"PHYTOPHYL" N.G.STAVRAKIS
LABORATORIES OF PHYTOMEDICAL PRODUCTS
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SHIMATARI VIOTIA, 32009 Fax: 0030 0262 58735 Tel: 0030 0262 58670
http://www.otenet.gr /phytophyl - email : nista@otenet.gr

TO:
National Organic Standards Board,
c/o Robert Pooler
Agricultural Marketing Specialist
USDA/AMS/TM/NOP, Room 2510-So
Ag Stop 0268, P.O. Box 96456
Washington, D.C. 20090-6456
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Athens 10/4/2003

Petition For The Inclusion Of Urea On The National Organic Standards Board List Of Approved Synthetic Substances.

ITEM A

With this petition "PHYTOPHYL" - N.G.STAVRAKIS is requesting the evaluation of urea for inclusion in:

- Synthetic substances allowed for use in organic crop production.

ITEM B

1. **Common name:** Urea, (Synonyms of common name: Carbamide, Carbonyl diamide, Carbonyldiamine,Carbamimidic acid).
2. **Manufacturer:** "PHYTOPHYL" N. G. STAVRAKIS , Shimatari-Viotia 32009 Greece, tel:+30-2262-058670, fax:+30-2262-058735, email:nista@otenet.gr.
3. **Current use:** The current use of urea is as pesticide. It is used as the potential active ingredient in an insect attractant preparation,. This preparation is used as bait against fruit flies, exclusively in insect traps without direct contact with crop or soil.
4. **List of the crop:** The substance is used for olive and fruit crops. It is the potential active ingredient of a 20% w/w urea preparation. This insect-attractant preparation is used as bait exclusively in insect traps after dilution with water and a final rate of 5% w/w in urea. The mode of use is exactly the same as ammonium bicarbonate. The slow progressively breakdown product of ammonia inside the traps serves as a long lasting attractant for fruit flies (*Bactrocera oleae, Ceratitis capitata*). So the mode of action is also exactly the same as ammonium carbonate already allowed for use in organic crop production.
5. **Source of substance:** We are contracting to urea-producer companies the manifacturing of urea (fertilizer or technical grade) on our behalf according to EU standards with total nitrogen of 46% and maxim. biurea of 1%, Basf is our main supplier. We also use this grade of urea in manufacturing *Bactrocera oleae* attractive preparations for bait sprays on ordinary crops without any problems since 1983. There are two registered products in Greece (9010/1983, 9031/1994).

6. **Summary of previous reviews:** We don't dispose written previous reviews of the petitioned substance about this usage in traps but the above mentioned insect- attractant is largely applied in organic olive-crop the last ten years in our country without problems.
7. **Informations regarding EPA, FDA:** We are sending you two recent memorandum of United States Enviromental Protection Agency about: A) the review of urea as an active ingredient and B) the Tolerance Reasseessment Eligibility Decision for Urea.
8. **CAS number of urea:** 57-13-6 (CIPAC NUMBER: 8352, EEC NUMBER: 200-315-5).
9. **Physical properties and chemical mode of action:** Urea reacts slowly with water and gives ammonia and carbon dioxide according to the reaction $NH2CONH2 + H2O \Rightarrow 2NH3 + CO2$ which is affected by the inert ingredients of the plant protection product formula, enviromental factors and the mode of application (design of traps).
10. **Safety information:** We are sending you an MSDS of EFMA about urea and the NTP CHEMICAL REPOSITORY from NIEHS and the International Chemical Safety Card of NIOSH for urea.
11. **Research information: --**
12. **Petition Justification Statement:**

The use of urea is necessary as potential attractive substance for mass trapping and control of *Bactrocera oleae* and *Ceratitis capitata*. The other synthetic substance which is used for the same purpose and in the same manner is ammonium bicarbonate which liberates the same exactly volatiles and is already included in the National List.

Urea has the advantage of easier regulation for longer liberation of volatiles.

The use of adhesive traps as alternative method was proved dangerous for beneficial insects, especially for them of small size.

The liquid insect attractant preparations of urea are used inside special traps with entrance's openings of small size. These openings are properly placed to favour the trapping of fruit flies because of their flying behaviour, but not the non target organisms.

In addition these traps render indispensable the entry in an interior place and restrain significantly the trapping of non target organisms.

In our country this practice using preparations of urea exclusively inside traps in organic olive crops, is observed as the best available today practice against *Bactrocera oleae*.

As you know without the inclusion of urea on your National List, many of the producers and the exporters from Greece in USA of organic olive oil and olives, can not have the necessary certification and so we supplicate you to do your best and if it is allowable and not fatiguing please inform us about it.

With thanks and due respect.

N. G. Stavrakis.

European Fertilizer Manufacturers Association

EFMA Publications

Guidance For The Complation of Safety Data Sheets For Fertilizer Materials

Guidance For The Complation of Safety Data Sheets For Fertilizer Materials

Table Of Contents

Guidance For The Compalation of Safety Data Sheets For Fertilizer Materials
Urea

1. IDENTIFICATION OF THE PRODUCT AND THE COMPANY

1.1 Identification of the Product

Designation	EC Fertilizer, Urea
Trade name	
Commonly used synonyms	Carbamide, Carbonyl Diamide
CAS Number	57-13-6
EINECS Number	200-315-5
EINECS Name	Urea
Molecular formula	$CH_4 N_2O$

1.2 Company

Address	Telephone No.
	Telefax No.
	Telex No.

1.3 Emergency calls

Company	Telephone No.
and/or	
official Advisory Body	Telephone No.

2. COMPOSITION/INFORMATION ON INGREDIENTS

2.1 Nature of ingredients and concentration

Product containing urea as essential ingredient (Total nitrogen 46%).

2.2 classification

Not classed as hazardous material according to EEC Directive 67/548/EEC.

3. HAZARDS IDENTIFICATION

3.1 Human health

The product has low toxicity. However, the following points should be noted.

Skin Contact

Prolonged or repeated contact may cause some irritation.

Eye Contact

Prolonged or repeated contact may cause some irritation.

Ingestion

Small quantities are unlikely to cause toxic effect.

Large quantities may give rise to gastro-intestinal disorders.

Inhalation

High dust concentrations of air-borne material may cause irritation of the nose and upper respiratory tract.

Long term effects

No adverse effects are known. Occurs naturally in the body.

Fire and thermal decomposition products

Inhalation of decomposition gases can cause irritation and corrosive effects on the respiratory system. Some lung effects may be delayed.

3.2 Other

Fire and heating

When heated, urea decomposes releasing ammonia. In a Fire, toxic fumes containing ammonia and NOX may be released.

4. FIRST-AID MEASURES

4.1 Product

Skin Contact

Wash the affected area with soap and water.

Eye Contact

Flush/irrigate eyes with copious amounts of water for at least 10 minutes.

Obtain medical attention if eye irritation persists.

Ingestion

Do not induce vomiting.

Give water or milk to drink.

Obtain medical attention if more than a small quantity has been swallowed.

Inhalation

Remove from source of exposure to dusts.

Obtain medical advice if ill effects occur.

4.2 Fire and decomposition products

Skin Contact

Wash areas in contact with molten material copiously with cold water.

Obtain medical attention.

Inhalation

Remove from the source of exposure to fumes.

Keep warm and at rest.

Persons who have inhaled decomposition gases should immediately obtain medical attention.

5. FIRE-FIGHTING MEASURES

5.1 If fertilizer is not directly involved in the Fire

Use the best means available to extinguish the Fire.

5.2 If fertilizer is involved in the Fire

Call the Fire brigade.

