually acellular; grade 5, acellular, collagenous, confluent.

The animals used were rats of the black-and-white hooded variety of the Medical Research Council strain. Their average weight was 200 g. The number of animals in each group was either 12 or 15. The experiments lasted for one year, and animals were killed at monthly intervals.

Results

Pathological findings

Some congestion and discrete collections of dust were found in the lungs of rats that died or were killed soon after receiving 70 mg. γ-aluminium hydroxide (HX1010). Firm, confluent, fibrotic patches were present in the lungs of animals killed at 150 days and after.

Rats receiving 14 mg. γ-aluminium hydroxide (HX1010), i.e. one-fifth of the previous dose, showed the expected smaller number of smaller focal accumulations of dust, which did not exceed 2-5 mm. in diameter. The collections were most numerous dorsally. The lesions were firm, discrete and only rarely confluent.

With Cera hydrate γ-aluminium hydroxide (60 mg.) small white lesions were found scattered over the lung surface of the rat killed at 30 days. They were larger at 150 days, but the dust collections remained discrete until the end of the experiment.

With γ-alumina (HX1010 heated to 950° C., 50 mg.) numerous small white patches (2-4 mm.), sometimes confluent, were found in the dorsal aspects of both lungs. As early as 60 days there were large white patches, and at 180 days there were firm fibrotic areas. The white, firm, consolidated areas appeared to increase in size as the experiment progressed.

With α-alumina (HX1010 heated to 1200° C., 50 mg.) there was a marked contrast with the previous sample. Only a few small (1-2 mm.) white areas were seen in the animal killed at 30 days. Although the areas were larger in animals killed later, no massive fibrosis was associated with the dust collections at any period.

The two iron hydroxides (α-FeOOH and γ-FeOOH) produced results indistinguishable from each other. Subpleural collections of the yellow-brown dusts were seen at 30 days. They were larger and

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ALUMINIUM AND IRON EFFECTS IN RAT LUNG

FIG. 2.—Electron micrographs of minerals used in animal experiments (see table I). Numbers as in fig. 1.

more numerous at 120 days, and usually dorsal. At the end of the experiment (one year) collections of dust were seen about the hilum of the lung.

The aluminium phosphates ($AlPO_4$, quartz and tridymite structures) produced similar gross appearances in the lungs. At 90 days small white lesions, concentrated dorsally, were dotted over the lungs. By 180 days, greyish-white patches of fibrous tissue were visible, and the patchy mottled appearance persisted until the end of the experiment. At one year the patches were firm and on the whole discrete. With these two dusts, the tracheobronchial lymph glands were greyish-white, firm and considerably enlarged.

The iron phosphate ($FePO_4$, quartz structure) produced little change other than scattered brown patches of dust dorsally in both lungs; these patches persisted until the end of the experiment.

Histology

With 70 mg. of γ-AlOOH (HX1010) there is a rapid development of fibrous nodules. By 30 days there are compact nodules of reticulin. During the remaining 11 months there is a steady maturation of fibrous tissue; grade 3 fibrosis, collagenous and still somewhat cellular, was not exceeded. The lesions were not as numerous and there did not appear to be as much dust in the lungs of the rat killed at one year as in those killed earlier (fig. 3).

With 14 mg. of γ-AlOOH (HX1010) there are numerous, small, irregularly-shaped aggregates of dust. At 30 days silver impregnation shows the presence of fine reticulin-fibrils within the nodule. Later the reticulin forms a loose meshwork within the lesion and the fibrils become thicker, with some collagen. Late in the experiment the nodules are composed largely of collagen, and grade 3 fibrosis is reached. The lesions are finally as advanced with the 14 mg. as with the 70 mg. dose, but they are much less numerous.

Cera hydrate, the well-crystallised variety of γ-AlOOH, shows only a slight macrophage response at 30 days. Dust lies loosely in the alveoli, some particles engulfed in phagocytes. At first there is no focal accumulation of dust cells, but by 150 and 180 days there are small collections, associated with a mild fibrous reaction (loose reticulin, grade 1 fibrosis), which show no further progress up to one year after injection (fig. 4).

The pathological action of γ-Al_2O_3 (HX1010 heated to 850° C.) is much greater. At 30 days large discoloured discrete collections of dust are found, containing compact fibrils of reticulin and some collagen (grade 2 fibrosis, maximum). At 90 and 150 days the lesions are less cellular and more collagenous (grade 3 fibrosis). Almost the whole of one lung in the animal killed at 210 days is a dense mass of fibrous tissue (grade 4 fibrosis). Later, fibrous nodules coalesce, and the resulting mass of confluent collagenous tissue largely fills the

lung (grade 5 fibrosis, fig. 5). In the last animal of this group, as in that of the 70 mg. aluminium hydroxide group, there appears to be less dust than had been seen earlier in the experiment.

By contrast with γ-Al_2O_3, α-Al_2O_3 (HX1010 heated to 1200° C.) appeared to be less pathogenic, the most advanced lesions consisting of compact nodules of reticulin (grade 2 fibrosis). There are numerous small compact aggregates of dust cells at 60 and 90 days, and at all stages most of the dust is concentrated in the focal accumulations (fig. 6).

The results obtained with α-FeOOH and γ-FeOOH in the various stages of the experiment were so similar that they are described together. At 30 days the particles are engulfed in macrophages, and focal accumulations of dust cells are found. The smaller collections consist of macrophages, laden with the brown particles, lying free in the alveoli. The larger collections are compact accumulations of many macrophages. The cellular nature of the foci is difficult to discern, because the brown dust in the macrophages obscures the nuclei. In some cases there is swelling of the alveolar septa. At 90 and 150 days the foci are more compact, but there is little increase of reticulin; at 300 and 365 days most of the dust is in the focal accumulations. A slight reticulinosis (grade 1 fibrosis, minimum) is the only evidence of reaction to the dust (fig. 7).

$AlPO_4$, quartz structure, and $AlPO_4$, tridymite structure, gave very similar results. Both were fibrogenic, though perhaps less so than γ-Al_2O_3. By 30 days both materials have provoked an active dust-cell reaction, and most particles are in macrophages. Cellular nodules are formed by the focal accumulation of macrophages, the larger ones obliterating the structure of the lung. Silver impregnation shows that the nodules were enmeshed and interwoven with reticulin fibrils with a little collagen (grade 2 fibrosis). The $AlPO_4$ particles are doubly refractile, and are confined to and concentrated within the nodules. The fibrous response to the tridymite-like $AlPO_4$ is a little less advanced at this stage than the response to the quartz-like $AlPO_4$. At 60 and 90 days the dust collections are compact, and the surrounding tissue almost free from dust in both groups. The lesions are larger and more fibrous, and collagen formation was prominent. By 120 and 150 days the lesions are noticeably less cellular and the coarse strands of collagen more numerous. Coalescence of nodules has occurred in some areas at 180 days. The lesions are mainly collagenous, but still contain some reticulin (grade 3 fibrosis, maximum). Fully collagenous and completely acellular nodules of grade 4 fibrosis are seen at 300 days. At 330 and 363 days there are areas in the lung sections consisting of compact, confluent masses of acellular collagenous connective tissue (grade 5 fibrosis). This is a somewhat more prominent feature with the quartz-like than with the tridymite-like $AlPO_4$. There appears to be less doubly-refractive dust in the lungs at the end of the experiment than at the beginning (figs. 8 and 9).

