Product Information

# DOWEX 66

## Ion Exchange Resin for Sweetener Applications

| Product | Type | Matrix | Functional group |
|---|---|---|---|
| DOWEX* 66 | Weak base anion | Styrene-DVB, macroporous | Tertiary amine |

| Typical Physical and Chemical Properties | | | |
|---|---|---|---|
| Ionic form as produced | | | FB (free base) |
| Total exchange capacity, min.<br>Weak base capacity, min. | | eq/l<br>eq/l | 1.6<br>1.35 |
| Water content | | % | 40 - 50 |
| Bead size distribution<br>Range<br>>1.2 mm<br><0.3 mm | <br>16 mesh<br>50 mesh | <br>mm<br>%<br>% | <br>0.3 - 1.2<br><2<br><3 |
| Total swelling (FB → HCl) | | % | 20 |
| Particle density | | g/ml | 1.04 |
| Shipping weight, approx. | | g/l<br>lbs/ft³ | 640<br>40 |

| Recommended Operating Conditions | |
|---|---|
| Maximum operating temperature (FB form) | 60°C (140°F) |
| pH range | 0-7 |
| Bed depth, min. | 91 cm (3 ft) |
| Flow rates:<br>Service<br>Backwash<br>Regeneration time<br>Displacement rinse<br>Fast rinse (if applicable) | <br>2-4 Bed volumes/hour<br>See figure 1<br>30-45 min.<br>30-45 min.<br>2-10 Bed volumes/hour |
| Total rinse requirement | 4-6 Bed volumes |

BASES

| Regenerants | NaOH† | $Na_2CO_3$ | $NH_4OH$ |
|---|---|---|---|
| Concentration (%) | 4 | 5 | 5 |
| Level, 100% basis*<br>lbs/ft³<br>kg/m³ | <br>5-6<br>80-96 | <br>7-8<br>112-128 | <br>5-6<br>80-96 |
| Temperature, max. | 60°C (140°F) | 60°C (140°F) | 60°C (140°F) |

†Recommended

*Regeneration level may be lower for counter-current regeneration systems.

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# DOWEX
# Ion Exchange Resins

For more information about DOWEX resins,
call Dow Liquid Separations:
North America .....1-800-447-4369
Latin America .....(+55) 11-5188-9345
Europe .....(+31) 20-691-6268
Japan .....(+81) 3-5460-2100
Australia .....(+61) 2-9776-3226
http://www.dow.com/liquidseps

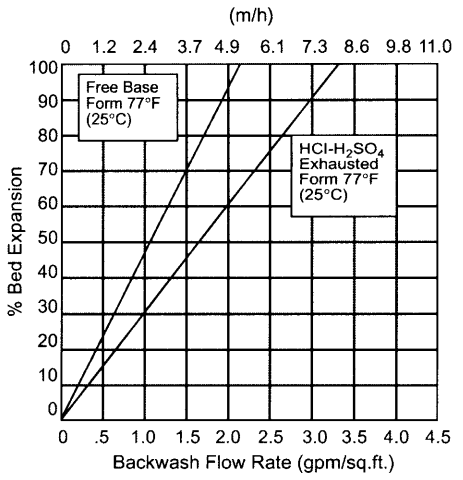
## Typical properties and applications:

DOWEX* 66 resin is a macroporous weak base anion resin for use in the deashing (demineralization) applications. The unique resin matrix provides high operating capacity and excellent mechanical strength.

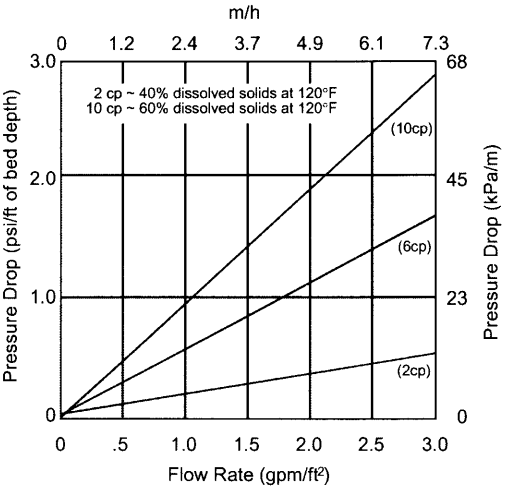
## Packaging

25 liter bags, 5 cubic feet fiber drums or 1 cubic meter super sacks.

### Figure 1. Backwash Expansion Data




### Figure 2. Pressure Drop Data




### For other temperatures use:

$F_T = F_{77°F}$ [1+ 0.008 ($T_{°F}$ -77)], where F ≡ gpm/ft$^2$
$F_T = F_{25°C}$ [1+ 0.008 (1.8$T_{°C}$ - 45)], where F ≡ m/h

### For other temperatures use:

$P_T = P_{20°C}$ / (0.026 $T_{°C}$ + 0.48), where P ≡ bar/m
$P_T = P_{68°F}$ / (0.014 $T_{°F}$ + 0.05), where P ≡ psi/ft

**Warning:** Oxidizing agents such as nitric acid attack organic ion exchange resins under certain conditions. This could lead to anything from slight resin degradation to a violent exothermic reaction (explosion). Before using strong oxidizing agents, consult sources knowledgeable in handling such materials.

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U.S. Food & Drug Administration
Center for Food Safety & Applied Nutrition
**Office of Premarket Approval**
**September 1995**
(Effective June 18, 2001, Office of Premarket Approval is now Office of Food Additive Safety. See updated contact information)

# Estimating Exposure To Direct Food Additives And Chemical Contaminants in the Diet

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## INTRODUCTION

The US Food and Drug Administration (FDA) regulates substances either intentionally added to food to accomplish a proven technical effect or inadvertently added through contamination, processing, or packaging.[1] The premarket approval process for food additives requires an estimate of the *probable* consumer exposure to the additive to determine whether its use or presence in a food at a given concentration is safe. **The intent of this document is to provide an understanding of the database and methodologies used by the Office of Premarket Approval (OPA) in FDA's Center for Food Safety and Applied Nutrition to estimate exposure to food additives and other substances (e.g., chemical contaminants) found in the diet.** This document is primarily directed at petitioners for food additive regulations. Illustrative examples of the calculations that the technical reviewers of OPA's Chemistry Review Branch (CRB)[2] perform to obtain the legally-required estimate of probabl exposure for substances added to food are included. It should also be useful to other parties interested in the means by which exposures to food additives and chemical contaminants can be estimated.

The key determinant in the safety evaluation of a substance found in or added to the diet is the relatio of its probable human exposure to the level at which adverse effects are observed in toxicological studies.[3] Simply, "the dose makes the poison." The implications of this adage as it pertains to food can be illustrated with two clear examples. While "pure" water can be viewed as the safest of foods, excessive intake can lead to a potentially fatal electrolyte imbalance. Conversely, pure concentrated sulfuric acid destroys human tissue, but it is affirmed as "Generally Recognized as Safe" (GRAS) by the FDA in the Code of Federal Regulations (CFR)[4] when used to control pH during the processing of alcoholic beverages or cheeses. Clearly, the use and the dose (i.e., exposure) are overriding considerations when discussing the safety of a component of food.

### Direct vs. Indirect Food Additives

The definition of a food additive in section 201 (s) of the Federal Food, Drug, and Cosmetic Act, as amended (hereinafter referred to as "the Act") refers to substances whose intended use results directly or indirectly in the substance becoming a component of food. The FDA refers to direct food additives as those added to a food to accomplish an intended effect. Indirect additives are those that

unintentionally, though predictably, become components of food. Components of plastic packaging materials that can migrate to food are indirect additives.

