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Toxicology Profiles of Chemical and Radiological Contaminants at Hanford

B. L. Harper
D. L. Strenge
R. D. Stenner
A. D. Maughan
M. K. Jarvis

July 1995

Prepared for the U.S. Department of Energy
under Contract DE-AC06-76RLO 1830

Pacific Northwest Laboratory
Operated for the U.S. Department of Energy
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1.0 Introduction

The Hanford Site Toxicity Document (Toxicity Document) is a compilation of toxicity values and qualitative health effects information necessary for preparing risk assessments at the Hanford Site. The Toxicity Document is a companion to the *Hanford Site Risk Assessment Methodology* (HSRAM) (RL 1995). HSRAM, in conjunction with other documents, provides exposure assessment information, including descriptions of exposure scenarios and exposure pathways, equations for estimating contaminant intake from soil, air, and water, and the assumptions and parameters used in estimating contaminant intake. The Toxicity Document provides toxicity information, which is combined with information developed in an exposure assessment to characterize health risks potentially associated with contaminants in soil, air, or water.

1.1 Purpose of the Document

This document summarizes toxicology information required under Section 3.3 (Toxicity Assessment) of HSRAM, and can also be used to develop the short toxicology profiles required in site assessments (described in HSRAM, Section 3.3.5). Toxicology information is used in the dose-response step of the risk assessment process. The dose-response assessment describes the quantitative relationship between the amount of exposure to a substance and the extent of toxic injury or disease. Data are derived from animal studies or, less frequently, from studies in exposed human populations. The risks of a substance cannot be ascertained with any degree of confidence unless dose-response relations are quantified.

This document summarizes dose-response information available from the U.S. Environmental Protection Agency (EPA). The contaminants selected for inclusion in this document represent most of the contaminants found at Hanford (both radiological and chemical), based on sampling and analysis performed during site investigations, and historical information on waste disposal practices at the Hanford Site.

1.2 Intended Users, Cautions, and Limitations

The information presented in this document is intended for use by risk assessment teams preparing qualitative risk assessments and other site risk assessments. Users should have some familiarity with the practice of risk assessment, and an understanding of the limitations of all toxicity factors, because these factors are one of the largest sources of uncertainty in risk assessments. Background information is provided before the nonradiological and radiological profiles that briefly explains how EPA uses the scientific evidence to develop toxicity factors.

The sources of toxicological information and toxicity factors used in risk assessment are described in Section 1.3. Periodically, EPA announces changes in toxicity factors for selected contaminants as new information on the nature and magnitude of health effects becomes available on those contaminants. While the toxicity values for most of the Hanford Site contaminants are unlikely to undergo changes, users are cautioned to consult the sources of toxicity information described in Section 1.3 to confirm the values used in risk assessments. At this time, regular updates of this toxicity document are not planned.

1.3 Sources of Toxicity Information

While several sources of toxicity information are mentioned in the HSRAM, only information obtained from EPA is discussed in detail in the toxicity document. The preferred source is EPA's Integrated Risk Information System (IRIS), and the secondary source is EPA's Health Effects Assessment Summary Tables (HEAST). In a few instances, EPA's Environmental Criteria Assessment Office (ECAO) provided information if none was available from the first two sources. Supplementary sources are also indicated in individual profiles. For radionuclides, the current EPA cancer slope factors are used.

IRIS is a database available through the ECAO in Cincinnati, Ohio. IRIS, prepared and maintained by EPA, is an electronic database containing health risk and EPA regulatory information on specific chemicals. Online access to IRIS can obtained for a small fee through the National Library of Medicine's MEDLARS information retrieval system. Further information can be obtained from the IRIS User Support in ECAO at 513-569-7254. HEAST, provided by the EPA Office of Solid Waste and Emergency Response (OSWER), is a compilation of toxicity values published in health effects documents issued by EPA. HEAST is intended for use in Comprehensive Environmental Response, Compensation, and Liability Act (Superfund) and Resource Conservation and Recovery Act (RCRA) programs. Further information on HEAST can be obtained through the Superfund and RCRA Hotline at 800-424-9346.

The EPA is currently in the process of revising the guidelines for carcinogen risk assessment. Once this revision is final, this document will be updated to reflect any changes in the methods.

1.4 Overview of the Document

This document provides summary tables of the toxicity values for carcinogenic and noncarcinogenic substances, and radionuclides; descriptions of the toxicity values; and toxicology profiles for individual contaminants.

1.5 References

U.S. Department of Energy, Richland Operations Office (RL). 1995. *Hanford Site Risk Assessment Methodology.* DOE/RL-91-45, Rev. 3, U.S. Department of Energy, Richland Operations Office, Richland, Washington.

2.0 Nonradiological Toxicology Profile

For purposes of risk assessment, chemical substances can be classified into two broad categories: carcinogens and noncarcinogens (Tables 2.1 and 2.2). This classification is used because health risks are calculated quite differently for carcinogenic and noncarcinogenic effects, and separate toxicity values have been developed for carcinogenic and noncarcinogenic effects. Toxicity studies with laboratory animals or epidemiological studies of human populations provide the data used to develop these upper bound toxicity values. The toxicity values are then combined with the exposure estimates (developed using assumptions provided in the HSRAM) to develop the numerical estimates of carcinogenic risk and noncancer health risks. These numerical estimates are then used in the risk characterization process to estimate upper bound potential adverse effects from chemicals originating in soil or groundwater.

2.1 General Description of Noncarcinogenic Substance Information

The dose-assessment process for noncarcinogens derives a quantitative relationship between the dose (or more generally the human exposure) and the probability of a toxic effect other than cancer. Chemicals that cause cancer can also cause noncancer effects, and so may be listed with both cancer and noncancer toxicity factors. Unlike cancer, noncancer effects are assumed to have an identifiable exposure threshold below which there are no observable adverse effects, and from which a regulatory standard may be derived.

Based on animal or human data, several types of chronic toxicity levels may be determined for a given chemical. These levels are the no observed adverse effect level (NOAEL), the no observable effect level (NOEL), the lowest observed adverse effect level (LOAEL), and the reference dose (RfD). These terms are described in the following text.

- **No Observed Adverse Effect Level (NOAEL):** The NOAEL is an experimentally determined dose at which there was no statistically or biologically significant indication of the toxic effect of concern.

- **No Observable Effect Level (NOEL):** The NOEL is slightly different than the NOAEL; there may be observable effects that are not generally considered to be toxicologically significant.

- **Lowest Observed Adverse Effect Level (LOAEL):** When a NOEL cannot be determined because the lowest dose used still caused an adverse effect, the lowest dose used becomes the LOAEL.

- **Reference Dose (RfD):** The RfD is defined by EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime."

Table 2.1. Summary of Systemic Toxicity Information for Contaminants of Potential Concern

Contaminant	Oral RfD (mg/kg-day)	Source of Information	Confidence Level	Critical Effect	Safety Factors	Modifying Factors	Inhalation RfD (mg/kg-d)	Confidence Level	Critical Effect	Uncertainty Factors	Modifying Factors
Acenaphthene	6.0E-02	1,4	Low	Hepatotoxicity	3000 (S,A)	--	--	--	--	--	--
Acenaphthylene	Pending	1,4	--	--	--	--	--	--	--	--	--
Aluminum	1.0E+00	5	Medium	Neurotoxicity	100 (H,A,L)	--	--	--	--	--	--
Ammonia	9.7E-01	3	--	--	--	--	3.5E-01	Medium	Respiratory lesions	30 (H,S)	
Anthracene	3.0E-01	4	Low	None	3000 (H,A,S)	--	--	--	--	--	--
Antimony	4.0E-04	1,2	Low	Longevity, blood glucose, cholesterol	1000 (A,L,H)	--	--	--	--	--	--
Arsenic	3.0E-04	3	Medium	Hyperpigmentation, keratosis, possible vascular complications in humans	3 (H)	--	--	--	--	--	--
Barium	7.0E-02	1,4	Medium	Increased blood pressure	3 (H)	--	--	--	--	--	--
Benz(a)anthracene	--	4	--	--	--	--	--	--	--	--	--
Benzene	--	1,4	--	--	--	--	--	--	--	--	--
Benzo(b)fluoranthene	--	4	--	--	--	--	--	--	--	--	--
Benzo(k)fluoranthene	--	4	--	--	--	--	--	--	--	--	--
Benzo(a)pyrene	--	4	--	--	--	--	--	--	--	--	--
Beryllium	5.0E-03	1,4,6	Low	None	100 (A,H)	--	--	--	--	--	--
Cadmium	5.0E-04 water 1.0E-03 dietary	2,4,7	High	Significant proteinurea	10 (H)	--	--	--	--	--	--
Carbon tetrachloride	7.0E-04	4	Medium	Liver lesions	1000 (H,A,S)	--	--	--	--	--	--
Chlordane	6.0E-05	1,4	Low	Regional liver hypertrophy in female rats	1000 (H,A)	--	--	--	--	--	--
Chloroform	1.0E-02	4	Medium	Fatty cyst formation in liver	1000 (L)	--	--	--	--	--	--
Chromium III	1.0E+00	1,3	Low	None	100 (A,H)	--	--	--	--	--	--
Chromium VI	5.0E-03	1,3	Low	None	500 (A,H,S)	--	--	--	--	--	--
Chrysene	--	4	--	--	--	--	--	--	--	--	--
Cobalt	6.0E-02 recommended	8	--	--	--	--	--	--	--	--	--
Copper	2.0E-2 to 7.0E-02	1,3,9	--	Gastrointestinal irritation in humans	--	--	--	--	--	--	--
Cyanide	2.0E-02	3	Medium	Weight loss, thyroid effects, myelin degeneration	100 (A,H)	5	--	--	--	--	--
Dieldrin	5.0E-05	4	Medium	Liver lesions	100 (A,H)	--	--	--	--	--	--
Bis(2-ethylhexyl)-phthalate	2.0E-2	4	Medium	Increased liver weight	1000 (A,H,L,S)	--	--	--	--	--	--
Dibenz(a,h)anthracene	--	4	--	--	--	--	--	--	--	--	--
Ethylbenzene	1.0E-01	3	Low	Liver and kidney toxicity	1000 (H,A,S)	--	3.0E-01	Low	Developmental toxicity	300 (H,A)	--

Table 2.1. (contd)