$FePO_4$, quartz structure, like the iron hydroxides, produced very little fibrous response. There is a macrophage reaction at 30 days and most of the particles are engulfed by cells, but there is little tendency for the dust to be aggregated into foci. Much of the dust lies loosely in the alveoli, and at 90 days there are still only a few focal accumulations. The appearance of the lungs is very similar at 180 days and later. Very little reticulin is formed, and until the end of the experiment most of the injected material remains dispersed in loosely associated dust cells in all areas of the lung (fig. 10). Neither

TABLE IV

Fibrosis produced in rats' lungs by aluminium and iron hydroxides and phosphates

Days	Aluminium hydroxides			Aluminium oxides		Iron hydroxides		Aluminium phosphates		Iron phosphate
	γ-AlOOH (HX1010) (70 mg.)*	γ-AlOOH (HX1010) (14 mg.)	γ-AlOOH (Cera hydrate) (56 mg.)*	γ-Al_2O_3 (850°) (50 mg.)	α-Al_2O_3 (1200°) (50 mg.)	α-FeOOH (100 mg.)	γ-FeOOH (100 mg.)	$AlPO_4$ (quartz structure) (50 mg.)	$AlPO_4$ (tridymite structure) (50 mg.)	$FePO_4$ (quartz structure) (100 mg.)
30	(4) D (1) K2+	(2) K1	(1) K0	(1) D (1) K2+	(1) K0	(3) D0 (1) K0	(1) D0 (1) K0	(1) K2	(1) K1 (1) D	(1) D0 (1) K0
60	(1) K2	(1) K1	(1) K0	(1) D	(1) K1	(1) K0	(1) K0	(1) K2+	(1) K2−	(1) K0
90	(1) K2	(1) K1	(2) K0	(1) K2	(1) K1	(1) K0	(1) K0	(1) K2	(1) K2+	(1) K0
120	(1) K2	(1) K1+	(1) K0	(1) K2	(1) K1	(1) K0	(1) K0	(1) K2	(1) K2	(1) K0
150	(1) K2	(1) K1	(1) K0	(1) K7	(1) K1	(1) K0	(1) K0	(1) K2+	(1) K2+	(1) K0
180	...	(1) K2	(1) K0	(1) K2	(1) K1	(1) K0	(1) K0	(2) K2	(1) K2+	(1) K0
210	...	(1) K1	(1) K0	(1) K4	(1) K1	(1) K0	(1) K0	(1) K2	(1) K2+	(1) K0
240	(2) D	(1) K1	...	...	(1) K1	(1) K0	(1) K0	(1) K2+	(1) K2	(1) K0
270	...	...	(1) K0	...	(1) K1	(1) K0	(1) K0	(1) K4	(1) K2+	(2) K0
300	...	(1) K1+	(1) K0	(1) K5	(1) K1	(1) K0	(2) K0	(2) K4	(2) K5	(2) K0
330	...	(1) K2−	...	(1) K4	(1) K1	(1) K1−	(1) K0	(2) K5	(2) K4	(1) K0
365	(1) K2	(1) K3	(2) K1	(1) K4	(1) K1	(1) K1−	(2) K1−			

* 70 mg. HX1010 and 56 mg. Cera hydrate = 50 mg. Al_2O_3.

Numbers in brackets = numbers killed (K) or dead (D), and the following numbers = grade of fibrosis, e.g., (2) K1 = 2 killed animals with grade 1 fibrosis in the lungs.
\+ = Maximum within the grade of fibrosis. − = Minimum within the grade of fibrosis.

iron hydroxide nor iron phosphate appears to diminish noticeably in the lungs with progress of time, but the amount of dust in the peribronchial and perivascular lymphatics visibly increases with time.

The assessment of the fibrosis, and the times of death or killing for all nine samples are set out in table IV.

COMMENT

The lesions produced by aluminium compounds after injection into rats' lungs showed the same type of development as do silicotic lesions; the grading given in table IV and in the previous paper is therefore valid and was used.

The grade of fibrosis reached depended on dosage and type of material. Fibrosis due to γ-Al_2O_3 was found to be the most severe in the present series. It reached grade 3 after three months and grades 4 or 5 after seven months. At the same level of 50 mg. Al_2O_3 per rat,

fibrosis due to Gardner's HX1010 reached grade 3 after four months and did not progress further. At one-fifth of this dosage it only reached grade 3 fibrosis after one year. Previously (King *et al.*, 1955) Gardner's HX1010 at 100 mg. per rat had also given grade 3 after four months; this had ultimately reached grade 5 in one animal after one year. α-Al_2O_3 was almost completely inert (grade 1 fibrosis) and the coarsely crystalline γ-AlOOH (Cora hydrate) was nearly inert up

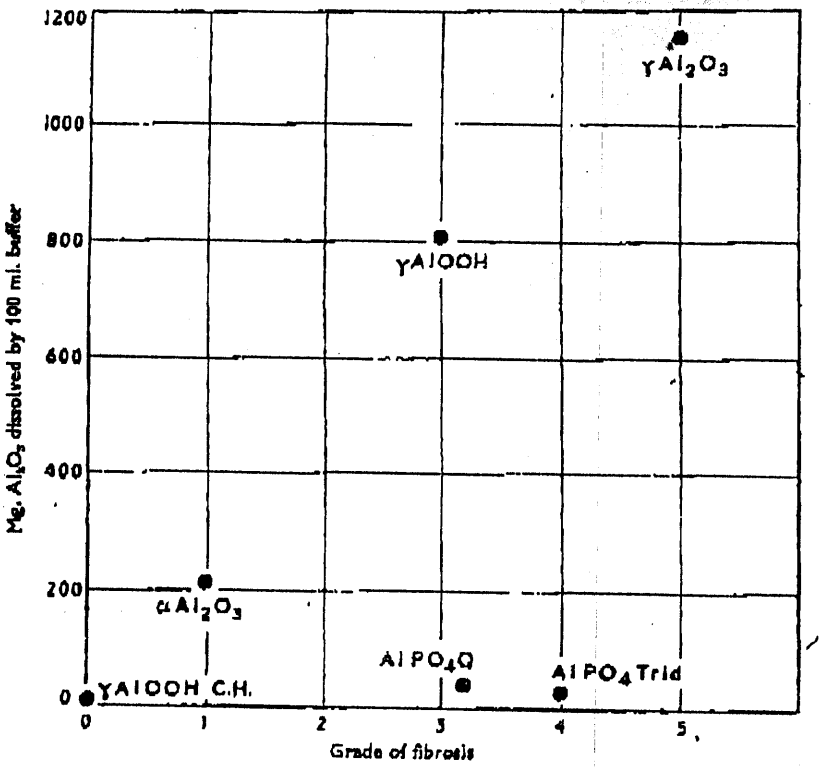

FIG. 11.—Relation between cumulative alumina solubility in 73 days and degree of fibrosis produced.

to one year. For these four samples there appeared to be a direct relation between alumina solubility and fibrogenic activity. This is shown in fig. 11 where the cumulative solubility after 73 days is plotted against the grade of fibrosis reached after 300 days. Fig. 11 also shows that the two forms of $AlPO_4$ did not follow this trend.

In animal experiments with silica, tridymite had been found to be more fibrogenic than quartz, and a similar effect has appeared likely with the closely similar crystal structures of the two $AlPO_4$ modifications. Both, however, produced lesions at about the same rate; these developed further than would have been expected from the alumina solubilities. At present we cannot explain this, especially

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PLATE LXXXIX

ALUMINIUM AND IRON EFFECTS IN RAT LUNG

FIG. 7.—Ferric hydroxide, 50 mg., 365 days. Compact accumulations of dust causing minimal reticulinosis. Hæmatoxylin and eosin. ×45.

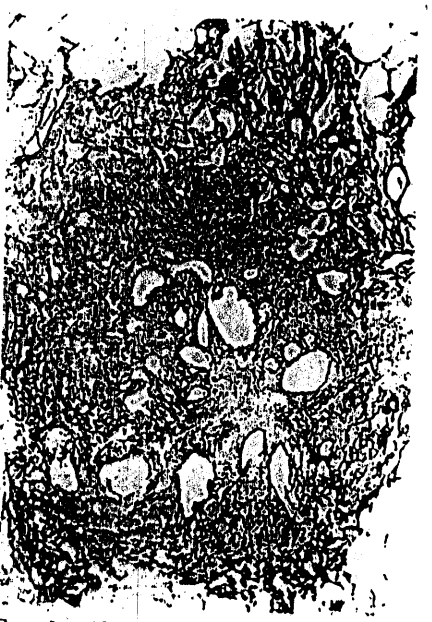

FIG. 8.—Aluminium phosphate, quartz structure, 50 mg., 330 days. Confluent lesions composed entirely of collagen, grade 5 fibrosis. Silver impregnation. ×50.

FIG. 9.—Aluminium phosphate, tridymite structure, 50 mg., 330 days. Confluent lesions composed entirely of collagen, grade 5 fibrosis. Silver impregnation. ×50.