Avoid breathing the fumes (toxic), stay up-wind of the fire.

Wear an approved breathing mask when fighting a Fire. Use a self-contained breathing apparatus if fumes are being entered.

Use plenty of water.

Open doors and windows of the store to give maximum ventilation.

Do not allow molten fertilizer to run into drains.

If water containing fertilizer enters any drains or watercourse, inform the local authorities immediately.

6. ACCIDENTAL RELEASE MEASURES

6.1 Environmental precautions

Take care to avoid the contamination of watercourses and drains and inform the appropriate authority in case of accidental contamination of watercourses.

6.2 Methods for cleaning

Any spillage of fertilizer should be cleaned up promptly, swept up and placed in a clean, labelled, open container for safe disposal.

Depending on the degree and nature of contamination, dispose of by use as a fertilizer on farm by spreading thinly on open ground or to an authorised waste facility.

7. HANDLING AND STORAGE

7.1 Handling

Avoid excessive generation of dust.

Avoid unnecessary exposure to the atmosphere to prevent moisture pick-up.

When handling the product over long periods use appropriate personal protective equipment e.g. gloves.

7.2 Storage

Locate away from the source of heat or Fire.

Ensure high standard of housekeeping in the storage area.

Any building used for the storage should be dry and well ventilated.

8. EXPOSURE CONTROL / PERSONAL PROTECTION

8.1 Occupational exposure limits

No specific official limit.

ACGIH recommended value (1995-96) for inhalable particulate:

TLV/TWA : 10mg/m^3.

8.2 Precautionary and engineering measures

Avoid high dust concentration and provide ventilation where necessary.

8.3 Personal Protection

Wear suitable gloves when handling the product over long periods.

Use suitable dust respirator if dust concentration is high.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance	White solid.
Odour	Odourless.
pH water solution (conc.10%)	9-10.
Melting point	133°C (decomposes).
Flammability (solids)	Not flammable (Method A10 EEC)
Explosive properties	Uncontaminated urea is not an explosion hazard. However it may form explosive mixtures subject to spontaneous detonation when contaminated with strong acid (nitric or perchloric) or nitrates.
Oxidizing properties	None.
Bulk density	700-780kg/m^3.
Solubility in water	1080g/l at 20°C.

10. STABILITY AND REACTIVITY

10.1 Stability

The product is stable under normal conditions of storage, handling and use.

10.2 Conditions to avoid

Heating above melting point.

Welding or hot work on equipment or plant which may have contained fertilizer without First washing thoroughly to remove all fertilizer.

10.3 Materials to avoid

Strong oxidizers, acids, alkalies, nitrates, sodium or calcium hypochlorite.

10.4 Hazardous reactions/decomposition products

Urea reacts with sodium or calcium hypochlorite to form explosive nitrogen trichloride. (See also Sections 3.2 and 9.)

11. TOXICOLOGICAL INFORMATION

11.1 General

See Section 3.1.

11.2 Toxicity Data

LD50 (oral, rat) > 2000mg/kg

12. ECOLOGICAL INFORMATION

12.1 Mobility

Soluble in water.

12.2 Persistence/Degradability

Substantially biodegradable in soil and water.

12.3 Bio-accumulation

Low potential for bio-accumulation.

12.4 Ecotoxicity

Has low intrinsic aquatic toxicity but will exert a substantial oxygen demand when significant quantities as in a spillage reach a watercourse and may cause damage to aquatic life.

13. DISPOSAL CONSIDERATIONS

13.1 General

Depending on degree and nature of contamination, dispose of by use on farm, by spreading thinly on open ground or to an authorised waste facility.

14. TRANSPORT INFORMATION

14.1 UN classification

Not classed, ie considered non-hazardous material according to UN Orange Book and international transport codes e.g. RID (rail), ADR (road) and IMDG (sea).

15. REGULATORY INFORMATION

15.1 EEC Directives

76/116/EEC (Law relating to fertilizers)

15.2 National laws

16. OTHER INFORMATION

The information in this safety data sheet is given in good faith and belief in its accuracy based on our knowledge of the substance/preparation concerned at the date of publication. It does not imply the acceptance of any legal liability or responsibility whatsoever by the Company for the consequences of its use or misuse in any particular circumstances.

Date of issue: Date of revision:

NTP CHEMICAL REPOSITORY
UREA

-IDENTIFIERS
==========

*CATALOG ID NUMBER: 000632

*CAS NUMBER: 57-13-6

*BASE CHEMICAL NAME: UREA

*PRIMARY NAME: UREA

*CHEMICAL FORMULA: CH4N2O

*STRUCTURAL FORMULA:

*WLN: ZVZ

*SYNONYMS:
CARBAMIDE
CARBONYLDIAMINE
NCI-C02119
CARBONYL DIAMIDE
AQUADRATE
UREAPHIL
UREOPHIL
CARBAMIMIDIC ACID

-PHYSICAL CHEMICAL DATA
==========

*PHYSICAL DESCRIPTIONS: White crystals or powder.

*MOLECULAR WEIGHT: 60.07

*SPECIFIC GRAVITY: 1.3230 @ 20/4 C

*DENSITY:Not available

*MP (DEG C): 135 C

*BP (DEG C): Decomposes

*SOLUBILITIES:
WATER : SOLUBLE

DMSO : SOLUBLE

95% ETHANOL : SOLUBLE

METHANOL : Not available

ACETONE : Not available

TOLUENE : Not available

*OTHER SOLVENTS:

Chloroform: Insoluble
Methanol: 170 mg/mL
Acetic acid: Soluble
Pyrimidine: Soluble
Concentrated Hydrochloric acid: Soluble
ETHER : Slightly soluble
BENZENE: Insoluble

*VOLATILITY :

*FLAMMABILITY(FLASH POINT):
Flash point data for this chemical are not available, however it is probably
non-flammable. Fires involving this material can be controlled with a dry
chemical, carbon dioxide or Halon extinguisher.

*UEL: Not available LEL: Not available

*REACTIVITY: Reacts violently with gallium perchlorate.

*STABILITY: This compound will slowly hydrolyze.

*OTHER PHYSICAL DATA: Refractive index: 1.484

-TOXICITY
========

*NIOSH REGISTRY NUMBER: YR6250000

*TOXICITY: **(abbreviations)**

typ. dose	mode	specie	amount	unit	other
LDLO	ORL	DOM	511	MG/KG	
LDLO	SCU	DOG	3000	MG/KG	
LDLO	IVN	DOG	3000	MG/KG	
LDLO	SCU	RBT	3000	MG/KG	
LDLO	IVN	RBT	4800	MG/KG	
LDLO	SCU	PGN	16	G/KG	
LDLO	SCU	FRG	600	MG/KG	

*AQTX/TLM96: OVER 1000 PPM.

*SAX TOXICITY EVALUATION: THR=MOD VIA SC, IV AND ORAL ROUTE.

*CARCINOGENICITY: Not available

*MUTAGENICITY: Not available

*TERATOGENICITY: Not available

*STANDARDS, REGULATIONS & RECOMMENDATIONS:
OSHA: None
ACGIH: None
NIOSH Criteria Document: None
NFPA Hazard Rating: Health (H): None
Flammability (F): None
Reactivity (R): None

*OTHER TOXICITY DATA: Not available

-OTHER DATA (Regulatory)
 ========================

*PROPER SHIPPING NAME (IATA): Not restricted

*UN/ID NUMBER:

*HAZARD CLASS: SUBSIDIARY RISK: PACKING GROUP:

*LABELS REQUIRED:

*PACKAGING: PASSENGER: PKG. INSTR.: MAXIMUM QUANTITY:
CARGO : PKG. INSTR.: MAXIMUM QUANTITY:

*SPECIAL PROVISIONS:

*USES:
Fertilizer, animal fedd, plastics, chemical intermediate, stabilizer in explosives, medicine, adhesives, separation of hydrocarbons (as urea adducts), sulfamic acid production, flame proofing agents, viscosity modifier for starch, casein-based paper coatings, reported helpful in treatment of sickle-cell anemia, diuretic, and antiseptic.