Contaminant	Oral RfD (mg/kg-day)	Source of Information	Confidence Level	Critical Effect	Safety Factors	Modifying Factors	Inhalation RfD (mg/kg-d)	Confidence Level	Critical Effect	Uncertainty Factors	Modifying Factors
Ethylene glycol	2.0E+00	3	High	Kidney toxicity	100 (H,A)	--	--	--	--	--	--
Fluoranthene	4.0E-02	4	Low	Nephropathy, increased liver weight, hematological alterations, clinical effects	3000 (A,H,S)	--	--	--	--	--	--
Fluorene	4.0E-02	4	Low	Decreased RBC, packed cell volume, hemoglobin	3000 (A,H,S)	--	--	--	--	--	--
Indeno(1,2,3-cd)pyrene	--	4	--	--	--	--	--	--	--	--	--
Lead	--	3, 10, 11, 12, 13	--	--	--	--	--	--	--	--	--
Manganese	5.0E-03 water 1.4E-01 food	3	Medium to Low, Medium	Central nervous system	1	--	1.75E-04	Medium	Impairment of neurobehavioral function	1000 (H,L,S)	--
Methylene chloride	6.0E-02	1,4	Medium	Liver toxicity	100 (H,A)	--	--	--	--	--	--
Mercury	3.0E-04	1,3	--	Kidney effects	1000	--	1.05E-03	--	Neurotoxicity	30	--
Naphthalene	4.0E-03 provisional	4,14	--	--	--	--	--	--	--	--	--
Nickel	2.0E-02	3,15	Low/ Medium	Decreased body and organ weights	300 (A,H)	--	--	--	--	--	--
Nitrate	1.6E+00	3	High	Early signs of methemoglobinenia in infants	1	--	--	--	--	--	--
Nitrite	1.0E-01		High	Blood, methemoglobinenia	1	10	--	--	--	--	--
Pentachlorophenol	3.0E-02	4	Medium	Liver and kidney pathology	100 (A,H)	--	--	--	--	--	--
Phenanthrene	--	4	--	--	--	--	--	--	--	--	--
PCBs	--	4	--	--	--	--	--	--	--	--	--
Pyrene	3.0E-02	4	Low	Kidney effects	3000 (A,H,S)	--	--	--	--	--	--
Selenium	5.0E-03	4	High	Clinical selenosis	3 (H)	--	--	--	--	--	--
Selenium sulfide	--	4	--	--	--	--	--	--	--	--	--
Silver	5.0E-03	3	Low	Argyria	3 (H)	--	--	--	--	--	--
Strontium	6.0E-01	1,3	Medium	Rickets	300 (A,H)	--	--	--	--	--	--
Tetrachloroethylene	1.0E-02	4,16	Medium	Liver toxicity	1000 (A,H,S)	--	--	--	--	--	--
Thallium compounds	8.0E-05	4	Low	None	3000 (S,A,H)	--	--	--	--	--	--
Toluene	2.0E-01	3	Medium	Change in liver and kidney weights	1000	--	1.0E-01	Medium	Neurological effects, degeneration of nasal epithelium	300 (A,L)	--
Tributyl phosphate	5.0E-03	3, 17, 18	Low	Urinary bladder hyperplasia	3000 (A,H,S)	--	--	--	--	--	--
1,1,1-Trichloroethane	--	4,19	--	--	--	--	--	--	--	--	--
Trichloroethylene	6.0E-03 provisional	4,20	Low	--	3000 (A,H,S)	--	--	--	--	--	--

Table 2.1. (contd)

Contaminant	Oral RfD (mg/kg-day)	Source of Information	Confidence Level	Critical Effect	Safety Factors	Modifying Factors	Inhalation RfD (mg/kg-d)	Confidence Level	Critical Effect	Uncertainty Factors	Modifying Factors
Uranium	3.0E-03	1,3	Medium	Kidney toxicity	1000 (A,H,L)	--	--	--	--	--	--
Vanadium	7.0E-03	1	--	--	100	--	--	--	--	--	--
Vanadium pentoxide	9.0E-03	4	Low	Decreased hair cystine	100 (A,H)	--	--	--	--	--	--
Vanadium sulfate	2.0E-02	4	--	--	100	--	--	--	--	--	--
Vinyl chloride	--	1	--	--	--	--	--	--	--	--	--
Xylenes	2.0E+00	3	Medium	Hyperactivity, decreased body weight, increased mortality	100 (A,H)	--	--	--	--	--	--
Zinc and compounds	3.0E-01	1,4	Medium	Decrease in erthrocyte superoxide dismutase concentration in humans	3 (H)	--	--	--	--	--	--

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H = variation in human sensitivity.
A = animal to human extrapolation.
S = extrapolation from subchronic to chronic NOAEL.
L = extrapolation from LOAEL to NOAEL.

Table 2.2. Summary of Cancer (Nonradioactive) Toxicity Information (Chemicals Only)

Contaminant	EPA Cancer Classification	Type of Cancer	Oral SF $(mg/kg\text{-}d)^{-1}$	Source of Information	Inhalation SF $(mg/kg\text{-}d)^{-1}$	Source of Information
Antimony	Not evaluated	--	N/A	-	N/A	--
Benz(a)anthracene	B2	--	N/A	-	N/A	--
Benzene	A	Leukemia skin, lung lymphoma	2.9E-02	1	2.9E-02	1
Benzo(b)fluoranthene	B2	--	N/A	-	N/A	--
Benzo(k)fluoranthene	B2	--	N/A	-	N/A	--
Benzo(a)pyrene	B2	--	7.3E+00	4	N/A	--
Cadmium	B1	--	ND	-	N/A	--
Carbon tetrachloride	B2	--	1.3E-01	4	5.3E-02	1
Chlordane	B2	--	1.3E+00	4	1.3E+00	1
Chloroform	B2	--	6.1E-03	4	N/A	--
Chrysene	B2	--	N/A	-	N/A	--
Dibenz(a,h)anthracene	B2	--	N/A	-	N/A	--
DEHP	B2	--	1.4E-02	4	ND	--
Indeno(1,2,3-cd)pyrene	B2	--	N/A	-	N/A	--
Methylene chloride	B2	--	7.5E-03	1	N/A	--
Nitrite	ND	--	ND	-	ND	--
Selenium sulfide	B2	--	N/A	-	N/A	--
Tetrachloroethylene	N/A	--	1.1E-02	2	6.0E-03	2
Trichloroethylene	B2	--	1.1E-02	4	2.0E-03	4
Acenaphthene	--	--	--	--	--	--
Acenaphthylene	D	--	--	--	--	--
Aluminum	D	--	--	--	--	--
Ammonia	--	--	--	--	--	--
Anthracene	D	--	--	--	--	--
Arsenic	A	--	5.0E-05	3	5.0E+01	3
Barium	--	--	--	--	--	--
Beryllium	B2	--	4.3E+00	1,3,6	8.4E+00	1,3,6
Chromium III	--	--	--	--	--	--
Chromium VI	A	--	--	--	4.1E+01	1,3
Cobalt	--	--	--	--	--	--

Table 2.2. (contd)

Contaminant	EPA Cancer Classification	Type of Cancer	Oral SF $(mg/kg\text{-}d)^{-1}$	Source of Information	Inhalation SF $(mg/kg\text{-}d)^{-1}$	Source of Information
Copper	D	--	--	--	--	--
Cyanide	D	--	--	--	--	--
Dieldrin	B2	--	1.6E+01	4	1.6E-01	4
Ethylbenzene	D	--	--	--	--	--
Ethylene glycol	--	--	--	--	--	--
Fluoranthene	D	--	--	--	--	--
Fluorene	D	--	--	--	--	--
Lead	B2	--	--	--	--	--
Manganese	D	--	--	--	--	--
Mercury	D	--	--	--	--	--
Naphthalene	D	--	--	--	--	--
Nickel	--	--	--	--	--	--
Nitrate	--	--	--	--	--	--
Pentachlorophenol	B2	--	1.2E-01	4	--	--
Phenanthrene	D	--	--	--	--	--
PCBs	B2	--	7.7E+00	4	--	--
Pyrene	D	--	--	--	--	--
Selenium	D	--	--	--	--	--
Silver	D	--	--	--	--	--
Strontium	D	--	--	--	--	--
Thallium compounds	D	--	--	--	--	--
Toluene	D	--	--	--	--	--
Tributyl phosphate	D	--	--	--	--	--
1,1,1-Trichoroethane	D	--	--	--	--	--
Uranium	--	--	--	--	--	--
Vanadium	--	--	--	--	--	--
Vanadium pentoxide	--	--	--	--	--	--
Vanadium sulfate	--	--	--	--	--	--
Vinyl chloride	A	--	1.9E+00	1	3.0E-01	1

Table 2.2. (contd)

Contaminant	EPA Cancer Classification	Type of Cancer	Oral SF $(mg/kg\text{-}d)^{-1}$	Source of Information	Inhalation SF $(mg/kg\text{-}d)^{-1}$	Source of Information
Xylenes	D	--	--	--	--	--
Zinc and compounds	D	--	--	--	--	--

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15) Agency of Toxic Substances Disease Registry (ATSDR). 1993. *Toxicological Profile for Nickel.* TP-92/14, U.S. Department of Health and Human Services, Division of Toxicology, Atlanta, Georgia.
16) Dollarhide, J. S. 1993. Memo to C. Sweeney. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio (February 26).
17) Dollarhide, J. S. 1992. Memorandum to C. Sweeney. U.S. Environmental Protection Agency, Region X, Environmental Criteria and Assessment Office, Cincinnati, Ohio.
18) Patty, F., ed. 1963. *Toxicology.* 2nd ed. Volume II of *Industrial Hygiene and Toxicology.* Cited in *CHRIS* (Volume 21 of TOMES) [CD-ROM], expires July 31, 1994. Micromedex, Inc., Denver, Colorado.
19) Dollarhide, J. S. 1993. *Chronic Inhalation RfD for 1,1,1-Trichloroethane.* U.S. Environmental Protection Agency, Superfund Health Risk Technical Support Center, Environmental Criteria and Assessment Office, Cincinnati, Ohio (October 14).
20) Dollarhide, J. S. *Risk Assessment Paper for: Provisional Oral RfD for Trichloroethylene (CAS #79-01-6).* Memorandum to P. Cirone, U.S. Environmental Protection Agency, Region X, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

The particular health effect on which the NOAEL or LOAEL is based will vary from experiment to experiment, and will not necessarily be the same for different substances. Because most substances have not been subject to a full battery of toxicology tests that span the range of potential effects, the confidence in the NOAEL or LOAEL will be lower for some substances than for others. In addition, different effects will be observable at different experimental doses. Generally, the experiment which shows the most sensitive effect at the lowest dose used among all experiments is chosen as the basis of the RfD.

Once the NOAEL or the LOAEL has been determined for the selected data set, a RfD is determined for the oral (**RfDo**) and/or inhalation (**RfDi**) route of exposure, depending on the exposure conditions of the original experiment. The RfD is determined using the following equation.

$$\text{RfD} = \text{NOAEL (or LOAEL)} / \text{Safety Factor}$$

The **safety factor** (**SF**) consists of factors representing a specific area of uncertainty inherent in the available data. Safety factors of 10 are typically used to account for

- differences in responsiveness between animals and humans
- variation in susceptibility among individuals in human populations
- use of subchronic data to estimate chronic effects and/or the use of a LOAEL instead of a NOAEL.