FIG. 10.—Ferric phosphate, quartz structure, 365 days. Remarkably loose distribution of dust in the alveoli, no fibrosis. H. and E. ×45.

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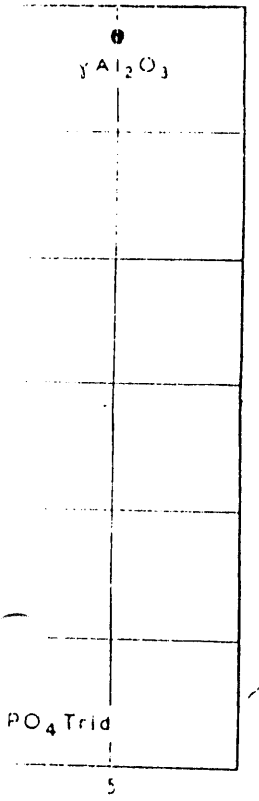

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ALUMINIUM AND IRON EFFECTS IN RAT LUNG

FIG. 3.—Rat lung. γ-aluminium hydroxide (HX1010), 70 mg., 365 days. Lesion composed of gross collagen fibres, grade 3 fibrosis. Silver impregnation. ×45.

FIG. 4.—Cera hydrate (highly crystalline γ-aluminium hydroxide), 60 mg., 365 days. Lesion with loose formation of reticulin fibres, grade 1 fibrosis. Silver impregnation. ×95.

FIG. 5. γ-alumina (aluminium hydroxide HX1010 heated to 850° C.), 50 mg., 365 days. Acellular lesions composed of dense collagen fibres, grade 5 fibrosis. Silver impregnation. ×45.

FIG. 6.—α-alumina (aluminium hydroxide HX1010 heated to 1200° C.), 50 mg., 320 days. Lesions composed of gross reticulin with some collagen fibres, grade 2 fibrosis. Silver impregnation. ×90.

as $AlPO_4$ with quartz structure had been found to be fairly inert by van Marwyck (1954) and Rüttner *et al.* (1956) in mice, and Pratt *et al.* (1953) in guinea-pigs.

The large range in alumina solubilities found was not necessarily due to the differences in crystal structure, but may have been mainly due to the very wide range of specific surface of the different samples. This could not be measured but only assessed roughly from the electron micrographs of the original HX1010 and the samples of γ-Al_2O_3 and α-Al_2O_3 derived from it. It is therefore not possible to give accurate figures for solubility per unit-surface or to separate the effects of crystal structure and size. But it appears significant that the histological sections showed evidence of loss of dust with the progress of time. Although the form of the lesions resembled that of silicotic lesions, their mode of formation may have been different insofar as it was caused by the products of dissolution of the aluminium compounds.

The iron compounds tested, including $FePO_4$ with quartz structure, were all equally inert and the iron dust deposits did not appear to diminish with time. This seems to be in conformity with experience in man, where iron-oxide deposits, in welders for instance, may give X-ray shadows but do not appear to cause a significant fibrosis if quartz is absent (benign siderosis).

The above experiments show certain aluminium compounds to be fibrogenic when injected into the lungs of rats. Although the lesions appeared similar to those seen in experimental silicosis, they may have been caused by a different mechanism. The fibrosis was probably due to dissolved aluminium ions reacting with proteins (see King *et al.*, 1956), and consequently the tridymite modification of $AlPO_4$ did not act more strongly than the quartz modification.

Summary

The fibrogenic activity of several hydroxides, oxides and phosphates of aluminium and iron was tested by intratracheal injection into rats, with histological observation up to one year after injection.

γ-Al_2O_3 was found to be the most fibrogenic material; this was followed by the quartz-like and tridymite-like modification of $AlPO_4$, which acted equally—in contrast to the differing fibrogenicity of the corresponding silica forms. A poorly crystallised sample of γ-AlOOH of very small size was fairly fibrogenic, but a well-crystallised sample of γ-AlOOH was inert. α-Al_2O_3 was almost inert, and all iron compounds tested were completely so.

There was a positive correlation for the aluminium oxides and hydroxides between alumina solubility and fibrogenic activity, but the alumina phosphates were more fibrogenic than their solubility suggested.

We are grateful to the Medical Research Council and the National Coal Board for grants covering part of the expenses of this investigation, to Mr J. Cartwright for the electron micrographs, and to Mr B. S. C. Hollands for skilled

technical assistance. This paper is published by permission of the Ministry of Power, and Crown Copyright is reserved for figs. 1, 2 and 11.

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CHAPTER TWENTY-NINE

The Metals

HERBERT E. STOKINGER, Ph.D.

1 ALUMINUM, Al

1.1 Source and Production (1)

Primary Al production in the United States in 1973 amounted to 4529 thousand short tons, representing an increase of 10 percent over that in 1972. Recovery of secondary Al was 1038 thousand short tons, also a 10 percent increase over that in 1972. Increased recovery of secondary Al and Al alloys (alloy zinc and steel) was projected by several Al smelting companies for the mid 1970s, including added tonnage of recycling of Al beer and soft-drink cans.

Aluminum is produced by the electrolysis of bauxite ($Al_2O_3 \cdot 2H_2O$) in a bath of molten cryolite ($3NaF \cdot AlF_3$), now mostly made synthetically from fluorspar (CaF_2) or fluosilicic acid (H_2SiF_6), which is a by-product of fluoride-containing gases evolved during the processing of phosphates in fertilizer production. Two types of electrolytic reduction cells are used and are related to the anode type. In the "prebake" pot or cell, the carbon anode is prebaked, whereas in the Soderberg process, the carbon paste is delivered directly to the cell and baked as the anode is consumed. For a detailed description of Al production, see Reference 2.

1.2 Uses and Industrial Exposures

The major use of Al is structural in the building industry; it is also used in consumer durables, in containers and packaging. In recent years increasing amounts have been used in the automotive industry to reduce weight, and the canning industry is a growing consumer. Another large user is highway products such as signs, fencing, lighting, and signal supports. Smaller quantities of Al as powder and flake are used in the paint

Appendix E
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the dose, during which time it is accumulating in the liver and kidneys. The phagocytized In is retained by the spleen and liver; next in diminishing order of retention are the kidneys, femoral bone, muscle, and lung.

Although both In compounds followed the usual excretion pattern with a fast and slow component, the fast component of In^{3+} accounted for about 50 percent of the dose in 1.9 to 2.1 days, whereas only half the amount was excreted during this time by the colloidal oxide. The slower component was similar for each, requiring 69 to 74.5 and 62 to 74 days for In^{3+} and the oxide, respectively. As could be expected, the partition between urine and feces favored the former for In^{3+} (52 vs. 35 percent) versus 9.7 and 53 percent for the colloid.

15.5.3 Mode of Action and Toxicity Prevention

Only one piece of indirect evidence for the manner by which In exerts its toxicity has been found; $InCl_3$ has been found to be a "direct calcifier," causing topical calcification at the site of injection when introduced into connective tissue, and acute, fatal, hepatic necrosis (639). Ferric dextran, prophylactically administered, not only prevented the calcifying action of In, but protected the liver against hepatic necrosis. Rats that had received a 2 mg dose $InCl_3$ intravenously on the sixth day after pretreatment on the first day with an intraperitoneal dose of ferric dextran (Imposil®) equivalent to 50 mg Fe showed no obvious sign of toxic injury at any time (11 days) and the hepatic lesions seen in the untreated rats were absent. The mechanism suggested by the authors was that Fe dextran interferes with the capacity of the liver to metabolize normally the PAS-positive organic matrix of soft tissue calcinosis under pathological calcification processes induced by In.

15.5.4 Industrial Experience

No industrial experience has been reported of exposures to In or its compounds.

15.6 Hygienic Standards of Exposure

A TLV of 0.1 mg/m³ for In, and for its compounds as In, was adopted by the American Conference of Governmental Industrial Hygienists in 1969 as a time-weighted average value for an 8-hr workday (640). A STEL (Short-Term Exposure Limit) of 0.3 mg/m³ was tentatively set by the TLV Committee in 1976. The TLV is based on the severity of effects on the lung from respiratory exposure to In salts.