The differences between direct and indirect additives are such that different methodologies are necessary to prepare estimates of probable human exposure. It is relatively straightforward to determine how much of a direct additive could be present in any given food. Indirect additives, on the other hand, cannot be treated in a parallel manner due to the great variety of packaging materials (glass, paper, coated papers, plastics, laminates, and adjuvants used in their manufacture), and the great variability in the use of packaged foods. Also, the fact that these additives are not intentionally added to food (which is to say that "use levels" in food cannot be defined), makes direct comparisons with methods used for estimating exposures to direct additives inappropriate.[5]

This document deals only with estimating exposure to direct additives and chemical contaminants. The procedures used to estimate exposure to chemical contaminants in food (including naturally occurring toxicants, such as mycotoxins) are essentially the same as those used for direct additives. Thus, contaminants will be considered in the discussion of direct additive exposure estimation. The procedures discussed herein are equally applicable to color additives, GRAS substances, prior-sanctioned ingredients, and pesticide residues.[6]

**Direct Additives and Chemical Contaminants**

Direct food additives are regulated in 21 CFR 172 (GRAS ingredients are regulated in 21 CFR 182 and 184). Secondary direct additives, a sub-class of direct additives, are primarily processing aids. These materials, which are used to accomplish a technical effect during the processing of food but are not intended to serve a technical function in the finished food, are regulated in 21 CFR 173. Secondar direct food additives are like indirect additives in that only residues of the additive, or its components are typically found in the food. The estimate of daily intake (EDI) for a secondary direct additive, however, is generally calculated in the same manner as those for direct additives and will be considered in this document.

Chemical contaminants are substances that are present in food or food additives either unavoidably or unintentionally. Typically, there are two types of chemical contaminants that are encountered: (1) those present in food additives (generally, from manufacture), and; (2) those present in food itself (du to manufacture, natural, or environmental contamination, e.g., lead, aflatoxin, or polychlorinated biphenyls). The practical difference between estimating exposure for contaminants and additives is th derivation of the concentration of the substance. Contaminant concentrations are usually determined experimentally, while additive concentrations or use levels are proposed by a petitioner[7] for specified uses of a food additive. The different procedures used for estimating exposure to additives and contaminants will be discussed in the remainder of this document, with detailed examples in the last section.

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## SOURCES OF DATA FOR ESTIMATING EXPOSURE

There are a number of sources available to OPA for data used in estimating exposure to substances in





the diet,[8] including:

- Food consumption surveys
- Food/component disappearance figures
- Market basket surveys
- Weights and analyses of foods
- Body burden/excretion measurements

Each of these sources has advantages and limitations. For a number of reasons, including cost and availability, breadth of data, and ease of data manipulation, OPA relies primarily on data taken from food consumption surveys. OPA has not used data from body burden/excretion measurements or weights and analyses of foods for estimating exposure. In the following sections, OPA's use of the data from consumption surveys, disappearance data, and market basket surveys will be outlined.

**Food consumption surveys**

OPA's use of food consumption survey data for estimating exposure to substances in the diet involves the linking of food intakes with independently-determined concentrations of the substances in foods. Because distributions of food intakes are generally available from a food consumption survey, estimates for mean exposure or for any point on the population distribution (e.g., 50th or 90th percentile) are possible.

OPA regularly uses national food consumption surveys to estimate dietary exposure to substances. These surveys measure food intake by one or more methods: 24-hour intake recall, food intake record (also called food diary), and food frequency record or recall. For the first two methods, participants recall or record the amounts and types of each food eaten during the day. For the food frequency methods, participants record or recall only the number of occasions each food was consumed over a time period that may vary from a few days to more than a year.[9] These eating-occasion frequencies are multiplied by an appropriate portion size (based on age-sex considerations) to obtain estimates of the daily food intake. Useful surveys include consumption data for foods eaten both at home and awa from home.

The USDA has surveyed food use by US households since 1936. In the 1960s, the surveys were expanded to include food intake by individuals. Traditionally, these surveys appraised the nutritional adequacy of American diets rather than the safety of food with respect to additives or contaminants. However, the information on food intakes found in the USDA surveys is now frequently used to assess exposure to additives and contaminants.

Marketing research groups in the United States, such as the Market Research Corporation of America (MRCA) and the National Purchase Diary (NPD) have also surveyed the food consumption patterns o individuals and households for the food industry. Surveys of this type are not common throughout the rest of the world, but the World Health Organization (WHO) has emphasized the need for such data i a publication prescribing its guidelines for monitoring intakes of chemical contaminants.[10] A review of food consumption surveys throughout the world was published by the Food and Agriculture Organization (FAO) in 1985.[11]



- must undergo review like all other contaminants.

2 issues:
1) Residues or components of processing aid
2) Contamination - chemical itself - (Resin degradation)

The FASEB report issued by its Life Sciences Research Office in 1988 examined in detail the theory behind the calculation of exposure estimates.[12] This report, prepared for the US FDA, listed several food consumption databases for use in estimating food intakes. These included national food consumption surveys conducted by the US government, such as the USDA's Nationwide Food Consumption Survey (NFCS) and Continuing Survey of Food Intake by Individuals (CSFII), as well as the National Health and Nutrition Examination Survey (NHANES), and commercially sponsored surveys, such as the MRCA Menu Census and the NPD Eating Trends surveys. OPA has historically relied on the USDA's 3-day Nationwide Food Consumption Surveys and the Market Research Corporation of America's Surveys (herein referred to as the MRCA Survey[13]). The USDA 3-day surveys, the CSFII, and the MRCA 14-day surveys are further described below.

*3-Day USDA/NFCS Survey and the CSFII*

Summary reports from the US Department of Agriculture's 3-day Nationwide Food Consumption Survey of 1977-78 were published in 1982 as "Foods Commonly Eaten by Individuals". The survey was repeated during 1987 and 1988, but, due to statistical problems resulting from low response rates in certain sub-populations, the results have not yet been published in summary report form.[14] The information was collected in two steps: the first involved an interviewer-recorded recall of all of the foods consumed during the first day; the second part was 2-day a recall/report completed by the participant. Detailed instructions, including measuring cups, spoons, and a ruler, were given to the participants to aid in accurately reporting their intakes. The participants were selected to avoid geographical bias, and the survey was conducted over a twelve month period to avoid any seasonal bias in eating habits.

The data in the summary reports are presented in tables, each addressing the intake of a broad food class, such as meat and poultry, or an associated sub-class, such as fried chicken. All of the reported intake figures are on an eaters-only[15] basis. The percentage of eaters in each classification is included. The raw data from USDA surveys have been accessible to reviewers at CRB; however, such access, until recently, has not been routine. For many years, the summary report food intake data from the 1977-78 survey have been used in estimating exposure.

The information available from this survey includes: 1) the total number of individuals consuming the food on one, two, or all three of the survey days; 2) quantities of each food type consumed, averaged over the three days or averaged for individuals consuming the food on one, two, or three days; and 3) the quantity consumed per eating occasion. The data pertaining to quantities consumed are presented both as overall averages and as a percentile distribution, ranging from 5th to 99th percentile intakes. Maximum quantities consumed on one day, three days, and per eating occasion are also included in the same formats.

The 1987-88 NFCS was conducted using the same data collection and reporting techniques used in the 1977-78 survey. The raw data from the 1987-88 NFCS, and the related 1989-90, 1990-91, and 1991-92 CSFII's, are accessible to CRB through a proprietary software package designed to use the data in producing exposure estimates.[16] The CSFII planned for 1994-1996 will be a two day survey, as will future NFCS surveys. Non-sequential days will be surveyed in order to assure that additional intra-individual bias is not introduced into the survey by the first day's food choices influencing choices





made on the second survey day.

*The MRCA 14-Day Survey*

The Market Research Corporation of America's 14-day food-frequency survey had until recently been a primary source of food intake information for OPA. The survey, which is updated annually, is intended to examine the number of eating occasions per day for any food consumed over a 14-consecutive day period. The most recent data available to OPA were compiled during the five year period from 1982 to 1987. This survey, which included over 25,000 participants, was also conducted in a manner to avoid geographical and seasonal eating biases.

The MRCA survey data are recorded by a single member of each surveyed household, usually the female head. For each member of the household, the number of eating occasions for each specific food consumed, both in-home and away-from-home, is recorded. Following the survey period, the recorder would submit the age, sex, weight, and diet status for each member of the household. The frequencies of eating occasions thus obtained need to be linked to appropriate portion size data to obtain the food intakes necessary for estimating exposure to substances in food (see discussion below in "Modeling exposure analysis".) This form of data collection allows estimates to be prepared for specific age/sex/demographic groupings, as well as for specific conditions, such as diabetics.