Safety factors of 100 or 1000 are common; in some cases where the data set consists of well-characterized human effects, the safety factor may be 1 or 10. A **modifying factor** (**MF**) is occasionally used if the data set (the original experiment plus any corroborating data) is considered of marginal quality. Finally, a description of the confidence that EPA has in the RfD and an identification of the critical biological effect on which the RfD is based are also identified in EPA's IRIS files and included in this document.

Potential health risks associated with exposure to noncarcinogenic substances are evaluated by calculating a hazard quotient. The hazard quotient is calculated as the ratio of the daily intake to the RfD, as follows:

$$\text{HQ} = \frac{\text{Intake}}{\text{RfD}}$$

If the estimated daily intake (using exposure assumptions appropriate to the actual situation) for any single chemical is greater than its RfD, the hazard quotient will exceed unity. A hazard quotient that exceeds unity indicates that there is a potential for adverse health effects associated with exposure to that chemical.

A hazard index is calculated to assess the potential for noncarcinogenic effects posed by more than one chemical. The hazard index approach assumes that simultaneous subthreshold exposures to several chemicals could result in an adverse health effect. It also assumes that the magnitude of the adverse effect will be proportional to the sum of the ratios of the subthreshold exposures to the acceptable exposure (the RfD). The hazard index is equal to the sum of the hazard quotients and is calculated as follows:

$$\text{HI} = \frac{E_1}{\text{RfD}_1} + \frac{E_2}{\text{RfD}_2} + \cdots + \frac{E_i}{\text{RfD}_i}$$

where E_i is the exposure level (or intake) for the i^{th} chemical, and RfD_i is the reference dose for the i^{th} chemical. E and RfD are expressed in the same units (mg/kg-day), and represent the same exposure period (i.e., chronic, subchronic [90-day] or short-term).

2.2 General Description of Carcinogenic Substance Information

Evidence of carcinogenicity of a chemical comes from two sources: lifetime studies with laboratory animals and human studies where excess cancer risk is associated with exposure to the chemical. If a carcinogenic response occurs at the exposure levels studied (typically high doses), responses are assumed to occur at all lower doses. Exposure to any level of a carcinogen is then considered to have a finite risk of inducing cancer. Cancer is generally considered to be a nonthreshold effect, that is, there is assumed to be (for regulatory purposes) no exposure level below which cancer could not occur or for which risk would be zero. The dose-response assessment for carcinogens derives a quantitative relationship between the dose (or more generally the human exposure) and the probability (or risk) of induction of a carcinogenic effect.

The major types of evidence that EPA uses to determine whether the agent in question poses a carcinogenic hazard in exposed humans consists of the following, as available: (1) human studies of the association between cancer incidence and exposure to the agent, and (2) long-term animal studies under controlled laboratory conditions. Supporting evidence is also considered, such as short-term tests for mutagenicity or other DNA damage, metabolic and pharmacokinetic properties, toxicological effects other than cancer, structure-activity relationships, and physical and/or chemical properties of the agent.

EPA uses a weight-of-evidence approach to classify the likelihood that the agent in question is a human carcinogen, based on human and animal evidence. The result is that each chemical is placed into one of the following five classes (note, class B also has two subcategories).

Class	Description
A	Human carcinogen
B	Probable human carcinogen B1 limited human evidence B2 sufficient evidence in animals and inadequate or no evidence in humans
C	Possible human carcinogen
D	Not classifiable as to human carcinogenicity
E	Evidence of noncarcinogenicity for humans

If a chemical is put in classes A through C, a dose-response assessment is performed. This entails an extrapolation from the generally high doses administered (generally in the feed or by gavage) to experimental animals or exposures noted in epidemiological studies to the exposure levels expected from human contact. Extrapolation is ordinarily carried out by fitting a mathematical model (generally

the linearized multistage model) to the set of animal data considered most appropriate, and then extending the model from the observed range down toward risks predicted at low-level chronic exposures. The linearized multistage model for low dose extrapolation is recommended by regulatory agencies (EPA 1986). Use of the linearized multistage model leads to a conservative upper bound estimate of risk. The linearized multistage model incorporates a procedure for estimating the largest possible slope at low doses that is consistent with experimental dose-response data generally obtained at higher doses (use of a large slope tends to produce a higher estimate of cancer risk). The most sensitive species of animal is used for extrapolation to humans (i.e., the assumption being that humans are as sensitive as the most sensitive animal species). The true risk is not likely to be higher than the estimate and is most likely lower, and could even be zero.

The slope of the 95% upper bound of this line is called the SF and is the number reported in the IRIS chemical files in units of (mg/kg)/day). When carcinogenicity data from animal studies are used, an animal-to-human scaling factor is used. Oral slope factors are available for most carcinogens listed in IRIS or HEAST. For some of the carcinogens in this document, an **inhalation cancer slope factor** is also given in the same units. If an inhalation slope factor is not available for a carcinogen, the oral slope factor is used along with estimates of inhalation exposure to characterize health risks through this route of exposure. This approach assumes that inhalation exposure is associated with cancer risks similar to the risks associated with oral exposure.

The slope factor is one measure of carcinogenic dose-response. Carcinogenic dose-response also can be expressed as risk per unit concentration in air or water, called the **unit risk factor (URF)**. The URF for inhalation exposure is expressed in units of $(\mu g/m^3)^{-1}$ in air, and the URF for oral exposure is expressed in units of $(\mu g/L)^{-1}$ in water.

Under an assumption of dose-response linearity at low doses, the SF defines an upper 95% confidence limit of the cancer risk caused by continuous constant lifetime exposure to one unit of carcinogen (in units of risk per mg/kg/day). Individual cancer risk is calculated as the product of exposure to a chemical (in mg/kg/day) and the SF for that chemical (in $mg/kg/day)^{-1}$, as follows:

$$\text{Risk} = \text{Intake} \times \text{SF}$$

Cancer risks from exposure to multiple carcinogens and multiple pathways were assumed to be additive, based on the EPA carcinogen risk assessment guidelines (EPA 1986).

2.3 Chemicals Included in This Document

The following chemicals are discussed:

1,1,1-Trichloroethane
Acenaphthene
Acenaphthylene
Aluminum
Ammonia
Anthracene
Antimony
Arsenic, Inorganic
Barium
Benz(a)anthracene
Benzene
Benzo(a)pyrene
Benzo(b)fluoranthene
Benzo(k)fluoranthene
Beryllium, Soluble Salts
Cadmium
Carbon Tetrachloride
Chlordane
Chloroform
Chromium III
Chromium VI, Soluble Salts
Chrysene
Cobalt
Copper
Cyanide, Free
Di(2-ethylhexyl)phthalate (DEHP)
Dibenz(a,h)anthracene
Dieldrin
Ethylbenzene
Ethylene Glycol
Fluoranthene
Fluorene
Indeno(1,2,3-cd)pyrene
Lead, Inorganic
Manganese
Mercury, Inorganic
Methylene Chloride
Naphthalene
Nickel
Nitrite
Pentachlorophenol
Phenanthrene
Polychlorinated Biphenyls (PCBs)
Pyrene
Selenium Sulfide
Silver
Strontium
Tetrachloroethylene
Thallium Compounds
Toluene
Tributyl Phosphate
Trichloroethylene
Uranium, Soluble Salts
Vanadium
Vanadium Pentoxide
Vanadium Sulfate
Vinyl Chloride
Xylenes
Zinc and Compounds

2.4 References

U.S. Environmental Protection Agency (EPA). 1986. "Guidelines for Carcinogen Risk Assessment." *Federal Register*. 51:33992. September 24.

U.S. Environmental Protection Agency (EPA). 1989. *Risk Assessment Guidance for Superfund. Human Health Evaluation Manual Part A, Final*. OSWER Directive 9285.701A. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables, FY - 1993*. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response and Environmental Criteria and Assessments Office, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables, FY - 1994, Supplement No. 2*. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response and Environmental Criteria and Assessments Office, Washington, D.C.

1,1,1-TRICHLOROETHANE

CASRN: 71-55-6
Synonyms: Chloroethene, Methyl chloroform, alpha-trichloroethane, 1,1,1-TCE

Oral Reference Dose - Chronic (RfDo):	Under review by EPA work group
Inhalation Reference Dose (RfDi):	Under review by EPA work group
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classified as to human carcinogenicity

The inhalation reference concentration for 1,1,1-trichloroethane was withdrawn from IRIS and HEAST and remains under review at this time. A review prepared by EPA (Dollarhide 1993) indicates that the reference concentration had been calculated using outdated methodology. The withdrawn reference dose (RfD) had been derived from a 6-month guinea pig study, using only a single dose, published in 1958. Calculated from the same data with current methodology, the value would be 2E+0 (mg/m^3). In a followup study, increased doses with shorter exposures did produce increased liver weight and lung inflammation, but the short exposures at high concentrations may not be appropriate for assessing chronic continuous exposures. Other studies may potentially be used as a basis for estimating a reference concentration, using neurotoxicity or liver effects; several studies support liver pathology as the critical effect. The Dollarhide memo describes how the reference concentration would be derived and concludes that either reference concentration might be supportable and are not substantially different.

Supporting Studies for the EPA Cancer Classification:

The IRIS record reviews the basis for the cancer classification. No human data have been reported. Animal studies to demonstrate carcinogenicity are inadequate. In one study, rats were given technical-grade 1,1,1-trichloroethane orally for 78 weeks, but a low survival of 3% precluded detection of tumors during the 32-week post-treatment observation period, and the observed tumors were common to aged rats and not dose related. Low survival in a similar mouse bioassay also resulted in inconclusive results. Another rat study in which rats inhaled 1,1,1-trichloroethane for 6 hours/day for 5 days/week for 12 months showed only an increase in liver cell changes in females at the highest dose; the doses used in this study may have been too low.

1,1,1-Trichloroethane has caused mutations in bacterial test systems, as well as some negative results. In most systems used to test for DNA damage, it has produced negative results. An isomer, 1,1,2-trichloroethane, is carcinogenic in mice. Other related compounds also cause cancer in rats and mice. A known contaminant of technical-grade 1,1,1-trichloroethane (1,4-dioxane) causes cancer in rats and mice.