Finland (1972) and Italy (1974) followed the precedent set by the TLV Committee and adopted the 0.1 mg/m³ limit.

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16 IRON, Fe

16.1 Source and Production (1, 2)

Domestic (U.S.) production of crude Fe ore, mainly taconite, a low grade ore composed chiefly of hematite ($FeO(OH)\cdot xH_2O$) and silica from the Great Lakes region, totaled 217.2 million long tons in 1974. Open pit mines produced 96 percent of the total, and nearly 98 percent of the crude ore that went to beneficiation plants. The average Fe content of crude ore mined was 33.7 percent. The Lake Superior district accounted for about 84 percent of the ore, Minnesota produced 69 percent usable ore, Michigan produced 13 percent, and the remaining 18 percent was produced by 19 other states. Taconite and natural ore pits were mined with rotary drills for blast holes, large-capacity shovels, and haulage trucks. Beneficiation of Fe ore varies from simple screening operations and washing to complex grinding, roasting, magnetic separation, or flotation. The metallurgy of Fe consists essentially of the passage of the ore, coke, and limestone through a blast furnace. As the mixture passes downward, C combines with O_2 of the ore, freeing Fe, which is tapped as a liquid from the furnace. The worldwide trend continues (10 countries) in the production of iron ore pellets for blast furnace operation, although large tonnages of direct-shipping ore containing 52 to 60 percent Fe will be available for at least several decades. Pellet plant operations in the United States, in the forefront of this trend, has a scheduled capacity for 1978 of 89 million tons. World production of Fe ore, concentrates, and agglomerates in 1974 had a total gross weight of 879,414 million long tons with a metal content of 503,677 million long tons, produced by almost every industrialized country in the world.

Steel production in the United States in 1974 amounted to 145.7 million short tons (raw steel, ingots and castings); 56 percent was produced by the basic O_2 process, 24 percent by open hearth, and 20 percent by electric furnaces. USSR production exceeded

that of the United States, by a few million tons. World production of raw steel totaled 779 million tons and of pig iron, 567 million tons.

16.2 Industrial Exposures

Mining and handling of Fe ores provide exposure to dusts of SiO_2 and Fe oxides. Carbon monoxide is a hazard in the operation of blast furnaces for the production of pig iron. The use of fluorspar (CaF_2) in steelmaking gives rise to gases containing SiF_4 and other F-containing substances, and the manufacture of alloy steels introduces hazards attendant on the use of metals such as Cr, Mn, Ni, V, W, Mo, and Cu. "Pickling" of Fe containing As and P liberates arsine (AsH_3) and phosphine (PH_3). Certain grades of ferrosilicon used in steelmaking decompose with explosive violence on contact with moist air, evolving various toxic gases such as acetylene, H_2S, SiH_4, AsH_3, and PH_3. Fatal intoxications have occurred from such accidents during transportation, particularly at sea (641) (see also Section 16.5.5).

16.3 Physical and Chemical Properties

The physical and chemical properties of Fe and a few of its many compounds are given in Table 29.16.1.

The *Handbook of Chemistry and Physics* for 1974–1975 (583) gives the physical properties of 102 inorganic compounds of Fe and 62 organometallic derivatives; the Toxic Substances List for 1976 (171) supplies acute animal toxicity data for 29 inorganic and organic derivatives.

Fe is the fourth most abundant element on the face of the earth (5 percent), existing as hematite, Fe_2O_3; limonite, $Fe_2O_3 \cdot 3H_2O$; magnetite, Fe_3O_4; taconite and siderite, $FeCO_3$; pyrites, FeS_2; and chromite, $Fe(CrO_2)_2$.

The physical properties of Fe, the metal, are profoundly affected by impurities and by changes in temperature and treatment. Iron is superior to all other elements in magnetic properties. Iron, in almost pure state, loses its magnetism when removed from an electric field; when Fe contains small amounts of C, Co, or Ni, the retention of magnetism is increased. When heated to 770°C, Fe loses its magnetism; on cooling, it retains this property. Iron undergoes a variety of structural changes (transformations) on heating that form the basis of the heat treatment of ferrous metals.

The principal compounds of Fe are ferrous (Fe^{2+}) and ferric (Fe^{3+}). In general, ferrous and ferric forms are mutually interconvertible. The oxidation potential against the normal hydrogen electrode for the ferrous form is −0.43 V, for the ferric form +0.77 V. Ferrous compounds are more stable than ferric when ionized, less stable when covalent. A large proportion of Fe salts are water-soluble; exceptions are carbonates, oxides, hydroxides, phosphates, sulfides, and ferrous fluoride. Iron of both valences tends to form complexes in which the commonest coordination number is 6. Iron has a strong tendency to combine with O, as in the form of OH groups, with resultant stable compounds, especially as chelates. Iron compounds exhibit marked catalytic activity in the

Table 29.16.1. Physical and Chemical Properties of Iron and Some of Its Compounds

Form of Fe	At. or Mol. Wt.	Sp. Gr.	M.P. (°C)	B.P. (°C)	Solubility
Iron (Fe)	55.85	7.86	1535	2750	Insol. hot or cold H_2O, alkalies, alcohol, ether; sol. acids
Ferrous oxide, black (FeO)	71.85	5.7	1420	—	Insol. hot or cold H_2O; sol. acid; insol. alcohol, alkalies
Ferric oxide, red-brown ($Fe_2O_3 \cdot xH_2O$)	159.69	5.24	1565	—	Insol. cold, hot H_2O; sol. HCl, H_2SO_4
Iron oxide magnetic, red (Fe_3O_4)	231.54	5.18	Dec. 1538	—	Insol. cold, hot H_2O; sol. conc. acid; insol. alcohol, ether
Ferric chloride ($FeCl_3$)	162.21	2.898 (25°C)	306	Dec. 315	744 g/liter (0°C); 5.35 kg/liter (100°C); v. sol. EtOH; MeOH, ether
Ferric nitrate hexahydrate [$Fe(NO_3)_3 \cdot 6H_2O$]	349.95	—	35	Dec.	1.5 kg/liter (0°C); inf. sol. hot H_2O
Ferric orthophosphate [$FePO_4 \cdot 2H_2O$]	186.85	2.74	Dec.	—	V. sl. sol. cold H_2O; 6.7 g/liter (100°C); sol. HCl, H_2SO_4; insol. HNO_3
Ferric sulfate [$Fe_2(SO_4)_3$]	399.87	3.097 (18°C)	Dec. 480	—	Sl. sol. cold H_2O; dec. hot H_2O; insol. H_2SO_4, NH_3
Ferrous sulfate [$FeSO_4 \cdot H_2O$]	169.96	2.970 (25°C)	—	—	Sl. sol. cold H_2O; sol. hot H_2O
Ferrocene, dicyclopentadienyl-Fe ($C_5H_5FeC_5H_5$)	186.04	—	172.5–173	Subl.	Insol. cold, hot H_2O; sol. EtOH, ether, C_6H_6, MeOH

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promotion of oxidations, both of chemical and biologic importance. Iron forms several carbonyls; their properties and uses are discussed.

An interesting aspect of Fe chemistry is the array of compounds with bonds to carbon. Cementite, Fe_3C, is a component of steel. The cyanide complexes of both ferrous and ferric iron are very stable and are not strongly magnetic in contradistinction to most Fe coordination complexes. The cyanide complexes form colored salts, including Prussian blue, $KFe_2(CN)_6$, made from ferric ion and potassium ferrocyanide, $K_4Fe(CN)_6$. The compound Turnbull's blue, made from ferrous ion and potassium ferricyanide, $K_3Fe(CN)_6$, is believed to be identical to Prussian blue. There are many compounds containing five cyanide groups and one other group (such as NO, CO, SO_3^{2-}, NO_2^-, NH_3, and H_2O) about the Fe. The compound $Na_2Fe(NO)(CN)_5 \cdot 2H_2O$ is one such compound; it can be used to test for sulfide ion.

Iron forms a large group of materials known as ferroalloys that are important as addition agents in steelmaking. Iron is also a major constituent of many special-purpose alloys developed to have exceptional characteristics with respect to magnetic properties, electrical resistance, heat resistance, corrosion resistance, and thermal expansion.