**Food/component disappearance data**

In the United States, information on the weight of commodities entering commerce is available annually from the Economic Research Service of the USDA.[17] Quantities are measured by deductin data on exports, year-end inventory, and non-food use from data on production, imports, and beginning inventories. These data are sometimes referred to as "disappearance" data because they represent the disappearance of food into the marketing system. Annual disappearance figures for a food commodity can be divided by the national population and by 365 days to obtain a "per capita" estimate of the food that is available for consumption per day (see example: Estimated Daily Intake for an Amino Acid in Sweet Pickles).

The food industry also measures the disappearance of specific products into the market. These data ar usually gathered to observe marketing trends and lack the specificity needed for use by regulatory bodies. When the data obtained reflect disappearance of all of the product being monitored, such as total alcohol or carbonated beverage consumption, crude estimates of per-capita intake can be made.

Food disappearance data may overestimate actual per capita consumption because they include spoilage and waste accumulated in the marketing system and in the home, and some food that is not available for human consumption, such as turkey parts used in pet foods.[18] For example, in 1987-88 the estimate of food energy available for consumption per capita per day in the United States was about twice the estimate of mean food energy intake by the US population based on reported food intake in a national food consumption survey.[19]

For certain years, annual poundages of some substances (food additives and ingredients) produced an used solely for addition to food in the United States have been compiled as a part of the National Academy of Sciences (NAS) Survey of Industry on the Use of Food Additives (National Research

Council, 1972, 1975, 1977, 1982, and 1987[20]). The reliability and validity of these data depend heavily on the completeness of the voluntary industry response for a given substance. A correction factor is applied to account for under-reporting in the NAS surveys before the adjusted poundage is determined for each substance of interest. This factor is related to the historical percentage of companies responding to the survey; for the 1982 and 1987 NAS poundage updates the correction factor is 0.6.

Disappearance data cannot be used to estimate exposure for targeted sub-populations (e.g., young children, diabetics, other age/sex groups), and dietary exposure cannot be expressed on a body weight basis. Because of the limitations inherent in this type of data, OPA uses disappearance data only in conjunction with exposures obtained using data from different sources (primarily to check the reasonableness of an estimate), or when no other data concerning a substance are available, if it can b inferred that the substance of interest is widely distributed in the food supply.

**Market basket studies**

FDA conducts a market basket study annually (The Total Diet Study[21]) to monitor trends in the levels of certain nutrients and contaminants in representative diets of various age-sex groups. These diets, compiled from over 200 foods, have been developed from national food consumption data. To estimate exposure using data from such a market basket study, commonly eaten foods representing th whole diet of the target population(s) are purchased from the marketplace, prepared for eating (e.g., cooked), and then analyzed to determine the concentrations of the substances of interest in each food. Food consumption data from another source are then merged with the food composition data to obtair the desired estimate.

The advantage of the market basket approach is that chemical analyses are performed directly on the foods. There is, however, a major drawback associated with the routine use of this approach for determining the exposure to food additives and contaminants in the diet: the total number of foods analyzed must be limited because of cost and time restrictions. Additionally, a food that is unusually high in the component of interest may not be included in a market basket. Also, obtaining the distribution of exposures to a substance over the consumer population is not feasible.

**Substance concentration data**

OPA typically estimates exposure by linking food intakes from surveys to independently determined concentrations of the substances of interest. The concentration data used depend on the nature of the specific exposure assessment. For a premarket safety evaluation of a food additive, the proposed levels of the substance in targeted foods are generally used. For substances already in the food supply and for naturally occurring or accidental contaminants, OPA obtains concentration data from various sources, such as agency records (FDA, EPA, USDA), users of the substance, the scientific literature, or chemical analyses of foods in which the substance is known to be used or can be found.

OPA evaluates the quality of the concentration data used for estimating exposure. For estimating exposure to additives and contaminants, analytical sampling methodology, the precision and sensitivity of the method, and method validation procedures are considered. Additional considerations are made when estimating exposure to contaminants. For example, it is important to recognize that a





contaminant is generally not distributed uniformly in a living organism: its concentration in plant root or animal flesh may differ significantly from that in the leaves of the plant or the skin of the animal. Therefore, the concentration of the contaminant in the edible portion(s) of the organism as prepared for consumption is estimated or determined before OPA uses the data to estimate exposure.

**Non-detects**

Trace levels of materials in foods often fall below an analytical limit of detection and are typically reported as "non-detects." A number of papers have been published discussing the treatment of data sets containing non-detects for use in estimating exposures.[22] Values of zero, one half the limit of detection, the limit of detection, or some other derived distribution of values have been assigned to non-detects. OPA uses all of these methods, selecting the most appropriate in each case on the basis o the quality and quantity of data available. To gauge the effect of non-detect values on an exposure assessment, the estimation process may be completed twice: once using zero as the non-detect concentration to determine the low end of the estimate range and again using the limit of detection as the non-detect concentration to determine the high end of the estimate range. The spread in this range is useful as a guide in assessing the importance of non-detect concentration values in a given exposur estimate.

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## MODELING EXPOSURE ANALYSIS

**Background**

Two factors are required for estimating exposure to a food substance. The first is the daily intake of the foods in which the substance is used or can be found. The second is the concentration or use level of the substance in each food. (A simple example of an exposure estimate is outlined in Exposure to a Volatile Antimicrobial.) In the early 1970s, data on food intake by individuals were available from only two nationwide food consumption surveys: the 1965 USDA NFCS and the Market Research Corporation of America's (MRCA) Menu Census survey. In conjunction with the FDA, the NAS developed a model for estimating exposure that combined the MRCA data with the USDA/NFCS information. The MRCA data provided information on the frequency of consumption of foods over a 14-day period; the USDA/NFCS data provided portion size information. The use of intakes derived from multiple-day survey of individuals was considered more representative of long-term intake than single-day survey-derived estimates. The relationship of food consumption frequency, portion size, and substance concentration data to the EDI for a single individual is captured in the following equation.

$$EDI_x = \sum_{f=1}^{F} \frac{Freq_f \times Port_f \times Conc_{xf}}{N}$$

where:

F = Total no. of foods in which x can be found

$Freq_f$ = No. of eating occasions for food f over N survey days

$Port_f$ = Average portion size for food f

$Conc_{xf}$ = Concentration of the substance x in the food f

N = No. of survey days

**Food intake distributions**

OPA typically estimates exposures to substances that may be consumed by the national population or a large sub-population. The most useful exposure information is derived from a distribution of exposures for the target population, rather than a single exposure figure. If OPA were assessing the safety of a food containing a substance that showed toxic effects in pregnant animals, the distribution of food intakes for women of child-bearing age would be used for the exposure analysis. For a national population, OPA is concerned with the potential for high exposure to food additives or contaminants for individuals who consume substantial quantities of the food(s) that may contain these substances. Information on food-intake distributions provides a means for estimating exposures to components of foods for the fraction of the population that can be considered "heavy" consumers of the foods of interest. OPA defines "heavy" consumers as those individuals who consume the food at o above the 90th percentile of the food intake distribution.

**Types of food intake estimates**

*Chronic Intake*

For the premarket evaluation of the safety of a food additive or to assess the risk associated with long term exposure to a contaminant, OPA evaluates data concerned with lifetime (chronic) exposures to the substance. Food intake data derived from a multiple-day food consumption survey are used. OPA assumes that consuming a variety of foods over a multi-day period reflects the probable eating pattern of a population over a long period of time. The concentration values for the substance are chosen to reflect the levels likely to be found over time. A regulatory upper use limit could be used for a food additive that is expected to be consumed at a relatively constant level over time. OPA may decide to use an upper limit in a specific exposure assessment because average levels might underestimate the intakes of heavy consumers who consume the treated product frequently, or have a preference for a brand treated with the highest concentration. On the other hand, for a persistent contaminant such as lead or heavy metals, OPA would use an analytically determined mean concentration, including non-detects, to reflect probable exposure conditions.