*COMMENTS:

-HANDLING PROCEDURES
 ====================

*ACUTE/CHRONIC HAZARDS:
This compound may cause eye irritation. When heated to decomposition this compound emits toxic fumes.

*MINIMUM PROTECTIVE CLOTHING: Not available

*RECOMMENDED GLOVE MATERIALS: Not available

*RECOMMENDED RESPIRATOR:
Where the neat test chemical is weighed and diluted, wear a NIOSH-approved half face respirator equipped with an organic vapor/acid gas cartridge (specific for organic vapors, HCl, acid gas and SO2) with a dust/mist filter.

*OTHER: Not available

*STORAGE PRECAUTIONS:
You should store this chemical under refrigerated temperatures, and protect it from moisture.

*SPILLS AND LEAKAGE:
If you spill this chemical, you should dampen the solid spill material with water,then transfer the dampened material to a suitable container. Use

absorbent paper dampened with water to pick up any remaining material. Seal your contaminated clothing and the absorbent paper in a vapor-tight plastic bag for eventual disposal. Wash all contaminated surfaces with a soap and water solution. Do not reenter the contaminated area until the Safety Officer (or other responsible person) has verified that the area has been properly cleaned.

*DISPOSAL AND WASTE TREATMENT: Not available

-EMERGENCY PROCEDURES
==========

*SKIN CONTACT:
IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently wash all affected skin areas thoroughly with soap and water.
If symptoms such as redness or irritation develop, IMMEDIATELY call a physician and be prepared to transport the victim to a hospital for treatment.

*INHALATION:
IMMEDIATELY leave the contaminated area; take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital.
Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used; if not available, use a level of protection greater than or equal to that advised under Respirator Recommendation.

*EYE CONTACT:
First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center.
Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician.
IMMEDIATELY transport the victim after flushing eyes to a hospital even if no symptoms (such as redness or irritation) develop.

*INGESTION:
DO NOT INDUCE VOMITING. If the victim is conscious and not convulsing,

give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control center. Be prepared to transport the victim to a hospital if advised by a physician.

If the victim is convulsing or unconscious, do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY transport the victim to a hospital.

*SYMPTOMS: Symptoms of exposure to this compound include eye irritation.

*FIREFIGHTING:

-SOURCES
=======

*SOURCES:

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Oak Ridge National Laboratory. Environmental Teratogen Information Center (ETIC), Bibliographic Data Base. Oak Ridge National Laboratory. Oak Ridge, TN. LISTED.

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[620] United States National Toxicology Program. Chemical Status Report. NTP Chemtrack System. Research Triangle Park, NC. November 6, 1990. Not listed.

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Please send queries, comments, and suggestions to:
ntpwm@niehs.nih.gov

Last revised: 13 August 2001

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International Chemical Safety Cards

UREA

ICSC: 0595

Carbamide
Carbonyldiamide
NH_2CONH_2 / CH_4N_2O
Molecular mass: 60.1

ICSC # 0595
CAS # 57-13-6
RTECS # YR6250000

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/ SYMPTOMS	PREVENTION	FIRST AID/ FIRE FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings: all extinguishing agents allowed.
EXPLOSION			
EXPOSURE		PREVENT DISPERSION OF DUST!	
•INHALATION	Cough. Shortness of breath. Sore throat.	Local exhaust.	Fresh air, rest.
•SKIN	Redness.	Protective gloves.	Rinse and then wash skin with water and soap.
•EYES	Redness.	Safety spectacles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
•INGESTION	Convulsions. Headache. Nausea. Vomiting.	Do not eat, drink, or smoke during work.	Give plenty of water to drink. Rest.

SPILLAGE DISPOSAL	STORAGE	PACKAGING & LABELLING
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Wash away remainder with plenty of water.	Separated from incompatible materials, (see chemical dangers).	R: S:

SEE IMPORTANT INFORMATION ON BACK

ICSC: 0595

Prepared in the context of cooperation between the International Programme on Chemical Safety & the Commission of the European Communities (C) IPCS CEC 2001. No modifications to the International version have been made except to add the OSHA PELs, NIOSH RELs and NIOSH IDLH values.

International Chemical Safety Cards

UREA

ICSC: 0595

IMPORTANT DATA		
	PHYSICAL STATE; APPEARANCE: WHITE CRYSTALS , WITH CHARACTERISTIC ODOUR. **PHYSICAL DANGERS:** **CHEMICAL DANGERS:** The substance decomposes on heating above melting point producing toxic gases. Reacts violently with strong oxidants, nitrites, inorganic chlorides, chlorites and perchlorates causing fire and explosion hazard. **OCCUPATIONAL EXPOSURE LIMITS:** TLV not established.	**ROUTES OF EXPOSURE:** The substance can be absorbed into the body by inhalation of its aerosol and by ingestion. **INHALATION RISK:** Evaporation at 20°C is negligible; a nuisance-causing concentration of airborne particles can, however, be reached quickly if powdered. **EFFECTS OF SHORT-TERM EXPOSURE:** The substance irritates the eyes, the skin and the respiratory tract. **EFFECTS OF LONG-TERM OR REPEATED EXPOSURE:** Repeated or prolonged contact with skin may cause dermatitis.
PHYSICAL PROPERTIES	Melting point: 132.7-135°C Density: 1.32	Solubility in water: miscible Octanol/water partition coefficient as log Pow: -3.00 to -1.54
ENVIRONMENTAL DATA		

NOTES

Temperature of decomposition unknown in literature.

ADDITIONAL INFORMATION

ICSC: 0595 **UREA**

EPA
United States
Environmental Protection
Agency

Office of Prevention, Pesticides,
and Toxic Substances

MEMORANDUM

PC Code: 085702

DATE: October 22, 2001

SUBJECT: Review of Urea, as an Active and Inert Ingredient

TO: Kathryn Boyle
Minor Use, Inerts and Emergency Response Branch
Registration Division (7505C)

Pauline Wagner
Reregistration Branch II
Health Effects Division (7509C)

FROM: Ibrahim Abdel-Saheb, Agronomist
Environmental Risk Branch II
Environmental Fate and Effects Division (7507C)

PEER REVIEW: Sid Abel, Environmental Scientist
ERB II/EFED (7507C)

THROUGH: Tom Bailey, Branch Chief
ERB II/EFED (7507C)

This memorandum addresses (1) the TRED (Report on FQPA Tolerance Reassessment Progress and Interim Risk Management Decisions) for the inert ingredient urea in formulation (CAS 57-13-6).

Introduction

Urea is an inert that is added to pesticide formulations. EFED was not provided with name(s) of active ingredients that are formulated with urea nor the amounts that may be found in formulations. Urea solution reduces the ice-nucleating activity of ice-nucleating bacteria which are naturally present on leaf surfaces.

Tier I estimated environmental concentrations for urea used on terrestrial crops and estimated maximum applications to avoid exceeding terrestrial and aquatic toxicity levels. The FQPA Index Reservoir Screening Tool (FIRST)[1] was used to estimate drinking water concentrations and the GENERIC Estimated Environmental Concentration (GENEEC 2.0)[2] model was used to estimate the surface water concentrations for urea to establish risk to aquatic organisms. The SCI-GROW[3] model was used to estimate groundwater drinking water concentrations. ELL-FATE model is used to estimate risk to bird and mammals.