Among the better-known type of Fe alloys is that with C, the principal ones of which are wrought Fe, cast Fe, and steel. Good wrought Fe contains no more than 0.035 percent C, but contains also 0.075 to 0.15 percent Si, 0.1 to 0.25 percent P, less than 0.02 percent S, and 0.06 to 0.1 percent Mn, not all of which are alloyed with the Fe.

Cast Fe contains 2 to 4 percent C and varying amounts of Si, P, S, and Mn, to obtain a wide range of physical and chemical properties. Alloying elements such as Si, Ni, Cr, Mo, Cu, and Ti may be added in amounts varying from a few tenths to 30 percent or more.

Steel is a generic name for a large group of Fe–C alloys in which the C content is about 2 percent. To this basic steel, other alloying elements may be added, the more common types of which are Al, Cr, Co, Cr–Ni, Cr–Al, Mn, Ni, Si, and W, each of which has particular uses arising from its special properties.

The several Fe oxide forms find use as paint pigments, polishing compounds, magnetic inks, and coatings for magnetic tapes. The soluble salts (Table 29.16.1) are variously used as dyeing mordants, catalysts, pigments, fertilizer, feeds, disinfectants, and in tanning, soil conditioning, and treatment of sewage and industrial wastes. Ferrocene is used as an additive to fuel oils to improve combusion efficiency and eliminate smoke, antiknock agent, catalyst, high temperature lubricant, and UV absorber. For uses of other Fe compounds not listed in Table 29.16.1, see Reference 642.

16.4 Analytic Determination

Many of the best spectrophotometric methods for Fe have used 1,10-phenanthroline. The 4,7-phenyl derivative introduced by Collins and Diehl (643a) and Reynolds and Monkman (643b) has increased the sensitivity and lessened the interference of the method, making it adaptable to air, dust fall, and biologic samples. Keenan and Minderman (644), using the α,α-dipyridyl derivative, had previously determined the

conditions necessary for accurate analysis of welding-fume samples containing high concentrations of Fe. With the phenanthroline method, 0.5 μg Fe can be determined on a standard linear curve that follows Beer's law from 0.0 to 12.5 μg Fe. However, separation of small amounts of Fe is often desirable; this is best done by means of cupferron (ammonium salt of nitrosophenylhydroxylamine) (645). Spectrographic determination of Fe is not particularly well suited for quantitative estimation of Fe in biologic specimens.

Neutron activation analysis using oxidizing air–acetylene as gases and at a wavelength of 2483 Å is now available. It has a sensitivity of 0.1 μg/ml and a range of 0.1 to 10 μg/ml (63).

16.5 Physiologic Response

16.5.1 Acute Toxicity

Orally, Fe salts of both valence forms are not strikingly toxic; on the other hand, when introduced directly into the bloodstream Fe salts are highly and instantaneously toxic, particularly ferric salts. For example, the intraperitoneal LD_{50} of anhydrous ferric chloride for the mouse is 68 mg/kg and orally it is 400 mg/kg; the corresponding intraperitoneal LD_{50} of the hexahydrate, $FeCl_3 \cdot 6H_2O$, is 260 mg/kg, from reports published in the 1960s and 1970s (171). The data in the older literature (*Hefter's Handbuch*, 1930) indicated considerably greater toxicity; for example, the intravenous LD_{LO} for $FeCl_3$ for the rabbit is given as 7 mg/kg. The oral mouse and rat LD_{50} of anhydrous $FeCl_3$ is reported to be 440 and 900 mg/kg, respectively (171).

The oral rat LD_{50} for $Fe(NO_3)_3 \cdot 9H_2O$ is given as 3250 mg/kg, and the corresponding LD_{50} for $FeSO_4$ is 1480 mg/kg; the lowest toxic dose, TD_{LO}, by mouth for an infant is given for $FeSO_4$ as 600 mg/kg with effects on the gatrointestinal tract (646); for an adult female the value is 60 mg/kg, with effects primarily on the central nervous system (647). The acute toxicity of reduced Fe powder, by comparison, was very low as determined orally in the rat; the LD_{50} was found to be 98.6 g/kg or about 1/100 that of $FeSO_4$ determined under the same conditions (648).

The immediate cause of death from these inorganic compounds of Fe in animals is respiratory failure. Clinical signs preceding death are anorexia, oligodipsia, oliguria, alkalosis, diarrhea, loss of body weight, hypothermia, and alternating irritability and depression. At autopsy there is loss of weight in most organs, accompanied by dehydration when death occurred early, and edema when death was delayed. Vascular congestion of the gastrointestinal tract, liver, kidneys, heart, lungs, brain, spleen, adrenals, and thymus gland is the dominant histopathological sign. Toxic signs began to disappear in survivors toward the end of 1 week, and had completely disappeared at 2 to 4 weeks (648). In human poisonings, symptoms of iron intoxication include vomiting, hematemesis, diarrhea, lethargy, coma, irritability, seizures, and abdominal pain. Signs may include an increased cardiac and respiratory rate, while a marked increase in total peripheral vascular resistance may maintain arterial blood pressure for variable periods

before manifestations of low output shock ensue. Biochemical consequences of acute iron intoxication include metabolic acidosis, due in part to the accumulation of lactic and citric acids, and hypoglycemia (649).

The lowest toxic dose (TD_{LO}) or the LD_{50}, determined on seven Fe substances of industrial or pharmaceutical interest relative to their screening for their neoplastic potential (Table 29.16.3) are listed in Table 29.16.2. To be noted is the wide difference between the TD_{LO}s when response was measured as neoplasia (compounds 3, 5–7) when dosages were small and repetitive at weekly intervals, and when response was measured as granulomata (compounds 1, 2) or as a lethal response (compounds 4, 7b) resulting from a single dose. The orders of magnitude difference is indicative of the body's capacity to metabolize small, widely spaced, repetitive doses, and its inability to handle a single large and overwhelming dose.

16.5.2 Chronic Toxicity

Apart from the tumor-screening work on Fe and its inorganic and organic derivatives, the bulk of the toxicologic information on Fe compounds is the result of long-term exposures, and has been determined largely in man (see Sections 16.5.5, 16.5.6).

Neoplastic Activity in Animals. Following the observation by Richmond in 1957 (653) on the tumorigenicity of an Fe–dextran, this complex, as well as other Fe derivatives, was further explored by Haddow and Horning (650) (Table 29.16.3). In the screening of Fe and its inorganic compounds by subcutaneous injection, it is noted that with the exception of one fibroma from ferrous sulfate, neither Fe nor any of its inorganic compounds, including hematite, was productive of any tumors; moreover, ferric

Table 29.16.2. Toxic Doses for the Mouse of Some Inorganic and Organic Compounds of Iron of Industrial and Medical Interest

Compound	TD_{LO} or LD_{50}	Route	Ref.
1. Magnetite (black Fe_3O_4)	400 mg/kg (TD)	Intrapleur.	651
2. Olivine ($Fe_2Mg_2OSiO_2$)	400 mg/kg (TD)	Intrapleur.	651
3. Fe–dextran	104 g/(kg)(13 weeks) (TD)	S.c.	650
4. Ferrocene	335 mg/kg (LD) 1550 mg/kg (LD)	I.p. Oral	652
5. Ferrous gluconate	2600 mg/(kg)(13 weeks) (TD)	S.c.	650
6. Ferrous lactate	4200 mg/(kg)(21 weeks) (TD)	S.c.	650
7. Ferrous sulfate	(a) 1600 mg/(kg)(16 weeks) (TD) (b) 100 mg/kg (LD)	S.c. I.p.	650 171

oxide given by inhalation or by intratracheal route (not shown in Table 29.16.3) was not found tumorigenic in the mouse, hamster, or guinea pig (654a, 655). Similarly, among the organic derivatives, ferrocene, ferritin, ferric citrate and salicylate, and Fe ascorbate were nonproductive of tumors. However, Fe–dextran, a complex with a molecular weight 180,000, introduced into clinical and veterinary medicine in the 1950s, did result in several types of tumors at the injection site, but only at massive doses; other results from administration of low doses of short duration, not shown in Table 29.16.3, gave no evidence of sarcoma development, indicating a threshold dose (656). Iron lactate and gluconate yielded a small number of tumors, but thymomas and thecomas are evidence that Fe derivatives can result in tumors distant from the site of injection. For carcinogenic response in humans, see Sections 16.5.5 and 16.5.6.