References:

Dollarhide, J. S. 1993 (October 14). *Chronic Inhalation RfD for 1,1,1-Trichloroethane.* U.S. Environmental Protection Agency, Superfund Health Risk Technical Support Center, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

ACENAPHTHENE

CASRN: 83-32-9
Synonyms: Naphthaleneethylene, 1,2-Dihydroacenaphthylene, Peri-ethylenenaphthalene

Oral Reference Dose - Chronic (RfDo):	6E-2 (mg/kg)/day
Critical Effect:	Hepatotoxicity
Safety Factor (SF):	3000
Confidence:	Low
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	Pending (10/01/94)

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

A subchronic study in mice was performed for the EPA in which CD-1 mice were gavaged daily for 90 days, followed by a toxicological evaluation. Liver weight changes were accompanied by cellular changes in mid-dose and high-dose mice, and seemed to be dose dependent. Significant increases in cholesterol levels were observed in both male and female mice. The LOAEL from this study was 350 mg/kg-day. The low-dose group had increased liver weight also, but without cellular or cholesterol effects, so this was considered to be adaptive rather than adverse; the NOAEL is therefore the low dosage (175 mg/kg-day). This study was used directly to derive the subchronic reference dose (RfD) (6E-1 mg/kg-day; HEAST). Three other studies were judged inadequate to derive a RfD.

A safety factor of 3000 reflects 10 each for inter- and intraspecies variability, 10 for the use of a subchronic study for chronic RfD derivation, and 3 for the lack of adequate data in a second species and the lack of reproductive and developmental data. The confidence in the study is low, because the observed effects were considered to be adaptive rather than adverse. Confidence in the database is low because of the lack of supporting chronic toxicity data and the lack of reproductive and developmental studies. Low confidence in the RfDo follows.

Note: An evaluation of acenaphthene is under review by an interagency work group on carcinogenicity. Therefore, no cancer or mutagenicity studies were cited in the IRIS record, if any exist.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual.* EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington D.C.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

ACENAPHTHYLENE

CASRN: 208-96-8
Synonyms: Cyclopenta(de)naphthalene

Oral Reference Dose - Chronic (RfDo):	Pending (10/1/93)
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
Inhalation Unit Cancer Risk:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the EPA Cancer Classification:

There are no human data on acenaphthylene. HEAST indicates that data are insufficient for quantitative risk assessment. The IRIS record indicates that a single mouse skin painting study published in 1932 was judged inadequate to determine animal carcinogenicity. Two bacterial mutagenicity studies have been published; one was positive and one was negative. No other references were cited in the IRIS record.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

ALUMINUM

CASRN: 7429-90-5
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	1E+0 (mg/kg)/day
Critical Effect:	Neurotoxicity
Safety Factor (SF):	100
Confidence:	Medium
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The RfDo is based on studies in mice. The effects of oral aluminum are neurotoxicity and decreased body weight gain resulting from a decrease in food intake. The results of three subchronic studies in which aluminum was administered in drinking water (as nitrate, chloride, or sodium phosphate salts) indicated no observed histopathological alterations in the heart, liver, kidney, spleen, brain, or cerebellum.

Many reports have been published regarding aluminum toxicity in humans. Patients who had received long-term hemodialysis for chronic kidney failure developed a degenerative neurological syndrome which was characterized by the gradual loss of motor, speech, and cognitive functions. After aluminum was removed from dialysis fluid, the incidence of the syndrome rapidly declined, thereby strengthening the argument that aluminum was a causative agent. It is now understood that many of these patients also received high oral doses of aluminum to act as phosphate binders during dialysis.

Aluminum has been implicated as having an association with Alzheimer's disease. There continues to be no evidence that aluminum plays a causative role in the development of this disease, even though increased amounts of aluminum are found in the brain tissue of Alzheimer's patients.

A secondary target organ for aluminum in both humans and animals is bone. Several studies have shown that exposure to high concentrations of aluminum may cause a condition characterized by low bone formation. Symptoms include fractures, bone and muscle pain, nearsighted-blurred vision, and lack of response to vitamin D therapy. However, conclusions for these studies are not clear because of possible interactions with calcium.

Aluminum absorption from the gastrointestinal tract is dependent on chemical forms, pH of the intestine, concentration of aluminum, and dietary factors. Of the aluminum compounds tested, the following order of increasing absorption was observed: borate < glycinate < hydroxide < chloride < lactate < nitrate < citrate with absorptions ranging from 0.27% to 2.18%. Dietary uptake may be influenced by phosphate, citrate, and fluoride ions. Depending on solubility and pH, the bioavailability of aluminum can differ as much as 10 fold (as reported in rabbits).

The database lacks a well designed two-generation reproduction study. The safety factor (SF) for aluminum is 100 and includes factors of 3 for use of minimal LOAEL (instead of a NOEL), 10 for interspecies extrapolation, and 3 to protect sensitive individuals.

Supporting Studies for the EPA Cancer Classification:

There are no adequate human or animal data to link exposure to aluminum with cancer or mutagenicity. Several studies on the carcinogenicity of aluminum in humans did not find significant changes in mortality due to lung disease among men employed in aluminum smelters during the 1950s to 1970s. Animal data are also available, but it provides inconclusive evidence for links to cancer resulting from exposure to aluminum.

Reference:

Dollarhide, J. S. 1993. *Toxicity and Carcinogenicity of Aluminum CAS #7429-90-5*. Memorandum to C. Psyk. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio (April).

AMMONIA

CASRN: 7664-41-7
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	9.7E-1 (mg/kg)/day (HEAST)
Inhalation Reference Dose (RfDi):	
Inhalation Reference Concentration (RfC):	1E-1 mg/m^3
Critical Effect:	Lack of evidence of decreased pulmonary function or changes in subjective symptomatology (for the NOAEL in humans); increased severity of rhinitis and pneumonia with respiratory lesions (for the LOAEL in rats).
Safety Factor (SF):	30
Confidence:	Medium
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	No data

Supporting Studies for the Inhalation Reference Concentration (RfC):

The RfC is based on occupational exposure and supported by experimental data in rats. In an occupational study of workers with long-term exposures to relatively low concentrations of ammonia, no difference in lung function was noted between this group and an unexposed comparison group; however, the exposed workers reported symptoms of eye, nose, throat, lung, and skin irritation. Nevertheless, those exposure levels were considered to be NOAEL levels. In a rat inhalation study, ammonia was studied for its ability to exacerbate the effects of inoculation with a microbiological agent causing murine pneumonia. Ammonia increased the severity of the infection and microscopic lesions. This study was used to derive the LOAEL, which was similar to the human NOAEL.

Other studies in animals and people indicate that higher doses of ammonia penetrate deeper into the respiratory tract. At lower doses, a greater fraction reacts with the upper respiratory tract. Also, because rats are obligate nose-breathers, the differences in air flow make extrapolation from rats to humans somewhat uncertain.

The safety factor of 10 was applied to the human NOAEL to protect sensitive individuals. Another factor of 3 was used due to lack of chronic data and lack of reproductive studies.

Additional studies of volunteers, exposed by inhalation to higher doses than the occupational study described above, reported irritant effects but no other gross clinical signs. In one followup to an acute high-dose exposure, possible residual effects related to the initial accident were noted. A minimal irritation level was derived from the human studies and supported by tests of impairment of tracheal ciliary movement in rats exposed by inhalation. A number of studies in mice, guinea pigs, chickens, and other species generally support the above findings.

Confidence in the critical human and rat studies was medium; additional subchronic and acute human studies support the NOAEL. Confidence in the database is medium to high due to lack of reproductive and chronic studies, although pharmacokinetic studies suggest that ammonia is unlikely to be distributed to tissues at low exposure levels.

Reference:

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

ANTHRACENE

CASRN: 120-12-7
Synonyms: Paranaphthalene

Oral Reference Dose - Chronic (RfDo):	3E-1 (mg/kg)/day
Critical Effect:	No observed effects
Safety Factor (SF):	3000
Confidence:	Low
Inhalation Reference Dose:	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The chronic RfD is based on a subchronic mouse study in which anthracene was administered orally to mice for 90 days. A wide range of toxicity was evaluated, and no treatment-related effects were noted. Therefore, the high dose is defined as the no-effect level (NOEL). In another study, a chronic dietary exposure with a long followup period of observation in rats did not cause adverse effects, but the range of effects examined was limited, and the study was therefore not used to derive the RfD.

A safety factor of 3000 was used. Factors of 10 were used for inter- and intraspecies variability, and another factor of 3 for the lack of adequate toxicity data in a second species and the lack of reproductive and developmental data. The additional factor of 10 is used because the chronic RfD was based on a subchronic study. Confidence in the principal study is low because it was a well-designed study which, however, failed to identify a LOAEL. Confidence in the database is low because of the lack of adequate toxicity information in a second species and the lack of reproductive and developmental studies. Overall confidence in the RfD is, therefore, low.

Supporting Studies for the EPA Cancer Classification:

There is no human data evaluating the carcinogenicity of anthracene. Animal data are inadequate. In an early study in which anthracene was given in the diet to rats, no tumors were noted, but experimental details were unclear. In another rat study in which anthracene was implanted into the lungs of rats, anthracene did not cause lung tumors. Four studies for complete or initiating carcinogenic activity in mouse skin painting studies have been negative.

Tests for DNA damage and mutation in bacterial and yeast test systems have generally been negative. Anthracene has also been negative in cultured mammalian cells tests for DNA damage, mutation, chromosome effects, and neoplastic transformation.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

ANTIMONY

CASRN: 7440-36-0
Synonyms: Antymon, Stibium

Oral Reference Dose - Chronic (RfDo):	4E-4 (mg/kg)/day
Safety Factor (SF):	1000
Critical Effect:	Longevity, blood glucose, and cholesterol
Confidence:	Low
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
EPA Cancer Classification:	

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

An experimental group of 50 male and 50 female rats was administered 5 ppm potassium antimony tartrate in water. Over the study period, growth rates of treated animals were not affected, but male rats survived 106 and females 107 fewer days than did controls at median lifespans. Nonfasting blood glucose levels were decreased in treated males, and cholesterol levels were altered in both sexes. A decrease in mean heart weight for the males was noted. No increase in tumors was seen as a result of treatment.

A safety factor of 1000 (10 for interspecies conversion, 10 to protect sensitive individuals, and 10 because the effect level was a LOAEL and no NOEL was established) was applied to the LOAEL to derive the reference dose. Confidence in the chosen study is rated as low because only one species was used, only one dose level was used, no NOEL was determined, and gross pathology and histopathology were not well described. Confidence in the database is low due to lack of adequate oral exposure investigations. Low confidence in the RfDo is a result.

In another study, mice were given potassium antimony tartrate in drinking water for 18 months. Lifespans were significantly reduced in both males and females, but the degree of antimony toxicity was less severe in mice than rats. Another study reported disturbances in glucose and cholesterol metabolism in rats ingesting antimony, but no signs of injury to the heart were observed in rats receiving doses up to 100 (mg/kg)/day. Substantially higher doses of antimony trioxide were tolerated by rats.