The Food and Drug Administration (FDA) has affirmed that this chemical is generally recognized as safe (GRAS) as a direct human food ingredient.

Conclusions

The Use of urea as an inert ingredient is not expected to cause acute risk to freshwater fish and invertebrates, and birds when applied at 12.5 lb/A. Toxicity data are not available to assess chronic risk to freshwater organisms, acute and chronic risks to estuarine/marine organisms, and chronic risks to terrestrial organisms.

Table 1. Estimated environmental concentrations (ppb) of urea in surface and groundwater.

Scenario	peak	long term average	use(s) modeled	PCA
Surface water (FIRST)	53.9	0.107	1 application @ 1 lb/acre	0.87
Surface water (GENEEC)	33.2	0.37	1 application @ 1 lb/acre	
Groundwater	0.002		1 application @ 1 lb/acre	

Environmental Fate

EFED has no fate data for Urea. Information on the environmental fate was found in previous EFED reviews and the open literature (http://www.toxnet.nlm.nih.gov October 2001).

Available data from literature reviews shows that urea degrades rapidly in most soils[4-6]. In general, urea is rapidly hydrolyzed to ammonium through soil urease activity. In various soils, complete hydrolysis may occur completely within 24 hrs[4], however, the rate of hydrolysis can be much slower depending upon soil type, moisture content, and urea formulation. For example, increasing the pellet size of urea fertilitizers can decrease the urea decomposition rate from days to weeks. Soil adsorption studies have demonstrated that urea adsorbs very weakly to soil[7]; therefore, leaching is possible. Ultimate urea degradation produces ammonia and CO_2 as volatile products[8].

Biodegradation is expected to be the major fate process in the aquatic environment. Various screening studies have demonstrated that urea can biodegrade readily[9-13] with the release of CO_2 and ammonia. The rate of biodegradation generally decreases with decreasing temperatures[12]; under cold winter-like conditions, biodegradation may be relatively slow (0-6% per day)[12]. The presence of naturally-occurring phytoplankton increases the degradation rate[10,13] because phytoplankton use urea as a nitrogen source[10] and because urea is decomposed by phytoplankton photosynthesis[13]. In phytoplankton-rich waters, degradation occurs much faster in sunlight than in the dark[13].

Abiotic hydrolysis of urea occurs very slowly in relation to biotic hydrolysis[14]. Abiotic hydrolysis yields ammonium carbamate which decomposes to form CO_2 and ammonia[14]; the enzyme urease catalyzes urea hydrolysis.

In one photodegradation study using a silica gel adsorbent[9] only 0.2% of applied urea photomineralized after a 17-hr irradiation with a UV lamp (>290 nm).

The adsorption of urea was measured in six different British soils with organic carbon contents ranging from 1.76 to 36.5%. No adsorption was measurable in five of the soils[15], in the sixth soil (36.5% organic carbon), a K_{OC} of 8 can be determined from the measured Freundlich isotherm[16].

Water Resources

-Surface Water

Monitoring

At the present time, the EFED has no monitoring data on the concentrations of urea in surface water.

Modeling

Surface water concentration estimates were modeled for the use of urea as an inert using FIRST and GENEEC Tier I models. The input parameters used in simulations are shown in Tables 2 and 3.

Table 2. Urea input parameters for FIRST.

Parameter	calculations/value	source
Crop name	N/A	
application rate (lb/acre)	1	
interval between applic. (day)	N/A	
Max No. application	1	
PCA factor (decimal)	0.87 (default)	Effland et al[17] (2000).
Koc (mL/g)	8	Hance (1965).
soil aerobic met. $t_{1/2}$ (d)	1 X 3	Scheunert I. (1987); FIRST User Manual.
pesticide to be wetted-in ?	No	EPA Reg. Lable No. 688915
method of application	aerial	EPA Reg. Lable No. 688915.
solubility (mg/L)	5.45×10^5	Yalkowsky S.H. (1989)[18].
aerobic aquatic met. $t_{1/2}$ (d)	0.042 (assumed to be 1 hour: readily degraded)	Freitag D. (1985).
hydrolysis (pH 7) $t_{1/2}$ (d)	1	Sankhayan et al. (1976).
aqueous photolysis $t_{1/2}$ (d)	stable (0.2% < degraded after 17 hours of radiation)	Freitag et al. (1985).

Table 3. Urea input parameters for GENEEC 2.0 modeling.

Parameter	calculations/value	source
Crop name	N/A	
application rate (lb/acre)	1	
interval between applic. (day)	N/A	
Max No. application	1	
Koc (mL/g)	8	Hance (1965).
soil aerobic met. $t_{1/2}$ (d)	1 X 3	Scheunert I. (1987); FIRST User Manual.
pesticide to be wetted-in ?	No	EPA Reg. Lable No. 688915
method of application	aerial	EPA Reg. Lable No. 688915.
Aerial droplet size distribution	fine to medium (default)	GENEEC Users Manual.
solubility (mg/L)	5.45×10^5	Yalkowsky (1989).
aerobic aquatic met. $t_{1/2}$ (d)	0.042 (assumed to be 1 hour: readily degraded)	Freitag (1985).
hydrolysis (pH 7) $t_{1/2}$ (d)	1	Sankhayan and Shukla (1976).
aqueous photolysis $t_{1/2}$ (d)	stable (0.2% < degraded after 17 hours of radiation)	Freitag (1985).

Groundwater

Monitoring

EFED has no monitoring data on the concentrations of urea in groundwater.

Modeling

The SCI-GROW model was used to estimate potential groundwater concentrations. SCI-GROW is a screening model based on a regression approach which relates the concentrations found in ground water in Prospective Ground Water studies to aerobic soil metabolism rate and soil-water partitioning properties of the chemical.

The input and output files used in SCI-GROW are shown in Appendix I.

Surface Water Ecological Exposure

To determine ecological risks from urea as an inert ingredient, estimated environmental concentrations (EECs) were generated based on an application of 1 lb/A. Results are reported in Table 4.

Table 4. Tier I upper tenth percentile EECs in Surface Water (GENEEC 2.0)

Method of Application	Application Rate (lbs/A)	Maximum (ppb)
Aerial	1	33.2

Ecological Toxicity

The following is a summary of the available ecological toxicity data submitted to the agency:

Urea: Avian Acute Oral Toxicity study with the Upland game bird (Bobwhite Quail). 1986; J. Grimes, MRID #40710801.

LD_{50}: >2250 mg/kg, CORE; Urea is practically non-toxic to Bobwhite Quail.

Urea: A Dietary LC50 Study with the Mallard Duck and Bobwhite Quail: 1986; J. Grimes, MRID #40410701, and MRID #40710901.

LC_{50} >5620 mg/kg; CORE. Urea is practically non-toxic to Mallard Duck and Bobwhite Quail.

Urea: A 96-Hour Flow-Through Acute Toxicity Test with the Bluegill Sunfish; 1986; J. Bowman, MRID# 4071401.

Urea: A 96-Hour Flow-Through Acute Toxicity Test with the Rainbow Trout; 1986; J. Bowman, MRID# 40710601.

LC_{50}: >1000 mg/L 95% C.I. CORE Urea is practically non-toxic to Bluegill Sunfish, and Rainbow Trout .

Urea: A 48-Hour Flow-through Acute Toxicity Test with the

Cladoceran (Daphnia magna); 1986; MRID# 40710501.