Apart from tumor screening, much of the long-term exposure effects, or lack of them, have been evaluated in humans (see Sections 16.5.5, 16.5.6). The radiographic stippling seen in the lungs of rouge polishers, however, has been reproduced by Harding in rats (657) following intratracheal injection of rouge. Highly significant was the finding by Gardner and McCrum (658) showing that even severe pulmonary irritation from welding fumes (and gases) does not favor infection with tubercle bacilli nor occasion progressive tuberculosis. The daily administration of from 0.2 to 0.8 g $FeCl_2$ to dogs produced no noteworthy physiological changes (659). For the toxicity of iron carbonyls see Section 23 on metal carbonyls.

16.5.3 Metabolism

An excellent review of the absorption and metabolism of Fe has been made by Gubler (660). The amount of Fe used daily by an adult for hemoglobin synthesis is 26 to 27 mg. Owing to extensive Fe reuse, this is far in excess of the daily dietary Fe requirement, which is about 1.2 mg of Fe/day, or the amount of Fe excretion barring blood loss. Allowing a factor of 10 for low absorption of food Fe, 10 mg/day is considered a normal daily allowance for a man and 12 mg for a woman. Ferrous Fe is generally absorbed from the gastrointestinal tract more readily than ferric Fe, presumably because of greater solubility of ferrous compounds. The amount of Fe absorbed is inversely proportional to the intake. A number of factors influence absorption; among them are acidity of the gastric juice, composition of diet (high phosphate and phytic acid reduce absorption), vitamin B_6, Ca, Cu, and others. Regulation of intestinal Fe absorption is not completely understood but it appears to depend on body stores and requirements. An intestinal "acceptor" is postulated, because a single, large dose of Fe can block absorption for several days. The protein apoferritin is believed to be the Fe acceptor and is synthesized as need occurs. The steps in Fe absorption and storage are pictured by Granick (661) in the following way. Iron passes as ferrous Fe into the intestinal mucosal cell. In the cell Fe^{2+} is converted to Fe^{3+} in ferritin. No Fe absorption as ferritin occurs until the cell is physiologically "depleted." However, Fe is withdrawn from ferritin as Fe^{2+} as need arises. Iron released directly into the bloodstream is quickly oxidized by dissolved O_2 to Fe^{3+} which complexes with the specific Fe-transport β_1-globulin (transferrin). Iron in the plasma in excess of the

Table 29.16.3. Neoplastic Potential of Iron and Compounds Determined in Animals

Substance	Incidence Tumors	Types of Tumors	Species (No.)	No. Weekly Injections	Dose	Months on Study	Ref.
Metallic sponge Fe	0/20		Mouse (20)	16	20 mg	15	650
Dialyzed Fe (Fe_2O_3, 5%)	0/20		Mouse (20)	16	0.2 ml	15	650
Fe_2O_3, "hematite" (synthetic)	0/20		Hamster (20)	15	3 mg	>12	654
Ferrous sulfate	1/20	Fibroma	Mouse (20)	16	2.5 mg	14	650
Fe-dextran (Inferon)	70/95	41 Sarcomas, 6 histiocytomas, 1 epithelioma	Mouse	11–30	0.2 or 0.3 ml	6–18	650
Ferrocene	0/20		Mouse	28	5 mg	7	650, 652
Ferritin	0/20		Rat	15	5 mg	7	650
Ferric citrate	0/20		Mouse	33	5 mg	9	650
Ferric salicylate	0/20		Mouse	36	5 mg	12	650
Iron ascorbate	0/20		Mouse	43	0.3 mg Fe	12	650
Ferrous lactate	1/20	Sarcoma	Mouse	21	5 mg	12	650
Ferrous gluconate	3/20	Fibroma, thymoma, thecoma	Mouse	13	5 mg	12	650

binding capacity of this β_1-globulin is loosely combined in a nonspecific way with plasma proteins. It is this fraction that causes toxic reactions, and is rapidly removed from the plasma. Mean, normal, human plasma Fe levels are 129 μg/100 ml for men, and 110 μg for women. This means that the β_1-globulin is normally about one-third saturated with Fe on the basis of its constituting 3 percent of the serum proteins, its molecular weight of 90,000, and its two atoms/molecule Fe-binding capacity. It is a very important fraction, however, although it comprises only 0.1 percent of total circulating Fe and serves as a sensitive index of Fe metabolism. Possibly more use should be made of plasma-bound Fe as an index of exposure in workers exposed to excessive amounts of Fe dust (see Section 16.5.6).

In addition to the above metabolic aspects, Fe functions in the transport of O_2 in hemoglobin in the blood, in myoglobin in the muscle, where it delivers its O_2 to the cytochrome system of the cells (a 4:1 complex of ferroporphyrin with cytochrome oxidase, and the cytochromes a, b, c). Catalase and peroxidase are two other ferroporphyrin enzymes present in nearly all tissues for the decomposition of peroxide oxygen.

Storage of Fe is divided into four main compartments. The normal human body contains 4.5 g Fe; of this, hemoglobin, which is almost entirely in the blood, comprises 72.9 percent of total Fe; myoglobin, 3.3 percent; parenchymal Fe (oxidative enzymes) 0.2 percent; and storage Fe (ferritin, hemosiderin, and unaccounted Fe) 23.5 percent. Most of the storage Fe is found in the liver, bone marrow, and spleen.

Because the erythrocytes are undergoing continual disintegration, mostly in the spleen, but to some extent in the bone marrow and other reticuloendothelial tissues capable of phagocytic action, the breakdown of hemoglobin in this process leads to the release of Fe and the formation of bile pigments. The average life-span of erythrocytes is about 120 days for humans, 100 days for dogs, and 32 days for chickens. The excretion of Fe in the urine is normally inconsiderable. Its excretion from the skin is continuous, and may be important in the daily economy of the body. Iron released from transferrin in the blood of the subcutaneous capillaries combines with the proteins in the dermis, and is carried slowly to the surface of the skin as the cells of the epidermis desquamate.

Because Fe is a critical element in the body's metabolism, it is understandable that its state (valence) and amount can be influenced as a result of exposure to many kinds of industrial substances. von Oettingen (662) lists 30 industrial substances with the potential to produce methemoglobinemia, in which normal, reduced hemoglobin with Fe of valence 2+ is oxidized to Fe^{3+} of methemoglobin; 20 substances in industrial use, capable of eliciting Heinz bodies in the red blood cells, which are believed to be particles of denatured protein freed of Fe; and at least 60 substances capable of causing hemolytic anemia, a condition brought on from relatively trivial exposures in those individuals who have glucose-6-phosphate dehydrogenase deficiency (663).

16.5.4 Mode of Toxic Action

It has been only recently, in the early 1970s, that the mode and site of toxic action of Fe have been hypothesized (649) with supporting evidence (664, 665); the second edition of

this book contained no section on mechanism. On the basis of electron microscopic observations of electron-dense deposits, believed to be Fe, between the inner and outer membranes of the mitochondria, as well as in the intracristae lumen and the matrix of the hepatocytes, the primary and initial site of injury, poisoning of the mitochondria was noted as early as 3 hr after ingestion of a toxic dose of Fe (664). The mechanism believed to explain these observations (649) is the uptake by the exogenous, excess Fe of electrons donated by ferric reductase in the mitochondrial membrane that normally catalyzes endogenous Fe^{2+} to Fe^{3+}, resulting in immediate cessation of aerobic synthesis of adenosine triphosphate, initiating a cellular energy crisis and cell death (665). This mechanistic explanation can be correlated with the elevated lactic and citric acid levels and the depletion of glycogen stores observed in Fe poisoning. The ferric reductase mechanism need not be restricted to the liver mitochondria, but can be equally applicable to the cardiovascular, neurological, and gastrointestinal manifestations associated with Fe intoxication.