In an accidental human exposure, 70 people became acutely ill after drinking lemonade containing 0.013% antimony. The lemonade had been prepared and left overnight in buckets coated with an enamel containing 2.88% antimony trioxide. Occupational exposures at higher concentrations have been reported. Myocardial effects are among the best-characterized human health effects associated with antimony exposure, but data are not adequate to derive reference doses directly from human exposure data. Parallel studies in rats and rabbits also demonstrated electrocardiogram (EKG) alterations. One study indicated that women workers exposed in an antimony plant experienced a greater incidence of spontaneous abortions than did a control group of nonexposed working women. A high rate of premature deliveries among women workers in antimony smelting and processing was also observed.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994. *Integrated Risk Information System*. Toxicology Data Network (ToxNet), National Library of Medicine, Bethesda, Maryland.

ARSENIC, INORGANIC

CASRN: 7440-38-2
Synonyms: Gray-arsenic

Oral Reference Dose - Chronic (RfDo):	3E-4 (mg/kg)/day
Critical Effect:	Hyperpigmentation, keratosis, and possible vascular complications in humans.
Safety Factor (SF):	3
Confidence:	Medium
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Unit Risk:	5E-5 (per μg/L proposed)
Inhalation Cancer Slope Factor:	5E+1 per mg/kg-day (HEAST)
Inhalation Unit Cancer Risk:	4.3E-3/$\mu g/m^3$
EPA Cancer Classification:	A; human carcinogen

Note: Cacodylic acid (dimethyl arsinic acid) has a separate IRIS record.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The RfD is derived from a human study in which symptoms were described in people drinking water naturally high in arsenic. The critical effect, which increases with age and increasing dose, is Blackfoot disease, characterized by hyperpigmentation and keratosis of the feet. In this study, skin lesions were also noted and may be a more sensitive indicator. The NOAEL and LOAEL were calculated from the average concentrations in the drinking water wells. Other studies support the general findings and also suggest an effect on nerve conduction velocity.

A safety factor of 3 was used to account for lack of reproductive toxicity data and because the NOAEL from the critical study may not account for all sensitive individuals. The supporting database of human studies is extensive but somewhat flawed; the database nevertheless does support the choice of the NOAEL. However, there was not a clear consensus among EPA scientists on the RfDo. Applying the EPA methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD. Risk managers should recognize the considerable flexibility afforded them in formulating regulatory decisions when uncertainty and lack of clear consensus are taken into account.

Arsenic has caused malformations in hamsters after intravenous injections of sodium arsenate. Rats and mice exposed to low levels of arsenic in the drinking water have shown no fetal effects. Absorption data are available; methylated arsenic species are 1 order of magnitude less well absorbed, less toxic, and less teratogenic. Confidence in the critical study and in the supporting database are both medium. The database is flawed in the area of estimations of total doses. Some evidence in several animal species suggests that arsenic might be an essential nutrient.

Supporting Studies for the EPA Cancer Classification:

Arsenic has been classified as a human carcinogen based on increased lung tumor and skin cancer incidences in several human populations. Several occupational cohorts (smelters) have shown

increased lung cancer rates. Workers manufacturing or applying arsenical pesticides have shown an increase in lung cancer, and one study of residents near a pesticide manufacturing facility have also shown an excess of lung cancer.

Arsenic has also been linked to skin cancer in populations exposed to drinking water with naturally high levels of arsenic. In a followup study in one of the community settings, there were also increases in several other types of cancer, and apparently these were dose related. Persons treated with arsenical medicines are also at an increased risk of skin cancer.

There has not been consistent demonstration of arsenic carcinogenicity in animals, perhaps due to an insufficient retention time in the lung. Arsenic causes neoplastic transformation and affects the DNA of cultured mammalian cells. It does not cause mutation in bacterial test systems but gives other indications of DNA effects.

The oral cancer slope factor has not received final approval. However, after extensive outside peer review, the EPA Administrator recommended that it be used, although it may be revised downward by as much as an order of magnitude. It is derived from the drinking water studies described above. The inhalation unit risk is based on the assumption that 30% of the arsenic that is inhaled is absorbed. The unit risk is derived from the geometric mean of several occupational studies plus another geometric mean calculated by EPA from distinct exposed populations. The range of estimates was within a factor of 6. Lung cancers occurring with occupational exposures are generally associated with the inhalation route of exposure.

Reference:

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

BARIUM

CASRN: 7440-39-3
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	7E-2 (mg/kg)/day
Critical Effect:	Increased blood pressure
Safety Factor (SF):	3
Confidence:	Medium
Inhalation Reference Dose (RfDi):	Under review
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
EPA Cancer Classification:	No data

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

No single study is appropriate to calculate a lifetime RfD for barium. Instead, the RfD is based on a weight of evidence approach which takes into account recent findings from human epidemiologic and rodent studies. A NOAEL of 10 mg/L was based on a study in which barium chloride was administered in the drinking water of 11 healthy male volunteers for 10 weeks. There were no changes in systolic or diastolic blood pressures or serum chemistry. There was an increase in serum calcium levels that was attributed to a decrease in serum albumin levels. This increase, although statistically significant, was considered borderline and not clinically significant. There were also no changes in electrocardiograms and no significant arrhythmias.

A retrospective epidemiology study was done which compared human mortality and morbidity rates in populations ingesting elevated barium levels (2 to 10 mg/L) in their drinking water to populations ingesting very little or no barium (less than or equal to 0.2 mg/L). Differences in mortality rates from all cardiovascular diseases were significantly higher ($p < 0.05$) in the communities with elevated barium. However, these differences were largely in the 65-and-over age group and did not account for confounding variables such as population mobility, use of water softeners, or medication.

The data summarized in IRIS2 support the finding that the critical effect is hypertension (which results from long exposure durations) and that the population most at risk is the adult male. Because of the focus on males and the reliance on several supporting studies, a three-fold safety factor (SF), instead of a ten-fold SF, was chosen as most appropriate to protect sensitive individuals within the population. Confidence in the critical study is medium, confidence in the database is medium, and overall confidence in the RfD is medium.

Additional Comments:

Occupational studies of workers exposed to barium dust have shown that workers develop "baritosis." Affected workers showed no symptoms, no abnormal physical signs, no loss of vital capacity or interference with function, although they had a significantly higher incidence of hypertension.

When rats were exposed to graded doses of barium in drinking water for 68 weeks, no significant histologic, carcinogenic, or cardiovascular (including hypertension) effects were observed except in the highest dose group, which exhibited ultrastructural changes in the kidney glomeruli and the presence of myelin figures.

In another study, weanling rats were given barium in drinking water for up to 16 months. There were no signs of toxicity at any barium dose level, except for an increase in systolic blood pressure measurements in animals exposed to 10 and 100 ppm, which might have been due to restricted intake of beneficial metals such as calcium.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

BENZ(a)ANTHRACENE

CASRN: 56-55-3
Synonyms: Benzanthracene, Benzo(b)phenanthrene, 1,2-Benzanthracene, Benzanthrene

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the EPA Cancer Classification:

Although there are no human data that specifically link benz(a)anthracene to human cancers, it is a component of mixtures that have been associated with human cancer. These include coal tar, soots, coke oven emissions, and cigarette smoke.

There is sufficient evidence of carcinogenicity in animals. Male mice exposed to benz(a)anthracene by gavage (15 treatments) showed increased incidences of pulmonary adenoma and hepatoma. As reported in the IRIS record, male mice given benz(a)anthracene by intraperitoneal injection on days 1, 8, and 15 of age showed a significant increase in liver carcinomas and liver adenoma or carcinomas; female mice did not develop liver tumors but did develop pulmonary adenomas. In other studies, subcutaneous injection of benz(a)anthracene caused injection-site sarcomas, and intramuscular injection caused fibrosarcomas and hemangioendotheliomas in mice.

Benz(a)anthracene demonstrated both complete carcinogenicity and initiating activity in three strains of mice in skin painting studies.

Benz(a)anthracene causes mutations in some bacterial test systems and in a fruit fly test system, DNA damage in rat and human cells in culture, and forward mutations in several other cultured cell lines. It causes chromosomal damage and neoplastic transformation in mammalian cells.

Benz(a)anthracene has a "bay region," the structure associated with carcinogenic and mutagenic activity in polyaromatic hydrocarbons. It is metabolized by mixed function oxidases to reactive bay region diol epoxides that are mutagenic in bacteria and tumorigenic in mouse skin painting assays.

Note: EPA is considering a toxicity equivalency approach for polyaromatic hydrocarbons in which carcinogenic potency is relative to that of benzo(a)pyrene. When these compounds occur in mixtures, this approach may be warranted.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

BENZENE

CASRN: 71-43-2
Synonyms: Benzol, Coal naphtha

Oral Reference Dose - Chronic (RfDo):	Not available
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	2.9E-2 per (mg/kg)/day
Inhalation Cancer Slope Factor:	2.9E-2 (mg/kg)/day (HEAST)
Inhalation Unit Risk:	8.3E-6 per ($\mu g/m^3$)
EPA Cancer Classification:	A; human carcinogen

Supporting Studies for the EPA Cancer Classification:

Leukemia and preleukemia were observed in several occupational studies of workers with known inhalation exposure to benzene in the shoe industry and rubber industry. Numerous other epidemiologic and case studies have reported an increased incidence or a causal relationship between leukemia and exposure to benzene.

Both gavage and inhalation exposure of rodents to benzene have resulted in development of neoplasia. Dose-related increased incidences of mammary tumors were seen after lifetime gavage studies in female Sprague-Dawley rats, as well as increases in Zymbal gland carcinomas, oral cavity carcinomas, and leukemia/lymphomas in rats of both sexes. In another study of mice and rats, increased incidences of Zymbal gland carcinoma were seen in male and female rats and mice. Male and female rats had oral cavity tumors, and males showed increased incidences of skin tumors. Mice of both sexes had increased incidence of lymphomas and lung tumors. Other tumors and a slight increase in hematopoietic neoplasms were seen as well. Other studies reported increases in neoplasms in various tissues in rats and mice by inhalation.

Numerous studies have found significant increases in chromosome aberrations of bone marrow cells and peripheral lymphocytes among workers exposed to benzene and in bone marrow cells from rabbits, rats, and mice. Benzene was not mutagenic in several bacterial and yeast systems, in the sex-linked recessive lethal mutation assay with *Drosophila melanogaster*, or in the mouse lymphoma cell forward mutation assay.

The oral cancer slope factor was derived from human data for inhalation exposure. The human respiratory rate was assumed to be 20 m^3/day and the human drinking water intake was assumed to be 2 L/day. The fraction of the administered dose absorbed via inhalation and via drinking water were assumed to be equal. The inhalation unit risk estimate is the geometric mean of four point estimates using the human studies.