$LC_{50:}$ >1000 mg/L (48-hour) 95% C.I. CORE Urea is to practically non-toxic daphnia.

Ecological Risks

Aquatic Organisms

The toxicity data indicate that urea is non toxic to aquatic organisms. Risk to aquatic organisms are determined based on risk quotient (RQ) calculations. Risk quotients are a function of the EEC and the toxicity endpoints. The RQ is compared to the level of concern (LOC) to determine risk. Based upon the available data and calculated risk quotients, exposure to urea at 1 lb/A does not exceed the acute LOC for risk to freshwater fish and invertebrates (Table 5). To determine the maximum application rate that can be applied and not cause an acute risk, the LOC for endangered aquatic species (0.05) was divided by the RQ for both freshwater fish and invertebrates. Based on this calculation and confirmatory GENEEC runs (see Attachment), EFED does not expect acute risk to freshwater fish and invertebrates at application rates of up to 12.5 lb ai/A.

Toxicity data are not available to assess chronic risk to freshwater organisms or acute and chronic risks to estuarine/marine organisms.

Table 5. Acute Toxicity of urea to Freshwater Aquatic Organisms (based on application rate of 1 lb/A).

Organism	Exposure Type	Most Sensitive Species	Toxicity (ppm)	EEC (ppm)[1]	Risk Quotient (EEC/Toxicity)
Freshwater Fish	Acute	Rainbow trout	LC_{50}= 1000	0.03	< 0.0001
Freshwater Invertebrates	Acute	*Daphnia magna*	EC_{50}= 1000	0.03	< 0.0001

[1] Maximum EEC generated using the GENEEC 2.0 model.

Terrestrial Organisms

The toxicity data indicate that urea is practically non-toxic to birds. For pesticides applied as a nongranular product (e.g., liquid, dust), the risk quotient (RQ) is a function of the estimated environmental concentrations (EECs) on food items following product application and the LC_{50} values. The RQ is compared to the level of concern (LOC) to determine risk. The RQ values indicate that use of urea at 1 lb/A does not exceed the acute level of concern for terrestrial organisms (Table 5). To determine the maximum application rate that can be applied and not cause an acute risk, the LOC for acute risk to terrestrial organisms (0.5) was divided by the RQ for birds. Based on this calculation and confirmatory EllFate runs (see Attachment), EFED does not expect risk to birds on an acute basis at application rates $\leq$12.5 lb/A.

Chronic risks to terrestrial organisms could not be determined because toxicity data are not available.

Table 5. Acute Toxicity of urea to Terrestrial Wildlife.

Animal Group	Exposure Type	Most Sensitive Species	Toxicity (mg/kg)	EEC (ppm)[1]	Risk Quotient
Birds	Acute	Mallard	LD_{50} = 5620	240	0.04

[1] The highest terrestrial residue anticipated. RQs were calculated using ELLFate model.

Terrestrial and Aquatic Plants

Data on the effects of urea on nontarget plants are not available. EFED does not expect risk to plants from use as an inert ingredient because review of the registered uses indicates low potential for exposure.

Uncertainties .

The model FIRST is designed to yield concentration values which exceed those predicted by the linked EPA PRZM and EXAMS models for all but the most extreme sites, application patterns and environmental fate properties. PRZM/EXAMS predictions may exceed FIRST predictions under the following circumstances:

(1) Applications to crops in managed environments known to produce excessive runoff (e.g. crops grown over plastic mulch).

(2) Applications at sites with hydrologic group D soils which also receive excessively high rainfall (e.g. EFED sweet potato scenario in southern Louisiana).

(3) Multiple applications over a window of 30 days or longer in exceptionally high rainfall areas (e.g. far southeastern US).

In each of these cases, FIRST will exceed PRZM/ EXAMS estimated peak concentrations values, but not always the annual average concentration values. Even then PRZM/EXAMS would not be expected to exceed the FIRST values by more than a factor of 2.

(4) For applications of chemicals with half-life values of 5 days or less at exceptionally high runoff sites the PRZM/EXAMS concentrations values may exceed both the FIRST peak and annual average values by a factor of 2. Allowing these few exceedences for extreme conditions makes FIRST a more reasonable predictive tool for the rest of the country.

For urea, the above situations are not likely to apply, thus, we would expect FIRST estimates to exceed the Tier 2 estimates.

The SCI-GROW model (Screening Concentrations in Ground Water) is used for estimating concentrations of pesticides in ground water under "maximum loading" conditions. SCI-GROW provides a screening concentration, an estimate of likely ground water concentrations if the pesticide is used at the maximum allowed label rate in areas with ground water exceptionally vulnerable to contamination. In most cases, a majority of the use area will have ground water that is less vulnerable to contamination than the areas used to derive the SCI-GROW estimate.

The environmental fate and ecological effects data used in this assessment were supplemental (i.e., the studies were not conducted following EFED guidelines). Therefore, EFED can not

conclude that the data were collected in a manner consistent with the Agency's guideline requirements.

Inert ingredients can enhance the toxicity of herbicide active ingredients to nontarget plants; therefore, this assessment may significantly underestimate the potential for adverse effects to nontarget plants. However, at this time, EFED is not aware of which formulated products will include urea as an inert.

Another area of uncertainty is the estimate of how great an application rate will exceed. While in most cases variability and slope may not matter, but we are assuming a positive correlation of application rate and effect (toxicity). So there may not be a direct positive correlation.

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APPENDIX I

FIRST output file

RUN No. 1 FOR urea ON * INPUT VALUES *

RATE (#/AC) ONE(MULT)	No.APPS & INTERVAL	SOIL Koc	SOLUBIL (PPM)	APPL TYPE (%DRIFT)	%CROPPED AREA	INCORP (IN)
1.000(1.000)	1 1	8.0	*******	AERIAL(16.0)	87.0	.0

FIELD AND RESERVOIR HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (RESERVOIR)	PHOTOLYSIS (RES.-EFF)	METABOLIC (RESER.)	COMBINED (RESER.)
3.00	2	N/A	.00- .00	.04	.04

UNTREATED WATER CONC (MICROGRAMS/LITER (PPB)) Ver 1.0 AUG 1, 2001

PEAK DAY (ACUTE) CONCENTRATION	ANNUAL AVERAGE (CHRONIC) CONCENTRATION
53.916	.107

GENEEC 2.0 input and output files

RUN No. 1 FOR urea ON * INPUT VALUES *

RATE (#/AC) ONE(MULT)	No.APPS & INTERVAL	SOIL Koc	SOLUBIL (PPM)	APPL TYPE (%DRIFT)	NO-SPRAY (FT)	INCORP (IN)
1.000(1.000)	1 1	8.0	*******	AERL_B(13.0)	.0	.0

FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (POND)	PHOTOLYSIS (POND-EFF)	METABOLIC (POND)	COMBINED (POND)
3.00	2	N/A	.00- .00	.04	.04

GENERIC EECs (IN MICROGRAMS/LITER (PPB)) Version 2.0 Aug 1, 2001

PEAK GEEC	MAX 4 DAY AVG GEEC	MAX 21 DAY AVG GEEC	MAX 60 DAY AVG GEEC	MAX 90 DAY AVG GEEC
33.17	8.29	1.58	.55	.37

SCI-GROW input and output

RUN No. 1 FOR urea INPUT VALUES

APPL (#/AC) RATE	APPL. NO.	URATE (#/AC/YR)	SOIL KOC	SOIL AEROBIC METABOLISM (DAYS)
1.000	1	1.000	8.0	1.0

GROUND-WATER SCREENING CONCENTRATIONS IN PPB

.001699

A= .167 B= 13.000 C= -.778 D= 1.114 RILP= -.867
F= -2.770 G= .002 URATE= 1.000 GWSC= .001699

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

November 28, 2001

SUBJECT: **Urea (Carbamide):** HED Science Assessment for Tolerance Reassessment Eligibility Decision (TRED) for the Frost Protectant Pesticide, Urea.