16.5.5 Clinical Experience with Fe Therapy

Carbohydrate complexes of Fe have been in use for two decades for the correction of iron-deficiency anemia in humans and baby pigs. The Fe–dextran complex, the one chiefly used for parenteral administration, consists of 5 percent wt./vol. Fe and 20 percent wt./vol. dextran. The therapeutic dose is 1 to 5 ml (50 to 250 mg Fe) daily by deep intramuscular injection. Investigations of the metabolism of Fe–dextran showed that it disappeared from the injection site in man rather rapidly; 60 percent in 24 hr and 95 percent in 5 days, with a peak plasma level in 24 hr and with very little Fe excreted in the urine. Following reports of sarcoma development in rodents, Fe–dextran was temporarily withdrawn from the market in 1960, only to be reintroduced in 1962, when the risk of malignancy in man was considered to be very low. Although no epidemiologic or long-term studies have been reported, a single case of undifferentiated soft tissue sarcoma at the injection site is all that has been recorded. The sarcoma appeared 3 years after six inoculations of Fe–dextran of 100 mg each for blood loss anemia. Histological examination of injection sites following usual therapeutic doses of Fe–dextran have shown little or no change. In two cases, massive doses produced some fibrosis and heavy accumulations of Fe in macrophages, but no fibroblastic proliferation indicative of neoplasia or preneoplasia. By 1967, it was estimated that the Fe–dextran market in the United States amounted to $3.2 million.

16.5.6 Industrial Experience

The hygienic significance of mottling of the lungs, siderosis or, as preferred by Sander (666), "iron pigmentation," is now considered that of a benign pneumoconiosis because it does not lead to fibrous proliferation, is of low order of severity, and usually requires 6 to 10 years of exposure before diagnosable roentgenographic changes occur (667). The condition commonly occurs in electric-arc welders after years of exposure, but may occur

in silver polishers or rouge users, according to McLaughlin et al. (668). Buckell et al. (669) X-rayed the lungs of 171 iron turners and found reticulation from Fe oxide present in 15 men. In five cases, workers had been at the trade for 20 years. The lung changes were moderate, symptoms were few, and only one man complained of shortness of breath, although six noted a tendency to cough. Healing of tuberculous lesions despite continuous exposure to Fe oxide fumes, first noted by Sander (666), has been repeatedly confirmed in humans (670) and animals (659). Physical examinations and tests of work capacity of welders with Fe pigmentation show that it causes little or no disability (670). Gardner (671) regarded Fe oxide as a retardant of the development of conglomerate silicotic fibrosis. (See, however, discussion of lung fibrosis of steel foundrymen and hematite miners below.) Chemical data on the Fe content of the lungs of workers in the dusty trades are given by Gerstel (672).

There is accumulating evidence, however, that Fe oxides may not act to prevent silicosis and tuberculosis in all types of exposure. Iron and steel foundrymen (England) subjected to high temperature Fe oxide fume along with silica were reported by McLaughlin and Harding (673) to develop "siderosis, silicosis, and mixed dust fibrosis." Moreover, a high incidence of bronchiogenic carcinoma was noted among the foundrymen. It would seem, in the face of apparent experimental evidence to the contrary (674), that Fe oxides freshly formed at high temperatures may act much the same way that Al_2O_3 and SiO_2 fumes act to produce Shaver's disease, a fibrotic condition of the lung.

The subject of hematite pneumoconiosis in Cumberland Fe ore miners has been reopened with a report by Faulds (675). It is a progressive, massive fibrosis, appearing as a modified form of infective pneumoconiosis; it was considered to be tuberculosis when first described, but may not be so invariably. However, tuberculosis is the terminal event in most cases, probably because of a relative increase in the degree of silica exposure. An increased incidence of lung tumors in the Fe ore miners was noted; of 238 necropsies, there were 24 cases of carcinoma, compared with less than one-third this number in nonminers.

A statistical-epidemiologic follow-up study of these miners concluded that although the miners suffered a lung cancer mortality of about 70 percent higher than "normal" for the area, it could not be concluded whether the risk was due to radioactivity of the mines (av. radon concentration 10 pCi/liter) or to a carcinogenic effect of Fe oxide, or both (676). In a similar vein, a report on the causes of death in a small number of nonfoundry Fe and steel workers in England revealed that silicosis was more prevalent than fibrosis from mixed, Fe-containing dust (677).

A definite correlation between serum Fe levels and radiographic findings in Fe workers in Bavaria has been reported (678); serum Fe levels are considered as a reflection of partial release of Fe in the lungs. Serum Fe levels of 47 pneumoconiotic workers averaged 160 μg percent compared with a normal of 127 μg percent in healthy nonexposed workers. The increase was proportional to the degree of exposure to the ore dust and the lung changes.

Phosphine liberation was reported (679) in the ambient air about the machining of

spheroidal graphite Fe; 6 ppm PH_3 was measured near the tool point, and 0.8 ppm at 20 cm. No coolant was used in machining.

16.5.7 Treatment of Acute Intoxication

Iron salts when taken in excessive amounts can be fatal. A review of the literature in 1958 revealed an overall mortality of 50 percent of the reported cases of Fe intoxication. Although fatal doses of $FeSO_4$ range from 3 to 18 g, a young child survived who had swallowed 20 g but had been treated within a few hours with 13.5 g desferrioxamine methanesulfonate (*Merck Index*, 9th ed., 1976, p. 374), a potent Fe chelator, by gastric tube and 500 mg intramuscularly. Intramuscular injections of 250 mg were continued at intervals of 8 hr, as was oral administration of the same dose for 5 days, with a complete recovery in 1 week. Of the 20 g $FeSO_4$ ingested (6 g Fe) about 1 g was recovered unabsorbed. The calculated dose of 46.5 g desferrioxamine was not administered because of possible side effects. Salmon-pink urine discoloration and quantitative estimation of urinary Fe are considered the best indicators of Fe overload (680).

16.6 Hygienic Standards of Exposure

The TLV of Fe oxide fume of 15 mg/m³ has been successively reduced since its first adoption in 1957 by the Threshold Limits Committee of the American Conference of Governmental Industrial Hygienists. At that time, 15 mg/m³ was the accepted limit for "inert" or nuisance particulates. In 1967, the TLV was revised downward to 10 mg/m³, not for health reasons, but to improve visibility in the workplace. In 1975, the TLV was still further reduced to 5 mg/m³, and in 1977 a 10 mg/m³ limit was proposed as a tentative short-term exposure limit (STEL), with the stipulations stated in the preface to the TLV booklet of 1976. Again, the reduction was not for health reasons but to prevent development of X-ray changes in the lungs on long-term exposure, changes not associated with any physical disability but that may present difficulties in differential diagnosis.

A TLV of 1 mg/m³ for soluble Fe salts was adopted in 1969, and in 1976, the first year of listing STELs, a tentative STEL of 2 mg/m³ as Fe was proposed, these values intended to reduce the likelihood of respiratory tract irritation and skin effects from contact with aerosols.

Hygienic standards in other countries follow: Germany, Fe oxide fume, 8 mg/m³ (1974); Sweden, Fe oxide fume, 5 mg/m³ (1974); Soviet Union, Fe oxide, 1 mg/m³ (1973). The OSHA standard is 10 mg/m³ (1978).

16.7 Flammability Limits

From the data that appear in Volume I of this book (3rd ed., 1978, p. 1432), minimum ignition temperatures for iron dust clouds range from 470 to 780°C; for layered dust, the range is 220 to 520°C.

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17 THE LANTHANIDES (RARE EARTH METALS)

The lanthanides (or lanthanons) are a group of 15 elements of atomic numbers from 57 through 71 in which yttrium (at. no. 39) is usually included (see Table 29.17.1).

Considerably more toxicologic information on this group of metals has become available since the publication of the second edition of this book in 1962, because of the development of methods of separating and purifying these chemically similar elements on a commercial scale and at greatly reduced cost. Nevertheless, their similar chemical and toxicologic properties warrant their being considered as a group.