The human studies were sufficiently large and were followed for an adequate time period. The increases in leukemia were statistically significant and dose related in one of the studies. The one-hit method was used for extrapolation. A total of 21 unit risk estimates were prepared using 6 extrapolation models and various combinations of epidemiologic data. These estimates range over slightly one order of magnitude.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

BENZO(a)PYRENE

CASRN: 50-32-8
Synonyms: B(a)P, BaP, 3,4-benzopyrene

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	7.3E+0 per (mg/kg)/day
Inhalation Cancer Slope Factor:	Not available
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the EPA Cancer Classification:

Human carcinogenicity data specifically linking benzo(a)pyrene to a carcinogenic effect are lacking, but lung cancer has been shown to be induced in humans by various mixtures of polycyclic aromatic hydrocarbons known to contain benzo(a)pyrene including cigarette smoke, roofing tar, and coke oven emissions. It is not possible, however, to conclude from this information that benzo(a)pyrene is the responsible agent.

The animal evidence of carcinogenicity is sufficient. The animal data consist of dietary, gavage, inhalation, intratracheal instillation, dermal, and subcutaneous studies in numerous strains of at least four species of rodents and several primates. In various species of animals, dose-responsive increases in tumors have been induced at the site of exposure; in the stomach and forestomach after gavage; in the forestomach, larynx, and esophagus after feeding; in the respiratory and upper digestive tract after intratracheal instillation; and at subcutaneous and intraperitoneal injection sites. Benzo(a)pyrene causes skin tumors in several species, and is both an initiator and a complete carcinogen in mouse skin bioassays. Increased incidences of tumors have been seen at a number of other tissue sites after other routes of exposure.

Benzo(a)pyrene is genotoxic in a broad range of prokaryotic and mammalian cell assay systems. In prokaryotes, it causes DNA damage, and forward and reverse mutations. In mammalian cell culture assays, it causes DNA damage, forward mutations, chromosomal effects, and cell transformation.

The oral cancer slope factor is based on the geometric mean of four slope factors obtained by different modeling procedures. Each slope factor estimate is based on a low-dose extrapolation procedure that entails the use of multiple assumptions and default procedures. The slope factor is derived from the combination of multiple data sets from two different reports using more than one sex and species. After considerable discussion about the interpretation of the data and the modeling procedures, EPA corrected the slope factor in June 1992. According to IRIS, the data are considered less than optimal, but acceptable. When several acceptable data sets are available, the use of the geometric mean of multiple slope factors is preferred because it makes use of more of the available data.

The carcinogenicity assessment is under review as of September 1, 1993.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

BENZO(b)FLUORANTHENE

CASRN: 205-99-2
Synonyms: 3,4-Benzofluoranthene, Benz(e)acephenanthrylene

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the EPA Cancer Classification:

Although there are no human data that specifically link benzo(b)fluoranthene to human cancers, it is a component of mixtures that have been associated with human cancer. These include coal tar, soots, coke oven emissions, and cigarette smoke.

There is sufficient evidence of carcinogenicity in animals. Benzo(b)fluoranthene caused a dose-related increase of lung tumors in rats after implantation into the lung. When benzo(b)fluoranthene was injected intraperitoneally into mice, liver tumors in male mice and lung tumors in male and female mice were increased. In another study, injection site tumors occurred in male and female mice after subcutaneous injections of benzo(b)fluoranthene. Benzo(b)fluoranthene has not been studied by oral administration, but tumors occur in several tissues after other routes of exposure.

Benzo(b)fluoranthene has yielded positive results for both initiating and promoting activity in mouse skin painting studies. In female mice, skin tumors developed within 8 months in the high-dose group and within 12 months in the mid-dose group. In a tumor promotion study, skin application of benzo(b)fluoranthene followed by treatment with a tumor promoter caused a dose-related increase in both the percentage of tumor-bearing animals and in the number of tumors per animal. Similar studies corroborate this result.

Benzo(b)fluoranthene causes mutations in bacterial test systems; some studies have shown mixed positive and negative results. Benzo(b)fluoranthene does not have a classic "bay region" structure but is metabolically activated to dihydrodiols, the typical reactive form of polyaromatic hydrocarbons. The 9,10-dihydrodiol metabolite of benzo(b)fluoranthene is positive in skin painting assays, suggesting the formation of a reactive diol-epoxide.

Note: EPA is considering a toxicity equivalency approach to polyaromatic hydrocarbons in which carcinogenic potency is relative to that of benzo(a)pyrene. When these compounds occur in mixtures, this approach may be warranted.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

BENZO(k)FLUORANTHENE

CASRN: 207-08-9
Synonyms: 11,12-Benzo(k)fluoranthene

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the EPA Cancer Classification:

Although there are no human data that specifically link exposure to benzo(k)fluoranthene to human cancers, it is a component of mixtures that have been associated with human cancer. These include coal tar, soots, coke oven emissions, and cigarette smoke.

There is sufficient evidence of carcinogenicity in animals. Benzo(k)fluoranthene caused a dose-related increase in lung tumors in rats when implanted into the lung. After intraperitoneal injection into mice, a slight but not significant increase in liver tumors was seen in male mice, as well as an increase in lung tumors in male and female mice; this study is considered to be a short-term lung tumor assay.

When applied to the skin of mice and followed by treatment which causes tumor progression, skin tumors developed. In two similar studies, both the percentage of tumor-bearing animals and the number of tumors per animal increased, and appeared to be dose related.

Benzo(k)fluoranthene causes mutations in bacterial test systems in the presence of an exogenous metabolic activating system.

Note: EPA is considering a toxicity equivalency approach to polyaromatic hydrocarbons in which carcinogenic potency is relative to that of benzo(a)pyrene. When these compounds occur in mixtures, this approach may be warranted.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

BERYLLIUM, SOLUBLE SALTS

CASRN: 7440-41-7
Synonyms: Glucinum

Oral Reference Dose - Chronic (RfDo):	5E-3 (mg/kg)/day
Critical Effect:	No adverse effects
Safety Factor (SF):	100
Confidence:	Low
Inhalation Reference Concentration:	No data
Oral Cancer Slope Factor:	4.3 $((mg/kg)/day)^{-1}$
Inhalation Cancer Slope Factor:	8.4 $((mg/kg)/day)^{-1}$
Inhalation Unit Cancer Risk:	2.4E-3 per ($\mu g/m^3$)
EPA Cancer Classification:	B2; probable human carcinogen.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The chronic RfDo is based on a lifetime study of rats in which beryllium sulfate was added to the drinking water. At natural death, gross and microscopic changes were noted in major organs after the single dose tested; however, no treatment-related effects were observed in these organs, in lifespan, or in blood chemistry parameters. In a similar study in mice, dose-related effects were not considered to be adverse.

A safety factor of 100 includes a factor of 10 for conversion of animal to human data and a factor of 10 to protect sensitive human subpopulations. Numerous inhalation studies are considered as low to medium in quality and thus do not provide support for the toxicity database for derivation of the RfDo.

Supporting Studies for the EPA Cancer Classification:

Human data on beryllium carcinogenicity are inadequate. Occupational exposure studies of inhaled beryllium have reported the occurrence of lung tumors. One study of deaths from cancer among white males employed in beryllium processing showed an increased incidence of lung cancer. A larger study of workers from various beryllium plants also found a statistically significant increase in lung cancer. These epidemiological studies, however, are considered inadequate for several reasons. They have been inadequately controlled for confounding factors such as smoking, have improperly calculated the expected deaths from lung cancer, have included employees in the beryllium industry who were not exposed to beryllium (e.g., salespeople, clerks), and have used inappropriate controls (ATSDR 1993). In addition, if findings are adjusted for smoking, the differences between those exposed and the control group are not significant.

Some beryllium compounds are carcinogenic in animals. Beryllium has been demonstrated to produce lung cancer via inhalation in both male and female rats and in monkeys. Lung tumors were observed in rats exposed to beryllium sulfate by inhalation. Lung tumors were also induced by intratracheal instillation of beryllium compounds in rats and monkeys. Slight increases in cancer were reported in rats administered beryllium sulfate in drinking water for their lifetime. In numerous studies, bone tumors were induced in rabbits by injection exposure. Many of the studies have been criticized for poor documentation, for being conducted at a single dose level, or for failure to include controls. Collectively, the animal data indicate that beryllium is carcinogenic in animals by several routes of exposure.

BERYLLIUM, SOLUBLE SALTS

Ambient air typically has insoluble beryllium compounds such as beryllium oxide and metallic beryllium, and water is characterized with soluble forms. The carcinogenic potency varies with the form of beryllium present in the environment. Beryllium compounds are absorbed rapidly through the lungs, while absorption through the gastrointestinal tract in animals is poor (ATSDR 1993).

References:

Agency of Toxic Substances Disease Registry (ATSDR). 1993 (April). *Toxicological Profile for Beryllium*. U.S. Department of Health and Human Services, Division of Toxicology, Atlanta, Georgia.

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

CADMIUM

CASRN: 7440-43-9
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	5E-4 (mg/kg)/day **(drinking water)**
Critical Effect:	Significant proteinuria
Safety Factor (SF):	10
Confidence:	High
Oral Reference Dose - Chronic (RfDo):	1E-3 (mg/kg)/day **(dietary)**
Inhalation Reference Dose (RfDi):	Under review
Inhalation Unit Cancer Risk:	1.8E-3 per ($\mu g/m^3$)
Inhalation Cancer Slope Factor:	
Oral Cancer Slope Factor:	No data available
EPA Cancer Classification:	B1; probable human carcinogen

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The RfD is based on the highest level of cadmium in the human renal cortex (i.e., the critical level) not associated with significant proteinuria (i.e., the critical effect). The above data were obtained from many studies on the chronic toxicity of cadmium in both humans and animals; there is sufficient human information available that IRIS does not present noncarcinogenic toxicity data for animals. Because the fraction of ingested cadmium that is absorbed appears to vary with the source, both food and drinking water reference factors are provided. High confidence in underlying databases lead to high confidence for both RfDs. The safety factor accounts for intra-human variability in the toxicity of this chemical in the absence of specific data on sensitive individuals.

Supporting Studies for the EPA Cancer Classification:

A two-fold excess risk of lung cancer was observed in cadmium smelter workers. Limited evidence from highly exposed workers in occupational epidemiologic studies of cadmium is consistent across investigators and study populations; the increased lung cancer risk was probably not due to the presence of arsenic or to smoking. Studies of human ingestion of cadmium are considered inadequate to assess carcinogenicity.

There is sufficient evidence of carcinogenicity in rats and mice by inhalation and intramuscular and subcutaneous injection, but there is inadequate evidence for carcinogenicity by the oral route. Exposure of rats by inhalation to cadmium as cadmium chloride (but not cadmium oxide) for 18 months, with an additional 13-month observation period, resulted in significant increases in lung tumors. Seven studies in rats and mice where cadmium salts (acetate, sulfate, chloride) were administered orally have not shown evidence of carcinogenic response. Results of mutagenicity tests in bacteria and yeast have been inconclusive. Positive responses have been obtained in mutation assays in Chinese hamster cells and in mouse lymphoma cells. Conflicting results have been obtained in assays of chromosomal aberrations in human lymphocytes treated in vitro or obtained from exposed workers.