EPA ID NO: PC Code: 085702 PRAT Case Number: 819300
DP Barcode: D274728 Reregistration Case Number: 4096
Submission Number: S596788 CAS Registry Number: 57-13-6

FROM: Becky Daiss, Environmental Health Scientist
Reregistration Branch IV
Health Effects Division (7509C)
and
Michelle M. Centra, Pharmacologist
Reregistration Branch III
Health Effects Division (7509C)

THRU: Susan Hummel, Branch Senior Scientist
Reregistration Branch IV
Health Effects Division (7509C)

TO: Joseph Nevola, Chemical Review Manager
Daniel Helfgott, Acting Branch Chief
Special Review Branch
Special Review and Reregistration Division (7508W)

Attached is the Health Effects Division's (HED's) science assessment supporting issuance of a Tolerance Reassessment Eligibility Decision (TRED) for urea. This document updates the tolerance exemption for this active ingredient issued by EPA in 1995. Supporting documents for the Urea TRED include:

- Toxicology Chapter of the TRED for the Pesticide, Urea. M. Centra (10/2/01)
- Tier 1 Drinking Water Estimated Environmental Concentrations for Urea. I Abdel-Saheb (10/11/01)

1. EXECUTIVE SUMMARY

1.1 Purpose

In 1995, the EPA granted a permanent exemption from the requirement of a tolerance for residues of the frost protectant urea in or on various raw agricultural commodities. Since this decision was made prior to the passage of the Food Quality Protection Act (FQPA, 1996), a revised hazard characterization that includes special sensitivity to infants and children is required for the urea Tolerance Reassessment Eligibility Decision (TRED) document.

1.2 Use Profile

Urea was registered by EPA in1995 for use as a frost protectant pesticide under the trade name Enfrost. Enfrost is a 43% liquid formulation of urea that can be applied commercially to a wide variety of field crops, vegetables, fruit trees and ornamentals to reduce frost damage. There are currently no residential uses for urea as a pesticide product. Enfrost is the only currently registered pesticide product containing urea as an active ingredient. Enfrost provides frost protection by modifying the protein produced by ice-nucleating bacteria. In addition to its use as frost protectant, several million tons of urea are produced annually for use in fertilizer and as an animal feed supplement. Urea is also use in the manufacture of dyes, fire retardant paints, plastisizers, and stabilizers for explosives.

1.3 Regulatory History

The active ingredient, urea, was affirmed to be Generally Recognized as Safe (GRAS) as a direct food ingredient by the Food and Drug Administration (FDA) in 1983 (21 Code of Federal Regulations (CFR) §184.1923). EPA has also listed urea as an inert ingredient exempted from the requirement of a tolerance when applied (as an inert or occasionally active ingredient) in pesticide formulations to: 1) growing crops or raw agricultural commodities after harvest as a stabilizer/inhibitor (40 CFR §180.1001(c)); 2) growing crops only as an adjuvant/intensifier for herbicides (40 CFR §180.1001(d)); or 3) animals as a stabilizer/inhibitor (40 CFR §180.1001(e)). Under §180.1001(a), an exemption from tolerance is granted when it appears that the total quantity of the pesticide or chemical in or on all raw agricultural commodities for which it is useful under current or proposed conditions of use will involve no hazard to the public health.

In 1995, in response to a request from Unocal Corp., EPA established a permanent exemption from the requirement of a tolerance for residues of urea used as a frost protectant in or on various agricultural commodities (40 CFR § 180.1117). EPA's tolerance exemption for the frost protectant urea was based on the following considerations. The primary basis was a series of toxicity studies performed on the product "Enfrost" which contains 43% urea; a review of these studies indicated that the product has a low toxicity to animals when administered via oral, dermal and inhalation routes of

exposure. EPA also cited previous regulatory actions to substantiate its decision, including FDA's designation of urea as a GRAS food ingredient and EPA's listing of urea as an inert ingredient in certain pesticide formulations with urea concentrations similar to those in the frost protectant. Finally, the Agency cited the natural occurrence of urea in crops and plants and in human and animal tissues and body fluids (humans excrete about 25 grams per day) as further basis for granting a tolerance exemption.

The 1995 rule established an exemption from the requirement of a tolerance for residues of urea when used before harvest as a frost protectant in or on the following raw agricultural commodities: alfalfa, almonds, apples, apricots, artichokes, asparagus, avocados, beans, bell peppers, blackberries, blueberries, broccoli, Brussels sprouts, boysenberries, caneberries, canola, cantaloupe, carrots, cauliflower, casaba, celery, cherries, chili peppers, Chinese cabbage (bok choy, napa), cooking peppers, corn, cotton, crenshaw, cucumbers, figs, grapefruit, grapes, honeydew melon, hops, kiwifruit, kohlrabi, lemons, lentils, lettuce, limes, macadamia nuts, musk melon, nectarines, olives, onions, oranges, peaches, pears, peanuts, peas, persian melon, pistachios, plums, potatoes, pumpkin, prunes, radish, raspberries, rice, safflower, sorghum, spinach, spinach (New Zealand), squash (winter and summer), strawberries, sugar beets, sunflower, sweet pepper, table beets, tangerines, tomatoes, walnuts, watermelon, and zucchini.

Enfrost was transferred from Unocal Corp to the Entek Corporation in 1995. Enfrost has not been actively produced or sold by Entek since the company acquired the registration for the product in 1995. However, Entek wishes to maintain active registration of Enfrost for potential future production and use. Therefore, as required by FQPA, EPA is now reassessing the 1995 exemption to determine whether infants and children exhibit enhanced sensitivity from exposure to the frost protectant urea..

1.4 Summary of Science Assessment Findings

From the available animal studies and human exposure data, HED has concluded that urea exhibits a low toxicity and exposures to urea used as a frost protectant present no unreasonable adverse human health effects. HED's analysis of extensive toxicology data in numerous species, including man, supports the 1995 decision to grant a permanent exemption from the requirement of a tolerance for residues of the frost protectant when used before harvest in the production of the raw agricultural commodities. Regarding FQPA, the data provide no indication of increased sensitivity of infants and children from exposure to urea. Therefore, the FQPA 10x factor to account for enhanced sensitivity of infants and children can be removed.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Chemical Name: Carbamide
Chemical Structure:

Empirical Formula:	$CO(NH_2)_2$
Molecular Weight:	60.66
Cas Registry No.:	57-13-6
PC Code:	084701
Trade Name:	Enfrost

Technical urea, $CO(NH_2)_2$ is the diamide of cargonic acid. It is a white, odorless, hygroscopic, crystalline solid with a melting point of 134-136 C and a density of 1.12 g/mL at 20 C. It is stable in the pure solid form and slowly hydrolyzes in water solutions to form carbon dioxide and ammonia. On standing, it may gradually develop a slight ammoniacal odor. Urea is highly soluble in water, glycerol and hot alcohol, but almost insoluble in chloroform and ether.