*Acute Intake*

OPA must also focus on very short-term, or even single, exposures, especially for contaminants associated with acute toxic effects. To estimate exposure in these cases, food intakes from single eating occasions or from one-day intakes (sometimes referred to as person-day intakes) would be used. Using a substance concentration from the high end of the distribution of measured levels would ensure that the risk assessment associated with the exposure assessment would be conservative for a heavy consumer of food containing the substance. When food intake data are not available, or are known to be underreported in food intake surveys (e.g., alcoholic beverages), eating scenarios may be developed for use in estimating exposure (an eating scenario is illustrated in the example Special





Cases - Dietary Scenarios.)

**Statistical approaches to data analysis**

The EPA guidelines for exposure assessment, published in 1992, concisely state: "Exposure assessments are done for a variety of purposes, and for that reason, cannot be easily regimented into a set format or protocol. Each assessment, however, uses a similar set of planning questions, and by addressing these questions the assessor will be better able to decide what is needed to perform the assessment and how to obtain and use the information required."[25] After defining the nature of the risk associated with the substance under consideration, the sub-populations at risk, and the food in which the substance may be found, information on the intakes of the foods affected and the concentration of the substance in each of those foods is compiled. At this point, the manner in which this information is used becomes paramount. Although the model for estimating exposure requires the incremental exposure to the substance from each food be summed to determine the total exposure to the substance, in reality this operation may be very different depending on whether raw or summary food intake data are available.[26]

When the raw data from a food consumption survey are available, reported food intakes for each individual in the survey can be combined with substance concentrations to estimate individual exposure to the substance. A distribution of the exposures for a target sub-population can then be derived and used in the risk assessment. OPA uses this methodology whenever possible because estimates of exposure obtained this way are more accurate than those obtained with summary intake data and should be considered the "state of the art." The proprietary software available to OPA for accessing the raw data from the 1987-88 NFCS, and the 1989-90, 1990-91, and 1991-92 CFSII's permits such an approach.

When only summary food intake survey data are available, assumptions must be made about how to combine exposures from the intake of the individual foods (or food groupings) containing the substance. An example of food intake summary data is presented in Table 1.

**Table 1**

| | Percent eaters | Food Intake (Eaters-only) | |
|---|---|---|---|
| | | mean (g/p/d) | 90th percentile (g/p/d) |
| **Food A** | 65 | 25 | 45 |
| **Food B** | 23 | 15 | 35 |

If the concentration of substance x is 10 µg/g in food A and 25 µg/g in food B, the exposure to x from the consumption of each food is shown in Table 2 below.

**Table 2**

| | Concentration (µg/g) | Exposure to X (Eaters-only) | |
|---|---|---|---|
| | | mean (µg/p/d) | 90th percentile (µg/p/d) |
| | | | |

| | | | |
|---|---|---|---|
| **Food A** | 10 | 250 | 450 |
| **Food B** | 25 | 375 | 875 |

The mean and 90th percentile exposures to substance x from the consumption of foods A and B cannot be taken from Table 2. The eaters-only exposure from food A in Table 2 cannot be added to that from food B because the 65% of the population that eats food A is not identical to the 23% of the population that eats food B. To sum individual exposures, the exposures must be placed in terms of the total sample. Total sample mean exposures can be summed. In the above example, the total sampl mean exposure to substance x (provided it is only found in foods A and B) would be 249 µg/p/d (65% of 250 plus 23% of 375).

To convert this total sample mean exposure to an eaters-only exposure, the percentage of the population that is consuming either foods A or B (or both) must be determined. The percentage of eaters of A or B (or both) in this example lies between 65 and 88%, as shown in Figure 1.

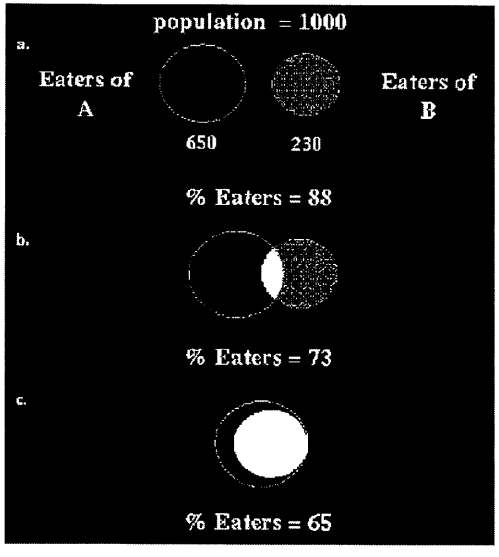


**Figure 1**

**Effect of Overlap of Eater Sub-Populations on Total Eater Population**

**a.) No overlap - Largest eater population**
**b.) Partial (statistical) overlap**
**c.) Total overlap - Smallest eater population**

In case a., the population of eaters of food A and the population of eaters of food B are different. Hence, the percentage of the total population that eats either Food A or B is 88 (65% + 23%). This





scenario represents the eaters of "either-or" type foods, e.g., coffee or tea, soda or diet soda, etc. In case b., a consumer's choice of one food, e.g., lasagna or chocolate ice cream, is unrelated to the choice of another food. The overlap of the two populations is a statistical sampling equal to the product of the two percentages of eaters (0.65 x 0.23 = 0.15).[27] Hence, the percentage of the total population that eats A or B (or both) is 73 (88%[28] - eaters of A and B (15%)). In case c., a consumer who has chosen to eat food A will also eat food B. For example, dieters might use packets of artificial sweetener (food B) and drink diet soft drinks (food A). The percentage of eaters of A or B in case c. would be 65%.[29]

The size of the eating population must be calculated on a case-by-case basis. Case a. is less likely to occur when many foods contain the substance of interest because almost everyone will consume one or the other of the treated (or contaminated) foods. The most conservative estimates of exposure are made by assuming the lowest possible eating population (case c.). In most cases, assuming the statistical blend (case b., above) should provide a reasonable estimate of the size of the eating population and hence a reasonable estimate of exposure (see example Multiple-Use Additives - Probable Exposure for an Emulsifier).

*Upper percentile estimates*

OPA estimates upper percentile exposure to substances in the diet to account for individuals who are considered heavy consumers of specific foods (the 90th, 95th and 97.5th percentile exposures are used by various regulatory bodies in the world; OPA typically uses the 90th percentile). Approaches for estimating upper percentile dietary exposure from summary intake data on individual foods or food groupings are discussed in this section.

An intake estimate for a specific percentile for each food represents the intake of that food for a specific population. Thus, summation of these percentile exposures from individual foods is incorrect and should be avoided, particularly in estimates for high consumption groups (e.g., the intake for corn at the 90th percentile and the intake for pizza at the 90th percentile would almost certainly not be representative of any one consumer).

Examination of food frequency and other types of food consumption surveys conducted in the United States, shows that intake at the 90th percentile for most commonly-consumed foods is roughly 2 times the mean intake for that food, and intake at the 95th percentile is roughly 4 times the mean intake. Thus, a crude approximation of intake at the 90th percentile of a substance can be obtained by doubling the calculated mean intake and at the 95th percentile by quadrupling the mean.

Computer-based Monte Carlo simulations have been used by OPA to calculate specific percentile intakes for substances using summary data.[30] These simulations are used to evaluate models in which one or more inputs (here, food intakes and substance concentrations) can be defined by a distribution of values. Rather than using a single value (e.g., a mean or 90th percentile food intake) for such an input, a computerized Monte-Carlo simulation selects a value at random from the distribution of possible values for the input, uses that value to calculate the outcome of the model, stores the result and then repeats the procedure a pre-determined number of times (iterations), using new values of the input taken from the distribution for each iteration. The resulting output from this procedure is a range of possible outcomes for the model. A probability distribution function is prepared from the range. An

exposure at a designated percentile may be obtained directly from the distribution function.[31] Because Monte Carlo modeling is a probabilistic technique that can use all the available food intake and concentration data, more accurate estimates at upper percentiles than those obtained using point values will result (see results in the example Multiple-Use Additives - Probable Exposure for an Emulsifier).