References:

Dollarhide, J. S. 1994. Memorandum to A. D. Maughan, Pacific Northwest Laboratory. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio (April).

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994. *Integrated Risk Information System*. Toxicology Data Network (ToxNet), National Library of Medicine, Bethesda, Maryland.

CARBON TETRACHLORIDE

CASRN: 56-23-5
Synonyms: Benzinoform, Carbon tet, Perchloromethane, Methane tetrachloride

Oral Reference Dose - Chronic (RfDo):	7E-4 (mg/kg)/day
Critical Effect:	Liver lesions
Safety Factor (SF):	1000
Confidence:	Medium
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	1.3E-1 per (mg/kg)/day
Inhalation Cancer Slope Factor:	5.3E-2 per (mg/kg)/day (HEAST)
EPA Cancer Classification:	B2; probable human carcinogen
Inhalation Unit Cancer Risk:	1.5E-5 per ($\mu g/m^3$)

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

When male rats were given carbon tetrachloride orally for 12 weeks, liver damage was observed in two dose groups; the lower of the two doses was established as the LOAEL, and the NOAEL was a lower dose that did not show the liver effects. Subchronic studies in mice support the critical effect and the NOAEL and LOAEL levels. The safety factor includes factors of 10 for inter- and intraspecies variability and for extrapolation from subchronic to chronic duration of exposure. IRIS assigns the study high confidence because it was well conducted and there was good response in the liver, the target organ. Confidence in the database is medium; four supporting studies are available, but reproductive and developmental studies are lacking. Overall confidence in the RfD, therefore, is medium.

Supporting Studies for the EPA Cancer Classification:

Human data on the carcinogenicity of carbon tetrachloride are inadequate. There have been three case reports of liver tumors developing after carbon tetrachloride exposure, and additional epidemiology studies of workers that suggest an excess risk of liver cancer, but the studies are insufficient for establishing clear evidence of human carcinogenicity.

There is sufficient evidence of carcinogenicity in animals. Carbon tetrachloride produces liver tumors in rats, mice, and hamsters. In three strains of rats given carbon tetrachloride by subcutaneous injection, liver tumors developed. In two other rat strains, nodules but not tumors were observed. Sensitivity to tumor formation varied inversely with the amount of cirrhosis seen. In another study, rats were given carbon tetrachloride orally for 78 weeks; again, liver tumors were increased. In a parallel study with mice, liver tumors increased with dose. Hamsters and five other mouse strains also developed liver tumors.

The carcinogenicity studies were all deficient in some respect, but similar results in all studies suggested a common biologic mechanism. Since the risk estimated from the available studies (in several species and strains) varies by only 2 orders of magnitude, the geometric mean of the estimate slope factors was used.

For the oral cancer slope factor, the linearized multistage model with extra risk was used to calculate the individual slope factors. For the inhalation cancer slope factor (since no inhalation studies

have been reported), the oral cancer data were used, and it was assumed that humans have a daily air intake of 20 m^3/day and a 40% absorption rate. A range of estimates of unit risk for inhalation exposures from the four oral studies was determined. The confidence in the inhalation slope factor is the same as for the oral studies on which it is based.

Studies of carbon tetrachloride for mutagenicity and DNA damage are generally negative. It is not mutagenic in two bacterial test systems and does not appear to cause chromosome aberrations and other evidence of DNA damage in mammalian cells, but it does produce mitotic recombination (chromosomal effects) in yeast at high concentrations. Carbon tetrachloride may be metabolized to reactive intermediates capable of binding to cellular macromolecules. Negative results in bacterial test systems may be due to inadequate metabolic activation.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

CHLORDANE

CASRN: 57-74-9
Synonyms: Chlorindan, Chlor kil, Corodan, Dowchlor, Other trade names

Oral Reference Dose - Chronic (RfDo):	6E-5 (mg/kg)/day
Critical Effect:	Regional liver hypertrophy in female rats
Safety Factor (SF):	1000
Confidence:	Low
Inhalation Reference Dose (RfDi):	Under review by EPA work group
Oral Cancer Slope Factor:	1.3E+0 per (mg/kg)/day
Inhalation Cancer Slope Factor:	1.3E+0 per (mg/kg)/day (HEAST)
EPA Carcinogen Classification:	B2; probable human carcinogen
Inhalation Unit Risk:	3.7E-4 per ($\mu g/m^3$)

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The NOEL was calculated from a 2-year dietary study. Liver lesions occurred in the mid-dose female rats, this was the "Lowest Effect Level." A NOEL was set at the low-dose level, which did not cause liver lesions. The safety factor of 100 was assigned due to the inter- and intraspecies differences. An additional SF of 10 was also used due to a lack of adequate reproductive studies, lack of a second mammalian species, the insensitivity of the endpoints used in the cited study, and the knowledge that chlordane is known to bioaccumulate over a chronic exposure duration. The database was assigned low confidence, while the critical study was assigned a medium confidence; overall confidence in the RfD is therefore low.

Supporting Studies for the EPA Cancer Classification:

Human data as to carcinogenicity are inadequate. While there are 11 case reports of effects in children exposed to chlordane and heptachlor, no information on dose or other confounding factors is available; therefore, no conclusions can be drawn. One epidemiologic study of pesticide workers and another of pesticide manufacturing workers following exposures to chlordane and/or heptachlor were considered to be statistically insignificant. Both studies were also confounded by exposures from other chemicals.

Animal data are sufficient. Chlordane has been studied in four long-term cancer bioassays in mice and four in rats. Dose-related incidences in liver cancer were the major finding in three mouse studies. Rats also developed liver tumors (one study), enlarged livers, and/or liver lesions in several studies. The geometric mean of the slope factors for the most sensitive species, mouse, was consistent with the slope factor derived from the rat data.

Chlordane does not appear to be mutagenic in bacterial test systems (three studies) but does cause neoplastic transformation in cultured mammalian cells. It causes DNA damage in yeast and plant assays, human cells, and fish. Five pesticides structurally related to chlordane have produced liver tumors in mice.

The inhalation cancer slope factor was calculated from the same oral data by a route-to-route extrapolation method (HEAST). The inhalation unit risk is derived from the oral data, using the linearized multistage procedure with extra risk (IRIS).

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

CHLOROFORM

CASRN: 67-66-3
Synonyms: Trichloromethane, Formyl trichloride, Methyl trichloride

Oral Reference Dose - Chronic (RfDo):	1E-2 (mg/kg)/day
Critical Effect:	Fatty cyst formation in liver
Safety Factor (SF):	1000
Confidence:	Medium
Inhalation Reference Dose:	Under review by EPA
Oral Cancer Slope Factor:	6.1E-3 per (mg/kg)/day
Inhalation Cancer Slope Factor:	8.1E-1 per (mg/kg)/day (HEAST)
Inhalation Unit Cancer Risk:	2.3E-5 per ($\mu g/m^3$)
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

Beagle dogs were administered chloroform in a toothpaste base in gelatin capsules for 7.5 years. Fatty cysts considered to be treatment-related were observed in livers of some dogs in both treatment groups. Microscopically altered liver cells were considered treatment-related but not dose-dependent. A dose-related increase in two serum liver enzymes was noted in the high-dose animals. In another rat study, chloroform caused changes in plasma cholinesterase and liver weights. Chloroform is considered to be highly fetotoxic, but not teratogenic. Other data in the literature also indicate changes in liver fat to be treatment-related.

The critical study was of chronic duration, used a fairly large number of dogs, and measured multiple endpoints; however, only two treatment doses were used and a NOEL was not determined. Therefore, confidence in the study is rated medium, and confidence in the RfD is medium to low.

Supporting Studies for the EPA Cancer Classification:

Human carcinogenicity data specifically linking chloroform to a carcinogenic effect are considered inadequate. There are no epidemiologic studies of chloroform itself. Several ecological and case-control studies of populations consuming chlorinated drinking water, in which chloroform was the major chlorinated organic, show small significant increases in the risk of rectal, bladder, or colon cancer on an intermittent basis. Many other suspected carcinogens were also present in these water supplies.

Carcinogenicity data in animals are sufficient. Chloroform has been tested for carcinogenicity in eight strains of mice, two strains of rats, and in beagle dogs. Rats and mice were treated orally with chloroform in corn oil 5 times/week for 78 weeks. Significant increases in kidney epithelial tumors in male rats and highly significant increases in liver tumors in mice of both sexes were observed. Liver cellular proliferation was observed in low-dose male mice not developing liver tumors. Liver tumors have also been seen in two strains of female mice given chloroform orally. In another study, designed to measure low-dose effects, rats showed significant increase in renal tumors. A pulmonary tumor bioassay in mice was negative as was one in which newborn mice were treated subcutaneously on days 1 to 8 after birth.

CHLOROFORM

The majority of tests for genotoxicity of chloroform have been negative, including tests for covalent binding to DNA, bacterial mutation studies, a mutation study in fruit flies, recessive tests for DNA damage, a mouse bone marrow chromosome damage test, and neoplastic transformation of cultured mammalian cells. Chloroform caused mitotic recombination in yeast and sister chromatid exchange in cultured human lymphocytes and in mouse bone marrow cells exposed in vivo. The carcinogenicity of chloroform may be a function of its metabolism to phosgene, which is known to cross-link DNA.

The inhalation quantitative risk estimate is based on data from a gavage study. Experimental data support complete absorption of orally administered chloroform under the conditions of the assay used. There are no apparent species differences in this regard. Extrapolation of metabolism-dependent carcinogenic responses from mice to humans on the basis of body surface area is supported by experimental data. The unit risk was prepared by taking a geometric mean of the slope factor derived from incidence data and assuming 100% adsorption for low doses of chloroform in air.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

CHROMIUM III

CASRN: 16065-83-1
Synonyms: Chromic ion, Chromium ion (3+), Chromium III ion

Oral Reference Dose - Chronic (RfDo):	1E+0 (mg/kg)/day
Critical Effect:	No effects observed
Safety Factor (SF):	100
MF:	10
Confidence:	Low
Inhalation Reference Dose (RfDi):	Pending
Oral Cancer Slope Factor:	Pending
Inhalation Cancer Slope Factor:	Pending
EPA Cancer Classification:	Pending

Note: This assessment is for metallic chromium III insoluble salts, such as chromic III oxide and chromium III sulfate. Chromium III is an essential nutrient required in trace quantities for carbohydrate metabolism. Compounds of chromium III have low toxicity in humans and animals. Chromium VI is discussed in a separate toxicity profile.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The principal study is a long-term (840 day; considered lifetime) dietary study in male and female rats in which rats were fed chromic oxide baked in bread. All major organs were examined histologically, and no effect due to treatment was observed at any dose administered. Therefore, this study was used to derive the NOAEL. This study is limited because other toxicologic parameters were not reported. In a parallel 90-day study that included some blood chemistry parameters, the only change observed was a reduction in the weights of liver and spleen in animals who received high doses. Other subchronic studies have been done at lower exposure levels, with no effects observed. The highest dose among these studies represents a NOAEL, but since the effects seen in the 90-day study were not explicitly examined in the lifetime study, that dose level might actually represent a LOAEL.