3.0 HAZARD CHARACTERIZATION

With the exception of six acute toxicity studies submitted by the registrant for the Enfrost formulation, the urea toxicity data base is comprised of the available literature data. These data are considered by HED's Toxicology Science Advisory Committee (TOX SAC) to be sufficient to assess the potential hazard to humans, including special sensitivity of infants and children. (D274740, M. Centra, 10/2/01)

3.1 Hazard Profile

3.1.1 Acute Toxicity

The six acute toxicological studies submitted by the registrant were performed on the end-use product "Enfrost" which contains 43.5% urea. Acute toxicity data from these studies are presented in Table I. A review of these data indicates that the frost protectant has a low toxicity to animals when administered via the oral, dermal or inhalation routes of exposure (Toxicity Categories III and IV). The lethal dose (LD_{50}) for an oral exposure in rats was 14,500 mg/kg which would be equivalent to a two pound ingestion of urea by an average size adult human. The acute toxicity of urea has also been evaluated in rabbits, cattle, sheep, dogs, and guinea pigs by oral, subcutaneous and intravenous exposures.

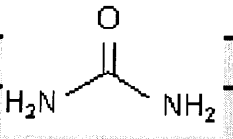

TABLE 1. ACUTE TOXICITY		PROFILE FOR ENFROST (Urea, 43% a.i.)			
Guideline	Study Type (Date)	(D	MRID	Results	Tox.Cat.
870.1100	Acute Oral-Rat (5/11/88)		40733304	*LD_{50} > 5000 mg/kg*	IV
870.1200	Acute Dermal-Rabbit (5/11/88)		40733305	LD_{50} > 2000 mg/kg	III

870.1300	Acute Inhalation-Rat (5/11/88)	40733301	LC_{50} > 4.8 mg/L	III
870.2400	Primary Eye Irritation-Rabbit (5/11/88)	40733302	Slight eye irritant	IV
870.2500	Primary Dermal irritation-Rabbit (5/11/88)	40733306	Slight dermal irritant	IV
870.2600	Dermal Sensitization-Guinea pig (5/11/88)	40733303	Non sensitizer	N/A

3.1.2 Data Waivers for Additional Toxicological Studies

In 1989 EPA granted data waivers for submission of additional toxicity studies for the use of urea as a frost protectant on food crops (Memoranda: Ritter to Wilson, dated 2/23/89 and Stolzenberg to Rossi, dated 6/13/89). HED's TOX SAC met on March 22, 2001 to consider a request to reaffirm the data waivers. The TOX SAC examined the 1978 Monograph on urea by the FDA Select Committee on GRAS Substances, the HED One Liners, and the 21 CFR Citation 184.1923, which affirms urea as GRAS as a direct human food ingredient. It was noted that the FDA GRAS affirmation was without limitations other than the current good manufacturing practice and that there are no prior sanctions for this chemical. Based on the information presented to the TOX SAC, the Council voted unanimously to affirm the toxicology data waivers and to recommend that no further toxicity studies be required. The affirmed toxicology data waivers are listed in Table 3. A summary of literature studies evaluated for this analysis is provided below.

TABLE 3. HED AFFIRMED TOXICOLOGY DATA WAIVERS FOR UREA

Study Type	Guideline Number
90 Day Oral Feeding Study in Rodents	870.3100
90 Day Oral Feeding Study in Nonrodents	870.3150
21 Day Dermal Toxicity Study	870.3200
90 Day Dermal Toxicity Study	870.3250
90 Day Inhalation Toxicity Study	870.3465
Chronic Feeding Studies in Rodents and Nonrodents	870.4100
Carcinogencity Studies in Two Mammalian Species	870.4200; 870.4300
Developmental Toxicity Studies in Rodents and Nonrodents	870.3700
Multigeneration Reproduction Study in Rodents	870.3800
Battery of Mutagenicity Studies	870.5100; 870.5300; 870.5385; 870.5375; 870.5395
General Metabolism Study	870.7485

3.1.3 Subchronic Toxicity

Urea produced no severe toxicity in dogs injected subcutaneously with 30-40 mL/kg/day of 10% urea solution for 45 days. With plasma levels ranging from 200-700 mg/100 mL (10-30 fold above normal), the only clinical symptoms observed were drowsiness and diuresis. Necropsy indicated no adverse organ pathology.

Rats fed rations containing 2 to 25 percent urea (2- 25 g/kg body weight daily) for periods up to 190 days showed systemic toxicities. Rats receiving14 percent urea in their diet and deprived of water died within a few days. (The lethal dose (LD_{50}) for an oral exposure in rats was 14.5 g/kg (14% urea) which would be equivalent to a two pound ingestion of urea by an average size adult human.) Animals allowed water survived for 20 to 76 days when fed the 20 percent urea supplement and 12 days when fed the 25 percent urea supplement. Weight loss and suppression of sexual function were observed at the lower levels of urea ingestion. Anemia and renal hypertrophy were also observed in some these animals. It is difficult to interpret these findings, however, because of the number of rats tested per treatment group was small (often 1 to 3) and no data were given on the actual food intake. The extreme weight loss observed in rats suggests that starvation was most likely the result of decreased palatability of the animal feed containing urea.

Clinical data on humans indicates that uremia (severe gastrointestinal, cardiovascular, mental and neurologic toxicity) does not occur even at relatively high blood concentrations of urea. Severe forms of uremia are not manifested in dialysis patients with blood urea concentrations above 300 mg/100 mL. (Normal human blood plasma concentration ranges from 20 to 30 mg/100 mL.) High blood concentrations of 181 to 600 mg urea/100 mL were maintained by intermittent dialysis in three patients suffering from advanced renal failure for periods of 7 to 90 days. When the urea concentration was kept below 300 mg/100 mL, no adverse effects were noted although this level is about 10 times greater than normal. Concentrations above 300 mg per 100 mL were associated with malaise, vomiting, bleeding tendency and headache. However, the more severe uremia were not observed. In eight patients with sickle cell disease, 40 to120 g (0.6 to 2.0 g/kg) urea was administered orally in divided doses each day for periods of 3 weeks to 9 months. The blood urea concentrations of the patients approximately doubled during the test periods. While the patients were ingesting urea, there was a slight decrease in blood volume, probably resulting from the chronic osmotic diuresis induced by the urea. The most obvious effects of the urea intake were thirst and diuresis and two patients were unable to complete the study because of nausea and vomiting.

3.1.4 Chronic Toxicity and Carcinogenicity

No toxicities from urea have been reported in humans after chronic exposures. Animal studies provide no evidence of adverse chronic or carcinogenic effects. One year feeding studies in male and female C57B1/6 mice and Fisher 344 rats reported no evidence of treatment-related cancer at doses up to 4.5% of the diet. Slight increases in the incidence of lymphomas occurring in mid-dose female mice, as well as interstitial cell adenomas of the testes occurring in high-dose male rats, were not considered biologically significant in this study. Studies in the susceptible mouse strain (Strain A) also indicate no evidence of urea tumorigenicity. Doses of 10 to 50 mg urea (0.5 - 2.5 g/kg) were injected subcutaneously in Strain A mice on a weekly basis over a period of 11 months. No tumors were evident after 15 months. Weekly intraperitoneal injections of 0.4 g/kg urea administered over a 13 week interval produced no lung adenomas in the mouse strain A.

3.1.5 Developmental and Reproductive Toxicity

In a developmental toxicity study, pregnant Wistar rats receiving a twice-daily dose of 25 g/kg urea by gastric intubation for 14 days produced healthy offspring with no reported evidence of teratogenic effects. A study of pregnant cows that had recovered from urea toxicity, exhibited no effects on reproductive performance nor were the calves affected. These animals were treated acutely with urea (0.44 g/kg) and kept under regular management for 12 months. There was no effect on the number of calves born, birth weight, weaning weight of calves, or rebreeding performance was.