The strength of the Monte Carlo modeling technique is that it allows for a more realistic estimation of exposure for the mean and for given centiles of a population of eaters when more than one food source for a substance is available than does summing individual food exposures from summary data. When modeling exposure with a Monte Carlo simulation, food intakes, use levels (or concentrations), and eater/non-eater variables can be accessed as distributions (or "Yes/No toggles" in the case of eater/non-eater), using the complete range of available information. Estimates of exposure are derived through Monte Carlo modeling for substances that are used or found in a number of foods; consumers food choices may be considered through the use of correlation functions. As an example, it is possible to test the scenario in which all peanut butter eaters are assumed to be jelly eaters (a reasonable assumption for the subpopulation of young children).

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U.S. Food & Drug Administration
Center for Food Safety & Applied Nutrition
**Office of Premarket Approval**
**September 1995**
(Effective June 18, 2001, Office of Premarket Approval is now Office of Food Additive Safety. See updated contact information)

## Estimating Exposure to Direct Food Additives and Chemical Contaminants in the Diet

# Examples and Summary

## EXAMPLES

The examples below show how OPA reviewers would determine the EDI for direct additives or GRAS ingredients based on the uses proposed by a petitioner and for contaminants based on experimentally determined concentrations in food. The examples were selected to illustrate the divers nature of the problems that OPA is asked to address. First, two simple examples (single-use additives) are used to highlight inherent conservatisms in OPA's estimates due to (1) the assumptions necessary for estimating eventual consumer use of the additive (broadest possible food groups considered and complete replacement of other technologically-equivalent additives by the new additive) and (2) the use of the maximum possible concentration of the additive in food. When the use of conservatisms leads to an EDI that is above the acceptable daily intake (determined toxicologically) the petitioner can submit additional data to allow a refinement (and perhaps a lowering) of the estimate. The responsibility for providing data for reevaluation remains with the petitioner. Second, examples are given of more complex cases (multiple-use additives), where the additive may be used in multiple food groups and additional assumptions are necessary to arrive at a reasonable estimate of probable exposure. Third, examples of exposure estimates pertaining to a secondary direct additive and to contaminant problems are presented. Finally, two special cases, requiring information or approaches not generally used, are provided.

### Single-Use Additives

*Exposure to a Volatile Antimicrobial*

A company petitioned OPA to affirm as GRAS a volatile antimicrobial (VAM) agent for general use in baked goods. This VAM was already affirmed as GRAS for use as an antimicrobial in one sub-category of baked goods. The company submitted data demonstrating that the VAM content of a baked good after storage with VAM vapor was between 0.4 and 1.5%, but requested a regulatory limi of 2%. For estimating exposure to the VAM, use of this proposed regulatory limit would be highly conservative. However, since the submitted data showed that 1.5% is the likely maximum residual level of the VAM, the use of this technical limit was considered sufficiently conservative for this EDI





The baked goods food category (21 CFR 170.3(n)(1)) is quite large, encompassing all breads, cakes and pies, crackers, pancakes, ice cream cones, and more. The chronic daily intake for someone (belonging to the all ages group) consuming baked goods at the mean level is approximately 140 grams/person/day (g/p/d), according to the databases available to OPA. The intake at the 90th percentile level of consumption is over 230 g/p/d.

OPA cannot predict the percentage of the baked goods market eventually captured by the petitioned product. If it is assumed that all baked goods will be treated with this antimicrobial, which is an extremely conservative assumption on both technical and market grounds, and that absorption into the food will be at the 1.5% level, the chronic mean EDI for this material would be 2.1 g/p/d (0.015 x 140 g/p/d).

This EDI is exaggerated because of the assumptions that all baked goods consumed will have been treated with the additive and because of the use of the intake from the broad baked goods subcategory (which includes home-prepared products). Only consumers who seek out products using this antimicrobial, a highly unlikely occurrence, would be expected to be exposed to the additive at levels comparable to that calculated. Refinements to this estimate could be made if the petitioner were to restrict the types of baked goods treated with the VAM.

*Estimated Daily Intake for an Amino Acid in Sweet Pickles*

A petitioner sought approval for the use of an amino acid as a flavor enhancer for sweetened pickles. The petitioner proposed to use the amino acid as a component of pickling spice at a level of up to 1%. Data from a trade association demonstrating that 4 pounds of brine are used to pickle 6 pounds of vegetable and a statement that the brine contains from 0.025 to 0.05% spice were supplied. The trade association also estimated that 50% of pickles are sweetened and that Americans consume 9 pounds o pickles per capita per year. This would result in 4.5 pounds per capita per year disappearance of sweetened pickles, or 5.5 grams per person per day.

For the estimate of chronic daily exposure to the amino acid, data from a food intake survey were used. Mean intake (eaters-only) of pickles (and related products) was 7 grams per person per day (g/p/d). Thus, the survey information is in good agreement with the disappearance data. The EDI for eaters of sweetened pickles was determined as follows:

- 7 g pickles/p/d x 4 g brine/6 g veg. = 4.7 g brine/p/d
- Brine contains 0.05% spice: 4.7 x 0.0005 = 2.4 x $10^{-3}$ g spice/p/d
- Amino acid is 1% of spice: 2.4 x $10^{-3}$ x 0.01 = 2.4 x $10^{-5}$ g/p/d or 25 µg/p/d.

The EDI for this amino acid resulting from the proposed use is conservatively high due to the assumptions that all of the pickling spice used is transferred to the pickle, and that all sweetened pickles will be treated with this flavor enhancer. The magnitude of the overestimate caused by using these conservative assumptions cannot be evaluated with the available information.

### Multiple-use Additives

*Probable Exposure for an Emulsifier*

A petitioner sought an amendment to a current regulation which would expand the number of uses of an emulsifier to include its use in "imitation" seafood. The emulsifier was already regulated for use in baked goods, baking mixes, dairy product analogs, frozen dairy desserts and mixes, and whipped milk products (as an emulsifier), biscuit mixes (as a texturizer), and certain fruits (as a coating component) at levels limited only by good manufacturing practices.

To estimate exposure from the regulated uses, OPA relied on typical use levels supplied in the earlier petition. The new petitioner supplied an estimated "typical" level for the proposed use in imitation seafood.

As a part of the original petition review, OPA had estimated exposure to the emulsifier from the then-proposed uses. The broad range of uses led reviewers to use food-frequency information for the total-sample rather than for eaters-only because it was deemed likely that the whole population would consume foods that had been treated. In developing the new exposure estimate that would include the proposed use, the food sub-category "crustacean shellfish" was selected because the imitation seafood is intended to replace crab and lobster meat.

The 14-day average food intakes and resultant estimation of chronic exposure to the emulsifier of 395 mg/p/d are outlined in the Table 3 below.

## Table 3

*Estimated Daily Exposure to the Emulsifier*
*(2+ years, mean intake, total sample basis)*

| Food Category (use level) | Food Intake (g/p/d) | Emulsifier Intake (mg/p/d) |
|---|---|---|
| **Fish, Seafood (0.3%)** | | |
| Shellfish (crustacean) | 1.1 | 3.3 |
| **Milk Products (0.5%)** | | |
| Chocolate Milk | 5.6 | 28 |
| Flavored Milk | 0.04 | 0.2 |
| Eggnog | 0.4 | 2.0 |
| Sour Cream | 1.1 | 5.5 |
| Creams | 1.4 | 7.0 |
| Diet Milk Products | 1.9 | 9.5 |
| **Cheese (0.5%)** | | |
| Processed Cheese | 6.6 | 33 |
| Cottage Cheese | 4.3 | 22 |
| Cream Cheese | 0.8 | 4 |
| Diet Cheese Products | 0.4 | 2 |
| Other Cheese Products | 1.7 | 8.5 |





| | | |
|---|---|---|
| **Baked Goods (0.5%)** | | |
| Breads, Rolls | 39 | 200 |
| Cakes | 6.4 | 32 |
| **Ice Cream, Milk (0.5%)** | | |
| Ice Cream | 6.6 | 33 |
| **Dairy Products, Analogues (0.5%)** | | |
| Toppings | 0.35 | 1.8 |
| Whiteners | 0.64 | 3.2 |
| **Total (simple sum)** | | 395 |

It can be seen that the petitioner's request constitutes an increase of less than 1% (3.3 mg/p/d) to the total mean EDI. The conservatisms built into this exposure estimate are as follows: complete replacement of other technologically-equivalent additives by the emulsifier and use of the emulsifier at the maximum level suggested by petitioners as typical in all regulated food groups.