17.1 Source and Production (563)

The only commercially useful ores are massive monazite and monazite sand, a phosphate of the Ce group metals; bastnasite and related fluocarbonate minerals of the Ce group; and minerals of the Y group—gadolinite, a silicate of Y, Ce, Cr, Be, and Fe; euxenite, a mineral containing Y, Ce, Er, Nb, Ti and U; and xenotime, mainly a YPO_4 mineral, which may contain Th and some of the Ce subgroup metals.

The most important sources of monazite sand are Florida (U.S.), Australia, the states of Rio de Janeiro, Espirito Santo, and Bahia (Brazil), and Travancore, India. Stream placer deposits of bastnasite are in commercial production in Idaho and North and South Carolina, and deposits in San Bernadino County, California are capable of supplying the industry for many years. Production of Y-group ores is considerably less than that of monazite or bastnasite; euxenite is recovered from a placer deposit near Bear Valley, Idaho, and some xenotime from some monazite placer deposits.

The relative abundance of certain of the lanthanides is quite high; the oxides of Ce, La, and Nd occur as 29.9, 17, and 11 percent, respectively, in Idaho monazite; in California bastnasite concentrate, the values are 47.1, 24.6, and 12.6 percent. The lanthanides are formed in the fission of U and Pu; indeed, Pm is derived solely from atomic reactors.

Table 29.17.1. The Lanthanides

Cerium Subgroup, "Light" Lanthanides	Yttrium Subgroup, "Heavy" Lanthanides	
Lanthanum, La	Samarium, Sm	Holmium, Ho
Cerium, Ce	Europium, Eu	Erbium, Er
Praseodymium, Pr	Gadolinium, Gd	Thulium, Tm
Neodymium, Nd	Terbium, Tb	Ytterbium, Yb
Prometheum (illinium), Pm	Dysprosium, Dy	Lutetium, Lu
	(Yttrium, Y)	

Table 29.17.2. Compositions of Commercial Rare Earth Metals

Metal	Percent Composition				
	Ce	Nd	Pr	Sm	La and Other Rare Earths
Lanthanum	<0.1	<0.1	<0.1	<0.1	99.9
Neodymium-praseodymium	1	78	15	2	4
Cerium	97	0.9	0.5	0.1	1.5
Misch metal[a]	52	18	5	1	24
La-enriched misch metal[a]	47	19	6	1	27

[a] Obtained from monazite, and often sold or referred to as "cerium metal."

In the extraction and separation of the lanthanides, monazite and bastnasite ores are generally "opened" by heating with sulfuric acid and the resulting sulfates separated from the reaction products with water. Thorium, from monazite sources, is removed from the lanthanide sulfate solution most commonly by precipitation as the pyrophosphate. The lanthanides, in turn, are recovered by precipitation as the oxalates or Na double sulfates. Oxalate precipitation is complete, but the double sulfate precipitate leaves some of the Ce earths and most of the Y earths in the liquor. If hydrated oxides are desired the precipitates are boiled with NaOH which yields granular hydroxides. Drying the hydroxides gives hydrated oxides. If oxides are desired, the oxalates or hydroxides are calcined. Separation of Ce, one of the lanthanides of greatest industrial use, depends on oxidation of Ce to the tetravalent state; this form has solubility properties that differ from nearly all the lanthanides, because it is the only lanthanide that exists as a quadrivalent ion in aqueous solution. Purification is done by precipitation as the basic salt.

Most commercial lanthanide salts are mixtures containing the lanthanides in much the same ratio as they occur in the ore. Separation of the remaining lanthanides is difficult because of great similarity of chemical properties. For separation of the Ce group, fractional crystallization of salts such as the double NH_4 or Mg lanthanide nitrates are used. For the heavy lanthanides, ion exchange methods are used for separation and purification (purities varying from 90 to 99.99 percent) of the remaining lanthanides and Y. The method consists of absorbing the mixed lanthanides on the top of a cation ion exchange resin column in the copper cycle, and then eluting the lanthanides selectively from the resin column with ammonium ethylenediaminetetraacetate solution. The various commercial and laboratory methods used for the preparation of lanthanon metals and salts are given in Reference 563. The composition of commercial lanthanide is given in Table 29.17.2.

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July 2, 1999

USDA, AMS, TMD,NOP
Room 2510 South Building
PO Box 96456
Washington, DC 20090-6456

Dear USDA,

I am an independent crop consultant with a client base of large organic vegetable farmers in the Salinas Valley area of California. In the last several years we have had some serious losses from snails and slugs, perhaps related to our winter cover crops and perennial beneficial insect habitats. None of the growers have achieved economic control using the available organic techniques and materials. It would be very helpful and economically beneficial to have an organic control material.

I understand formal organic acceptability for a new slug and snail bait based on iron phosphate is a possibility, based on a favorable review. I strongly endorse an organic slug and snail bait and hope that this product's review will be completed as soon as possible.

Sincerely,

Doug O'Brien, Ph.D.

USDA, AMS, TMD,NOP
Room 2510 South Building
PO Box 96456
Washington, DC 20090-6456

Dear USDA,

Crown Packing Co., Inc., which farms and ships vegetables in the Salinas Valley, is farming and transitioning approximately 200 acres of organic cauliflower, lettuce and celery in addition to our conventionally farmed acreage. We have problems with slugs in our crops most years. We do not have any reasonably priced and effective organic control measures. We really need an organic control product, especially in wet years.

I understand that there is a new slug and snail bait based on iron phosphate, for which formal organic acceptability is being sought. I strongly endorse an organic slug and snail bait and hope that this product's review will be completed as soon as possible.

Sincerely,

David Bunn

David Bunn
Crown Packing Co., Inc.
PO Box 247
Salinas, CA 93902

PHIL FOSTER RANCHES
400 Duncan Ave., San Juan Bautista, CA 95045
(831) 623-2806 FAX: (831) 623-9319

USDA, AMS, TMD, NOP
Room 2510 South Building
P.O. Box 96456
Washington, DC 20090-6456

Wednesday, June 02, 1999

Dear USDA,

As an organic grower of approximately 250 acres of mixed vegetable crops, I have problems with slugs in my crops. I have not found any cost-effective organic control measures for these pests, which cause significant damage to our crops every year. An organic control product is desperately needed to keep these pests in check and to conform with strict quarantine regulations by the state of Florida, where some of my products are shipped.

I understand that there is a new slug and snail bait based on the active ingredient iron phosphate, for which formal organic acceptability is being sought. I strongly endorse an organic slug and snail bait and hope that this product's review will be completed as soon as possible.

Sincerely,

Phil Foster
Owner

USDA, AMS, TMD,NOP
Room 2510 South Building
PO Box 96456
Washington, DC 20090-6456

Dear USDA,

I farm about two thousand acres of vegetables in the Pajaro Valley area, including several hundred acres of organic crops. I also run a cooler and produce sales company. In some of my farms, particularly those near water, slugs and snails often cause problems. We have not been able to control them economically using organic techniques and materials. It would be very helpful have an organic control material.

I understand formal organic acceptability for a new slug and snail bait based on iron phosphate is a possibility, based on a favorable review. I strongly endorse an organic slug and snail bait and hope that this product's review will be completed as soon as possible.

Sincerely,

Dick Peixoto
Dick Peixoto Co./Lakeside Organic Gardens
577 Judd Rd.
Watsonville, CA 95076

RURAL DEVELOPMENT CENTER
Post Office Box 5415
Salinas, California 93915
(408)758-1469

USDA, AMS, TMD, NOP
Room 2510 South Building
PO Box 96456
Washington, DC 20090-6456

Dear USDA,

I work for the Rural Development Center, a 112 acre certified organic vegetable farm in the Salinas Valley, CA that provides land and instruction to farm workers learning to become farmers. Regularly, we have had problems with brown garden snail contamination in our organically farmed crops. Our broker has had quarantine problems when shipping products to Florida, which does not allow any snails to pass its borders. We have not been able to control them economically using cultural techniques or organic materials. It would stabilize our shipping options and increase profits to have an organic control material.

I understand formal organic acceptability for a new slug and snail bait based on iron phosphate is a possibility based on a favorable review. I strongly endorse an organic slug and snail bait and hope that this product's review will be completed as soon as possible.

Sincerely,

Luis Sierra
Marketing Program Coordinator
Rural Development Center
PO Box 5415
Salinas, CA 93915