Urea has also been evaluated in monkeys and humans for its ability to induce abortion. In humans, intra-amniotic injection of 80 grams "Ureaphil"/210 mL in 5% dextrose was effective in inducing abortion at 14 weeks without adverse effects to the mother. The mode of action is similar to the hyperosmolar effect of large doses of hypertonic saline and dextrose where a highly localized hyperosmolar solute passes from the amniotic fluid into the fetus causing death. However, such high intrauterine exposures would not occur from environmental exposure to urea. Urea is currently classified by FDA in category C for therapeutic use, "Safety for use during pregnancy has not been established".

3.1.6 Mutagenicity

Several *in vitro* studies have reported that urea is associated with chromosomal aberrations in human leukocytes, hamster fibroblasts and lung cells. All of these studies were conducted with urea concentrations ranging from 50 mM (millimoles) to 8 M. At physiological levels (1mM), urea causes no chromosome effects. However, at concentrations of urea greater than or equal to 50mM, the production of chromosome fragmentation is probably due to a non-specific, hyperosmolarity effect on cell division and not a direct effect of the urea molecule. Sodium phosphate, another normal body fluid constituent also produces chromosomal damage at 50 mM concentrations.

3.1.7 Absorption, Metabolism, and Excretion

Urea is extremely soluble in water and oral doses are rapidly absorbed and distributed through the most body tissues and fluids, in proportion to their water content. The penetration of urea into fatty tissue such as the brain is lower than for most other tissues. Also, the colon has been reported to be relatively impermeable to urea. A study of pregnant rats injected subcutaneously with urea indicates that urea penetrates rapidly into maternal tissues and organs and also readily passes through the placenta. The absorption of urea is very rapid in humans also. In one study, blood urea concentration was generally found to peak within 30 minutes after oral administration.

Urea is a normal human body constituent and is constantly being produced during amino acid

and protein metabolism. Urea is formed metabolically through a cyclic mechanism. Free ammonia arising from the oxidative deamination of glutamate in liver mitochondria combines with carbon dioxide to form carbamoyl phosphate. The carbamoyl group is transferred to ornithine to form citrilluline, which in turn reacts with aspartate to produce arginosuccinate. This is hydrolysed enzymatically to liberate free arginine and fumarate. The fumarate returns to the pool of tricarboxylic acid cycle intermediates, while the arginine is cleaved by arginase to produce urea and ornithine. A 70 kg adult excretes urea in the amount of 25-30 g/day (350-420 mg/kg/day). The ability of the kidney to remove urea from the blood provides one method of assessing renal function. Genetic deficiency of any of the enzymes required in the urea cycle produces protein intolerance, elevated amounts of blood ammonia, metabolic disturbances, neurological symptoms and brain damage.

Urea has long been used as a dietary supplement for ruminants as a source of nitrogen for protein synthesis. Bacterial action in the gastrointestinal tract, particularly in the colon, produces ammonia which is absorbed and mixed with the metabolic pool of nitrogen. Urea nitrogen can also contribute part of the amino acid requirements in humans. Utilization of urea nitrogen has been demonstrated both in malnourished children and adults.

3.1.8 Therapeutic Uses

Urea is approved for several therapeutic uses in humans with relatively few toxicities. Urea is used primarily as an osmotic agent for inducing diuresis and reducing intraoccular and intracranial pressure (Ureaphil, 30% urea solution). Intravenous doses of 1-1.5 g/kg urea (30% urea solution) are considered optimal for neurosurgical procedures with no adverse effects. Urea has also been used as a topical anesthetic for the treatment of mouth and throat inflammation (10-15% urea gel, liquid or solution), to debride necrotic and infected tissues, i.e. fingernails and toenails (2-40% formulations). It is also used in the treatment of sickle-cell anemia and to ammoniate dentrifices as well as a basic ingredient in the synthesis of medically important compounds such as barbiturates and urethanes.

3.2 FQPA Considerations

The Office of Pesticide Program's Inert Ingrediant Focus Group (IIFG) evaluated the available hazard and exposure data for urea on November 6, 2001. The IIFG concluded that the data provide no indication of increased sensitivity of infants and children from exposure to urea. Therefore, the FQPA 10x factor to account for enhanced sensitivity of infants and children can be removed. (11/6/01 IIFG Decision Memo, C. Boyle & K. Leifer)

3.3 Dose Response Assessment

Establishment of toxicity endpoints for use in risk assessment was not required for urea due to its low intrinsic hazard.

4.0 EXPOSURE ASSESSMENT

Based on the hazard assessment of urea, exposures to this compound resulting from reasonably anticipated patterns of usage present no unreasonable adverse human health effects.
Given the low toxicity of this compound, a more detailed assessment of risks resulting from exposure to urea used as a frost protectant is unnecessary.

5.0 ENVIRONMENTAL FATE AND TRANSPORT

The Environmental Fate and Effects Division (EFED) has no fate data for urea. Available data from literature reviews show that urea degrades rapidly in most soils. In general, it is rapidly hydrolyzed to ammonium through soil urease activity. In various soils, the hydrolysis may near completion within 24 hrs; however, the rate of hydrolysis can be much slower depending upon soil type, moisture content, and urea formulation. Soil adsorption studies have demonstrated that urea adsorbs very weakly to soil; therefore, leaching is possible. Ultimate urea degradation produces ammonia and CO_2 as volatile products. Biodegradation is expected to be the major fate process in the aquatic ecosystem. Various screening studies have demonstrated that urea can biodegrade readily with the release of CO_2 and ammonia. The rate of biodegradation generally decreases with decreasing temperatures; under cold winter-like conditions, biodegradation may be relatively slow (0-6% per day). The presence of naturally-occurring phytoplankton increases the degradation rate because phytoplankton use urea as a nitrogen source and because urea is decomposed by phytoplankton photosynthesis; in phytoplankton-rich waters, degradation occurs much faster in sunlight than in the dark. Abiotic hydrolysis of urea occurs very slowly in relation to biotic hydrolysis. Abiotic hydrolysis yields ammonium carbamate which decomposes to form CO_2 and ammonia; the enzyme urease catalyzes urea hydrolysis. (D277581, Ibrahim Abdel-Saheb, 10/11/01)

At the present time, the EFED has no monitoring data on the concentrations of urea in surface water. EFED did provide Tier I estimated drinking water concentrations for urea use on citrus (D277581). However, because of the low toxicity of urea and the subsequent lack of toxicity endpoints for use in risk assessment, HED did not calculate drinking water levels of comparison (DWLOCs) for urea.

6.0 CONCLUSION - Recommended Exemption from Tolerance Requirement

Based upon reevaluation of existing data, HED believes there is sufficient basis for granting a permanent exemption from the requirement of a tolerance for residues of the frost protectant urea when used before harvest in the production of the raw agricultural commodities currently listed under 40 CFR §180.1117.

Pooler, Bob

From: Nick Stavrakis [nista@otenet.gr]
Sent: Monday, May 05, 2003 1:11 PM
To: Pooler, Bob
Subject: Petition of urea.

Importance: High

Dear sir,

I have sent you by email (nlpetition@usda.gov) at 10/4/2003 a petition for the inclusion of urea in National list. Please confirm me by fax or email if you have received it. It is very important for us to know, because we are in the beginning of a new period for olive crop.

Yours sincerely.
Nick Stavrakis

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urea petition

Dear Dr. Stavrakis,

The NOP has received your petition to include urea onto the National List. Thank you for submitting your petition to the NOP. The current status for your petition is that we have initiated the National List petition review process.

Richard Mathews, the NOP Program Manager, has asked me to ensure you that the NOP will periodically provide you with an update on the status of your petition or, if needed, will request additional information to clarify information in the petition.

Regards,

Bob Pooler

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