As discussed above, a crude estimate of the 90th percentile exposure to a substance can be made, assuming that it is approximately 2-fold higher than the mean. For this emulsifier, using this procedure, the 90th percentile exposure would be approximately 800 mg/p/d. Further evaluation of the exposure estimation at the 90th percentile for this material was accomplished by the use of a Monte Carlo analysis. In this procedure, log-normal distributions of the intakes of each of the foods were combined with a triangular distribution of use levels to obtain distributions of incremental exposures to the emulsifier from each food. These exposure distributions were then combined to derive the distribution of overall exposure to the emulsifier. The 90th percentile exposure in this example is 650 mg/p/d.

Continuing the analysis of this exposure calculation, it was noted that the petitioner included a per-capita estimate of the increase in exposure to the emulsifier that would occur as a result of the regulation of the proposed use. The exposure was based on market data for imitation seafood products currently available commercially. The petitioner assumed: 150 million pounds of seafood product, a US population of 240 million people, 55% imitation seafood in products, and an emulsifier level of 0.3%. The resulting increase in per-capita exposure to the emulsifier would be 1.3 mg/person/day (mg/p/d). OPA's estimate of a 3.3 mg/p/d increase is in good agreement with this figure, given that the two estimates were obtained by approaches that were independent of each other, and provides assurance that OPA's estimate is reasonable.

**Secondary Direct Additives**

As previously discussed, a secondary direct additive is not intended to remain in the food after its technical effect has been accomplished or to have any intended effect in the food should residues remain. Therefore, the use level information supplied by the petitioner is not pertinent to preparing the EDI unless, as a worst-case scenario, the assumption that all of the additive will be carried over to or remain in the treated food is being employed. Such an approach, however, is rarely used for secondary directs.

Generally, the concentration data used for preparing an EDI for a secondary direct additive is obtained by analyzing the treated food for residues of the additive. This information is then used in conjunction with the appropriate food intake data to obtain the EDI. There are secondary direct additives, however, for which this procedure is not sufficient to determine the EDI. **An ion exchange resin, used as the support for an immobilized preparation of glucose isomerase in the preparation of high fructose corn syrup, presents such a case, as shown in the next example.**

EDI ion exchange resins are not calculated by common methods

*Exposure to Enzyme Immobilizing Agents and Their Residues*

A company petitioned OPA to authorize the use of its ion exchange resin as a fixing agent for the immobilization of glucose isomerase preparations.

The company had calculated daily intakes for the resin based on assumptions concerning the useful lifetime of the resin in the preparation of high fructose corn syrup (HFCS). These were:

1. The resin is 8% of the enzyme preparation.
2. 1 gram of enzyme preparation produces 11,000 grams HFCS over the lifetime of the preparation
3. 20% of the preparation is lost into the HFCS through column leaching over the column's lifetime.
4. 60 grams/day intake of HFCS (per capita 1990 USDA estimate)

The resulting exposure to the resin is 87 µg/p/d. This EDI reflects the typical conservatisms: all HFCS entering the marketplace will be produced using this preparation; all column degradation leachate will remain in the HFCS (the company supplied no data concerning the removal of leachate during processing, but merely stated, without supporting data, that greater than 90% was removed); and the resin will always be used at the maximum enzyme preparation-to-syrup ratio.

**Chemical Contaminants (natural or man-made)**

The procedures for estimating exposure to a contaminant in a food generally parallel those described above for direct additives. It is usually imperative, however, to examine the nature of the concern for the contaminant in question. As mentioned previously, there are two general contaminant cases: contaminants in food additives (that require premarket approval) and contaminants in food (or food substances that do not require premarket approval). In the former case, the burden of proof of safety is on the petitioner. OPA could rely on a specification maximum for preparing the EDI and determining whether a safety concern exists. The petitioner may be able to supply additional data on the actual level of contaminant in an additive to allow an adjustment of the EDI, if needed. In the case of a contaminant in food, the burden of proof of hazard is often on FDA. It may be necessary to prove that the presence of a contaminant in a food or food substance may render it injurious to health. The concentration chosen for use in calculating an intake estimate would depend on the nature of the risk. The concentration used for a contaminant posing an acute risk would probably be at the maximum of the observed experimental levels. If the risk is due to chronic exposures, however, a mean concentration level, representing the likely lifetime level of exposure would be more appropriate. Again, each contaminant must be dealt with on a case-by-case basis.

For the simple case (no acute risk) where there is a safety concern due to the presence of a contaminant in a single product or class of products, it is sufficient to use the mean concentration of



Jow: "Resin Degradation"



the contaminant in the food and the intake of the food in order to estimate the exposure to the contaminant. The next example illustrates the case of a naturally-occurring contaminant in an additive with a limited use. More complex cases would require the use of the same assumptions (substitution, etc.) described above for multiple-use food additives.

*Exposure to Residues in a Refined Food Oil*

A company submitted a petition for GRAS affirmation of a refined food oil for use in candies and confections (chocolate products) at levels from 5-30%. The company reported that the crude oil contains 3-7% unsaponifiable matter that could be reduced to a specified maximum of 1.5% upon refining. The unsaponifiable material remaining after refining consisted primarily of triterpene alcohols and sterols, including alpha-spinasterol. The presence of alpha-spinasterol was unique to this oil among the edible oils. Therefore, it was necessary to estimate exposure to this natural contaminant as part of the safety evaluation for this petition.

The exposure to the oil from its use in chocolate products was first evaluated. The chronic EDI was calculated to be 2.2 g/p/d (all ages). The company submitted data showing that the typical residual sterol level in the oil was approximately 0.05%, 40% of which is alpha-spinasterol. Therefore, use of the oil in chocolate would result in a total potential exposure to sterols and methyl sterols of approximately 1.1 mg/p/d. This exposure was determined by multiplying the exposure to the oil by th level of the sterol in the oil as follows:

0.05% sterol in oil x 2.2 g oil/p/d = 1.1 mg sterol/p/d

The probable exposure to alpha-spinasterol would be 40% of that for all sterols, i.e., 0.4 mg/p/d.

*Mercury Contamination in Shark*

This example illustrates some assumptions that might be made when none of the available food intake databases contain information sufficient to allow a straightforward estimation of exposure.

A state's health officials had collected 25 samples of shark meat from retail fish outlets. The species collected were not known, nor were the locations of the catch sites. Analysis for methylmercury showed an average level of 1.48 ppm with a range of 0.35 to 3.9 ppm. Based on these results, the state's health department advised that adults should eat shark no more than once a week. Children and women of childbearing age were advised to eat shark no more than once a month. Following this health advisory bulletin FDA was asked to prepare an estimate of methylmercury intake that might result from consumption of shark.

Mercury in shark

Mercury values obtained by FDA from domestic and import compliance and surveillance samples were used as the basis for establishing the concentration to use in the exposure assessment. For 113 samples, the average mercury concentration was 0.96 ppm (+/- 0.61 SD). These samples were taken from those shark meats used as food, and so should reflect levels of methylmercury actually ingested.

Shark consumption

Preparation of an estimate of shark consumption using a straight per capita disappearance figure (ca. 0.035 g/person/day)[35] would have given an inappropriately low estimate of likely shark intake for actual consumers of shark.

Shark is an infrequently consumed food. Consequently, the consumption information presented in dietary surveys such as the USDA 3-day survey and the MRCA 14-day survey can be expected to overestimate, to varying degrees, the average daily intake of shark consumed by the individual[36]. Of these surveys, the MRCA survey, due to its longer time base, is more likely to capture the consumption of infrequently consumed foods . However, due to the extremely low consumption rate for shark, even the MRCA survey would likely overestimate chronic exposure to shark for eaters of shark in the general population. Therefore, to more accurately estimate chronic shark intake, an average daily intake was first calculated using a modified per capita approach, in which the amount of shark disappearing into the U.S. food supply was divided by the population of shark eaters as determined using percentage of eaters information from the state's seafood consumption survey.

According to the state's survey, approximately 1% of the general population are eaters of shark. Thus, of a total estimated U.S. population of 260 million people (1994), there might be 2.6 million people nationwide who are consumers of shark meat.

According to recent (1993) National Marine Fisheries Service (NMFS)[37]. figures, $8.9 \times 10^6$ lbs of shark fillets and steaks were produced in the U.S. in 1993. Therefore, the average daily intake of shark is:

$$\frac{8.9 \times 10^6 \text{ lbs shark}}{2.6 \times 10^6 \text{ eaters}} = 3.4 \text{ lbs shark/eater/year}$$

$$= 1554 \text{ g/eater/year or } 4 \text{ g/eater/day.}$$

This average was then used (as noted below) to create a distribution of intakes for shark meat by assuming a standard deviation equal to the mean intake and assuming that the data were distributed in a log-normal fashion[38].

Intake of methylmercury

According to the NMFS, methylmercury comprises 90-100% of total mercury in most fish. For the purpose of this estimate, it was assumed that mercury in shark is 100% methylmercury. To estimate the intake of methylmercury resulting from consumption of shark, log-normal distributions based on the mean shark intake and the mean methylmercury concentration in shark (and their associated standard deviations) were used in a Monte Carlo simulation[38]. That is, exposure was calculated assuming that 4 +/- 4 g shark is the mean daily consumption for eaters and that shark is contaminated with methylmercury at a level of 0.96 +/- 0.61 ppm. The log-normal distributions of these data sets were combined to give a methylmercury intake distribution for shark eaters. The results of this calculation are as follows:





**Exposure to Methylmercury from Shark, µg/person/day (Eaters-Only)**

| Consumption Percentile | Methylmercury Intake |
|---|---|
| mean | 3.8 |
| 90th | 8.4 |
| 95th | 12.3 |
| 99th | 25.0 |
| 100th | 142 |

A possible subset of shark eaters consists of individuals who consume shark on a regular and frequent basis, perhaps eating one shark meal per week. This is the group to which the state's health advisory was directed. Assuming that such persons eat a serving of shark equal in weight to the USDA mean portion size of 145 g for fish consumption, the mean shark intake for these regular and frequent consumers of shark would be 21 g/person/day. This scenario reflects the consumption behavior of slightly less than 1% of shark eaters (i.e., consumption at the 99.2th percentile of shark eaters). If the shark were contaminated with methylmercury at the mean observed level of 0.96 ppm, methylmercury intake would be 20 µg/day. This is below the tolerable daily intake (TDI) of 30 µg/p/d, established through animal studies[39].

**Special Cases**

The above examples point out some of the considerations routinely used by OPA in preparing an EDI There are many cases, however, where additional, or entirely different, assumptions must be made concerning the factors taken into account for evaluating exposure. Two of these cases will be discussed: estimating exposure to components of tablets (e.g., vitamin and mineral supplements), and the use of dietary scenarios for estimating exposure.

*Potential Exposure to Tabletting Agents*

Numerous companies have petitioned to have tabletting agents regulated for use in the preparation of vitamin and mineral supplements. Because the pattern of vitamin and mineral consumption is different from the pattern of intake of typical food, it has been necessary to evaluate exposure to supplements using a novel approach. FDA personnel determined, through a telephone survey in 1980, that the average intake of vitamin or supplement pills in the United States was one tablet per day (J. Am. Diet Assoc., **1985**, 1585-90). In recent years, however, the daily intake of vitamin/supplement pills by many individuals appears to have increased substantially. Using 600 mg as the weight of a typical supplement tablet, it is possible to readily evaluate exposure to materials used in the tablet formulation. For example, one company petitioned for permission to use a fatty acid ester as a formulation aid in tablets at a level of 1-3%. Using the typical vitamin tablet size of 600 mg, the maximum level of the fatty acid ester per tablet would be 18 mg, and the EDI from a single tablet would be 18 mg/p/d. The company petitioning for the fatty acid ester stated that a maximal user of vitamins might ingest six tablets a day. Therefore, the maximum exposure to this fatty acid ester from its use in tablets would be 108 mg/p/d. These estimates are highly conservative in that they assume that all vitamins consumed on a daily basis would be formulated with the fatty acid ester.

*Dietary scenarios*

When specific food intake or substance concentration data are not available, a dietary scenario may b developed to complete an exposure analysis. For example, CFSAN may be asked to determine the safety of one lot of a rarely eaten food product that is being considered for regulatory action because of contaminants that may pose a health risk. In this instance, a scenario can be devised to estimate the amount of food consumed per eating occasion (or per day) and substance concentration can be used that has been either experimentally determined or chosen to be representative of the lot. The exposure thus determined may then be used to evaluate the risk of ingestion of the substance in the food (based on chronic or acute effects).

Two topical examples demonstrate the use of dietary scenario assumptions. Dioxins, a family of related chlorinated compounds associated with the bleaching of wood and paper products, have been determined to be carcinogenic at extremely low levels. Fish caught downstream from paper mills wer found to contain elevated levels of the dioxins. Because fish intake data were not available at the time for the target population of subsistence fishermen, it was assumed that a fisherman's normal intake of fish protein would equal that of the average person's red meat, chicken, and fish intake. Thus, red mea and chicken intakes from a national food consumption survey were used with dioxin levels of fish caught near paper mills to model dioxin exposure for subsistence fishermen.

The use of macronutrient substitutes, such as fat replacers that could affect the nature of some consumers' diets, serves as the second example for which the use of a dietary scenario is illuminating. The availability of fat replacers might result in highly motivated individuals substituting the replacer for all added fat in their diet. The exposure estimate for a fat replacer that would be available to the consumer for home food preparation, including baking and frying, can be based on considerations of food energy obtained from fat intake. If the maintenance of an appropriate weight for a man (19-50 yrs. old) is assumed to require an average of 2900 calories, of which 40% are derived from fat intake (not unusual for a substantial fraction of the US population), then 1160 calories a day are derived fron fat. At 9 calories per gram of fat, fat intake in this diet would amount to 129 grams per day. Approximately 50% of fat in the diet is estimated to be derived from added triglycerides (lard, tallow, butter, margarine, vegetable oils, shortening)[40]. Thus, "added fat" would amount to 64 grams per day. If the fat replacer were intended to substitute for "added fat" on a one-to-one basis, the EDI would be 64 g/p/d. When the fat replacer is not caloric, i.e., it is a non-metabolizable substance, the 6 grams of replacer represents a decrease of about 576 (9 x 64) calories from the reference daily intake of 2900 calories. Assuming that the consumer would unconsciously eat, on average, 576 additional total calories[41] to compensate for the shortfall and continue to maintain a 2900 calorie diet, additional fat replacer would be consumed as part of these extra calories, presumably in the same proportion of calories from fat in the total diet (40%). This would result in an additional exposure to the replacer of 13 g/p/d (576 total cal x 0.4 cal fat/total cal x 0.50 g added fat/g total fat x 0.111 g fat/cal fat), bringing the total exposure to 77 grams per day as an upper limit for an average man.

The use of such scenarios must be based on assumptions that are reasonable reflections of a consumer's actions. The assumptions must be clearly delineated and defensible. If possible, a second approach to estimating exposure should be used to provide corroboration of the result obtained using dietary scenario.





## SUMMARY

There is no single method for estimating the probable exposure to a substance found in or added to food. This document has outlined cases where a substance's concentration in specific foods was known or could be predicted; therefore, OPA used intakes for those specific foods to estimate exposure. Special cases have been considered, such as the use of dietary scenarios to estimate exposure to fat replacers, where new methodologies have been developed to estimate exposure. Limitations caused by data availability (or lack thereof), such as the intakes of specific foods or the variability in the concentrations of contaminants in different foods, are often the determining factors i the method used to estimate exposure. This document is not an attempt to be an all-inclusive consideration of OPA's deliberations in preparing exposure estimates. Rather, it is intended to be an overview of some of the general principles and assumptions used, while emphasizing the case-by-cas nature of the process.

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# Ion Exchange Resins

An ion exchange resin is a plastic, often a co-polymer of styrene and divinylbenzene. In a water softener, the resin is formed into porous beads, of about 1 mm or less in diameter.

Resins can be produced to selectively exchange with either positive or negative ions by treatment of the plastic bead material. In order to produce a resin that can remove water hardness ($Mg^{2}+$ or $Ca^{2+}$ ions), the resin must be treated to produce negative sites to which the positive ions can attach. These sites are typically either carboxyl ( $-COO^{-}$) or sulfonate ($SO_3H^{-}$) groups which can be created by treatment of the resin with acetic or sulfuric acids. The resins are then washed with sodium hyrdoxide, which neutralizes the acid, and produces the sodium salts of the treated resin molecules: R COONa or $R\text{-}SO_3HNa$

Resin beads gradually break down. This can be because of mechanical degradation, or because chlorine in the water will gradually oxidize the cross-linkages in the polymer. Therefore the resin in a water softener must be periodically replaced (perhaps every 5 - 10 years in home use).

acid treatment

chlorine can also break down resins. ? by-products

some types of acids used to regenerate columns

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## Ion Exchange Resins 124

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This report is concerned with the manufacture of synthetic ion exchange resins, particularly those based on styrene-divinylbenzene (DVB) copolymers. Most modern ion exchange resins, or ion exchangers, consist of a synthetic polymer backbone or matrix to which is attached a functional group that gives each ion exchanger its specific proper- ties. Ion exchange resins are produced in various physical forms depending on the end use for the resin. Most commonly, they are used as small spherical beads or granules, but they can be made into membranes, fibers, tubes, cloth, or foams. By special manufacturing techniques, the polymers, especially in the bead form, may be made with porous structures instead of the conventional solid gel resin structure. Such resins are called macroporous or macroreticular resins.

The functional groups that are distributed throughout the resin structure contain fixed electric charges or ion-active groups, each of which is associated with a mobile counter ion of opposite charge. These mobile ions are capable of reacting with or exchanging with other ions of like sign when they are in contact with a solution containing such ions. It is important that ion exchange resins swell to a certain extent in aqueous solution so that the solution can diffuse into the resin and come into contact with the active sites.

When the fixed electrical charges within the resin matrix are negative (when the fixed functional group is a sulfonic group, for example), the mobile ions are cations and the resin is said to be a cation exchange resin. Conversely when the fixed groups are positively charged, the mobile ions are anions and the resin is an anion exchanger.

The polymer matrices are usually cross-linked to make them insoluble and to give them mechanical strength and stability. The extent of cross-linking must be controlled so as to give good mechanical properties to the resin while permitting enough water absorption and swelling to ensure good ion exchange activity. The most common resins are styrene-divinylbenzene (DVB) copolymers in which DVB is the cross-linking agent, typically present in 4-12X concentration. Other polymers include acrylates, methacrylates, phenol formaldehyde condensates, and epichlorohydrin amine condensates.

Ion exchange has been defined as the reversible interchange of ions between a solid and



other synthetic based resins



a liquid phase in which there is no permanent change in the structure of the solid. This means that ion exchangers are not consumed by ordinary usage, but when they are exhausted, they can be regenerated or reconverted to their original state and reused. Ion exchange is regarded as a unit process in chemical engineering and it has many applications. One of the best known and largest applications is water softening, in which calcium and magnesium ions, which cause water hardness, are removed from the water and exchanged for sodium ions from the resin. When the resin is exhausted, it is brought back to its original state by treatment with a sodium chloride solution. By a more complex process, water may be not only softened, but completely deionized. Ion exchange resins are widely used to treat boiler feed water, process water, and to perform a large number of separations and reactions in the manufacture of chemicals, foods, pharmaceuticals, electronic devices, and many other products.

Ion exchange is a widespread phenomenon in nature, occurring in living cells and in soils, for example. Ion exchange materials include silicates, phosphates, flourides, humus, wool, proteins, cellulose, alumina, glass, and many others. The first industrial ion exchangers were probably inorganic aluminum silicates, used for softening water and treating sugar solutions. Later on, it was discovered that sulfonated coal was a relatively effective ion exchange material, but such materials were fragile and were useful only under restricted operating conditions. In the United States nearly all ion exchange applications use synthetic polymer resins.

The older PEP reports' abstracts are listed to provide a complete historical archive of PEP reports. The production cost estimates are updated in the PEP Yearbook. A list of more recent PEP reports are available.

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### Other PEP Related Web Pages

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other types of ion-ex. resins that are more 'natural'

4/3/02

**Production and Handling Question and Answer**

Q. Under the National Organic Standards, can the certifying agent approve ion exchange for the processing of organic foods?

A. The National Organic Standards do not prohibit the use of ion exchange in organic food processing as a technology. However, the National Organic Standards do prohibit the use of synthetic substances used in or on processed products unless included in National List section 205.605 as an allowed substance. Accordingly, ion exchange may not be used in the processing of organic foods unless the synthetic substances used in the ion exchange process are listed as approved substances in National List section 205.605.

in a rule

is styrene divinyl benzene on the list?

original prop. '97 - yes to ion exchange
- incidental ingredients.
- functionally changed

Materi

- USDA changing meaning of additives?

**Consumers Union**

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**Comments of Consumers Union**
**on**
**Recommendations of the NOSB**
**Regarding the "Guidelines for determining whether a processing technology shall be reviewed by the NOSB"**
**December 5, 2001**

Consumers Union appreciates the opportunity to comment on the National Organic Standards Board (NOSB) recommendations regarding the guidelines for determining whether a processing technology shall be reviewed by the NOSB drafted December 5, 2001. We support the NOSB's efforts to provide additional guidance to organic processing. However, we urge the NOSB to be explicit in upholding the definition of organic and not allow any loopholes in the regulation to be created.

The use of genetic engineering is strictly prohibited in organic production as outlined in the National Organic Program. The NOSB recommended guidelines for organic processing do not explicitly prohibit the use of this technology. By stating that the definition of organic processing, "appears to allow most, if not all, mechanical, and biological processes" is misleading and inaccurate. Genetic engineering is a type of biological process that should be explicitly prohibited at all stages of organic production, including processing. It is inaccurate to infer that all biological processes are or will be acceptable in organic production. Biologic process should therefore be reviewed by the NOSB. Enzymes, acids, and additives are examples of substances that can be derived from or made with nonpathogenic bacteria for use in organic production. Bacteria are also used directly in production of certain foods such as yogurt. These genetic modification of these bacteria should be explicitly prohibited. The National Organic Program (NOP) should leave no room for misinterpretation of the meaning of organic. This oversight would not meet consumer's expectation of organic.

1. Consumers Union agrees with the NOSB recommendation that processes that introduce nonagricultural substances, both synthetic and non-synthetic, require NOSB review. However, processes accepted and rejected into the NOP by the NOSB should be required to be added to the National List.

2. Biologic processes can also make or break covalent bonds and should also fall under the review of the NOSB. The guidance should read as, "Processes other than mechanical, that are primarily intended to, or inadvertently, make or break covalent bonds are subject to review by the NOSB before being allowed in the processing of organic food products."

3. CU agrees with the NOSB recommendation.

4. Any process, other that mechanical, that removes specific chemical ingredients from food should be reviewed. For example, any biologic process used to extract an ingredient should also be reviewed.

5. CU agrees with the NOSB recommendation.

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