There is a safety factor of 100 applied to the RfD, reflecting a factor of 10 for conversion from experimental animals to humans and a factor of 10 to protect sensitive human subpopulations. The modifying factor of 10 was adopted because 1) the effects observed in the 90-day study were not explicitly addressed in the 2-year study, 2) the absorption of chromium is low and is influenced by a number of factors and, therefore, considerable variation in absorption exists, and 3) histology was not performed until the animals died naturally. The confidence in the supporting study is low because the effects seen in the 90-day study were not explicitly reported in the lifetime study and because of the lack of an observed effects level. The RfD is said to be conservative by EPA.

Reproductive effects have not been seen at high dietary dose levels (5% chromic III oxide) in animals. There are limited data suggesting that chromium III may have adverse respiratory effects in humans.

Supporting Studies for the EPA Cancer Classification:

Chromium III has been evaluated by the EPA for human carcinogenicity. This evaluation is currently under review and will be included on IRIS when complete.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables*. EPA 540-R-93-058, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

CHROMIUM VI, SOLUBLE SALTS

CASRN: 18540-29-9
Synonyms: Chromium ion, Chromium ion (6+), Chromium VI ion

Oral Reference Dose - Chronic (RfDo):	5E-3 (mg/kg)/day
Critical Effect:	No effects reported
Safety Factor (SF):	500
Confidence:	Low
Inhalation Reference Dose (RfDi):	Pending
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	4.1E+1 $([mg/kg]/day)^{-1}$
Inhalation Unit Cancer Risk:	1.2E-2 $\mu g/m^3$
EPA Cancer Classification:	A; human carcinogen

Note: This assessment is for metallic chromium VI soluble salts, such as potassium dichromate, sodium dichromate, potassium chromate, and sodium chromate.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The major supporting study is a 1-year drinking water experiment with male and female rats. There were increased tissue concentrations of chromium, but no adverse pathological effects. Similar no-effect results have been reported in dog and human studies. Female dogs were given chromium VI in drinking water for 2 years with no observed significant effects. No adverse health effects were noted in humans who drank chromium VI at approximately 1 mg/L for 3 years.

The safety factor of 500 includes a factor of 10 to convert from experimental animals to humans, a factor of 10 to protect sensitive human subpopulations, and a factor of 5 to adjust for the shorter than lifetime study duration. Confidence in the study is low because of the lack of toxic effect at the highest dose and the small population tested. No studies were located on teratogenic effects resulting from the ingestion of chromium. There is some evidence to indicate that hexavalent chromium is converted in part to trivalent chromium in vivo and vice versa. Trivalent chromium is an essential nutrient.

Supporting Studies for the EPA Cancer Classification:

Eighteen epidemiological studies of chromate manufacturing facilities have been performed. These studies have established an association between chromium exposure and lung cancer. Most of these studies did not attempt to determine whether trivalent or hexavalent chromium was the responsible agent. European studies of the chrome pigment industry have found an association between occupational exposure to chromium VI and lung cancer. Six epidemiological studies are inconclusive while one was negative. Only the inhalation route has been evaluated for human carcinogenicity, and only the inhalation route is considered carcinogenic in risk assessments.

Chromium VI has been found to be carcinogenic in animal studies. In rats and mice, tumors at the site of chemical injection or implantation were detected (intramuscular, intrapleural, intrabronchial, and subcutaneous sites). However, hexavalent chromium compounds have not produced lung tumors in experimental animals via inhalation exposure.

Chromium VI has been found to be mutagenic in bacterial and yeast assays, while trivalent chromium is not. Both chromium III and VI affect the fidelity of DNA synthesis and cause chromosome breaks in cultured cells. Chromium VI also affects DNA synthesis in mammalian cells and causes neoplastic cell transformation.

Results of human exposure studies are consistent across investigators and countries; a dose-responsive relationship for lung tumors has been established. The inhalation cancer slope factor and unit risk are based on one of the occupational studies and assumed that the ratio of chromium III to chromium IV was 6:1. This may lead to an underestimation of risk by 7-fold. The exposure levels in the critical occupational study may have been underestimated, which might result in an overestimation of risk. Further overestimation of risk may be due to the assumption that the smoking habits of chromate workers were similar to those of the U.S. white male population; however, it is generally accepted that the proportion of smokers is higher for industrial workers than for the general population.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA-540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

CHRYSENE

CASRN: 218-01-9
Synonyms: Benzo(a)phenanthrene

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Evidence for Classification as to Human Carcinogenicity:

Although there are no human data that specifically link exposure to chrysene to human cancers, chrysene is a component of mixtures that have been associated with human cancer. These include coal tar, soots, coke oven emissions, and cigarette smoke.

There is sufficient evidence of carcinogenicity in animals. Intraperitoneal injections of chrysene in male mice caused a dose-response increase in the incidence of liver tumors and lung tumors, and a significant increase in malignant lymphoma in the low dose but not the high dose group. In similar studies with another strain of mouse, lung tumors were slightly elevated, and liver tumors were significantly elevated. These studies are regarded as short-term exposure (3 injections) with only one year (half a lifetime) allowed for tumor development.

In mouse skin painting studies, chrysene tested positive in both initiation and complete carcinogen studies. Chrysene has produced positive results for initiating activity in several mouse strains when applied with several promoting agents, producing skin papillomas and carcinomas.

Chrysene causes mutations in a bacterial test system. Chromosomal effects were observed in hamster and mouse cells following oral exposure. Neoplastic cell transformation was seen with cultured hamster cells. Structure activity studies indicate that chrysene, like other carcinogenic and mutagenic polyaromatic hydrocarbons, has a "bay-region" structure.

Note: EPA is considering a toxicity equivalency approach for polyaromatic hydrocarbons, in which carcinogenic potency is relative to that of benzo(a)pyrene. When these compounds occur in mixtures, this approach may be warranted.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

COBALT

CASRN: 7440-48-4
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	No data (see text)
(Recommended value by ECAO):	6E-2 (mg/kg)/day
Inhalation Reference Dose (RfDi):	No data
EPA Cancer Classification:	No data

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

EPA's Environmental Criteria and Assessment Office (ECAO) has reviewed the data available for cobalt and identified no human or animal information that justify the derivation of a RfDo for cobalt. However, the ECAO, for the purposes of assessing risk from oral exposure to cobalt, has recommended the use of 6E-2 (mg/kg)/day (the upper range of normal dietary intake by children). The IRIS record indicates that a risk assessment is under review.

Cobalt, as a component in vitamin B_{12}, is an essential human nutrient which is commonly found in the diet. Average intakes of cobalt range from approximately 0.002-0.008 mg/kg body weight/day for adults and 0.01-0.06 (mg/kg)/day in children.

Cobalt has been found to stimulate the production of red blood cells in humans. When patients with kidney disease have been treated with cobalt (0.18 (mg/kg)/day as cobalt chloride) for 12 weeks, their hemoglobin count has increased significantly. Following cessation of treatment, hemoglobin concentrations returned to previous levels. Similar effects were observed in nonanemic humans and animals. However, treatments of pregnant human females at higher dose levels (0.5-0.6 [mg/kg]/day for 90 days) did not elevate hemoglobin levels. Individuals who have been exposed to cobalt either dermally or by inhalation have been shown to exhibit dermatitis (e.g., eczema). Oral ingestion of cobalt has also been associated with dermatitis reactions. This sensitivity is apparently displayed when cobalt becomes available systemically. Cobalt has been used to stabilize the foam in beer. The intake of this treated beer by some people who drank large quantities (8-30 pints daily for periods of years) proved to be fatal. These individuals were receiving cobalt doses that ranged from 0.04-0.14 mg cobalt/kg/day. For these ingested concentrations, approximately 43% of individuals died within several years. Breakdown of the heart muscle tissue was the cause. It is highly probable these individuals were already at risk due to protein-deficient diets and liver damage from alcohol abuse. Cobalt is no longer used in the brewing of beer.

Additional Information:

No significant effects on fetal growth or survival were found in exposed rats, although nonsignificant increases in low-weight fetuses were found for animals treated with high cobalt concentrations. Maternal effects, however, included reduced body weights and food consumptions and altered hematological parameters.

References:

Poirier, K. A. 1992. *Oral Toxicity Assessment for Cobalt*. Memorandum to P. Cirone, March 6. Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, Cincinnati, Ohio.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

COPPER

CASRN: 7440-50-8
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	Not available
(HEAST recommends the use of the drinking water standard: 1.3 mg/L)	
Critical Effect:	Gastrointestinal irritation in humans after a single dose
Safety Factor (SF):	Not applicable
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the EPA Cancer Classification:

There are no human or adequate animal data to link exposure to copper compounds with cancer or mutagenicity.

Gilman (1962) administered intramuscular injections containing 20 mg of cupric oxide (16 mg copper), cupric sulfide (13.3 mg copper), and cuprous sulfide (16 mg copper) into the left and right thighs of 2 to 3-month-old Wistar rats. After 20 months of observations, no injection-site tumors were observed in any animals, but other tumors were observed at very low incidence in the animals receiving cupric sulfide (2 of 30 animals) and cuprous sulfide (1 of 30 animals). As the relevance of the organic copper compound to the observation of sarcoma induction is uncertain and the incidence of tumors in rats treated intramuscularly with inorganic copper was very low, these data are considered inadequate for classification.

References:

Gilman, J. P. W. 1962. "Metal Carcinogenesis. II. A Study of the Carcinogenic Activity of Cobalt, Copper, Iron, and Nickel Compounds," *Cancer Res.* 22:158-166.

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual.* EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

CYANIDE, FREE

CASRN: 57-12-5
Synonyms: Cyanide ion

Oral Reference Dose - Chronic (RfDo):	2E-2 (mg/kg)/day
Critical Effect:	Weight loss, thyroid effects and myelin degeneration in rats
Safety Factor (SF):	100
MF:	5
Confidence:	Medium
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

Hydrogen cyanide readily dissociates in acidic (i.e., gastric) environments to free cyanide and hydrogen. The principal study was a 2-year dietary study in which rats were given food fumigated with hydrogen cyanide. There were no treatment-related effects on growth rate, no gross signs of toxicity, and no histopathologic lesions. In another dietary study at lower doses, a decrease in weight gain and thyroxin levels, and myelin degeneration were noted in rats. Other chronic studies have either suggested higher effect levels or used a subcutaneous route of administration. One further study in lactating pigs suggested a lower NOAEL but used too few animals to be adequate for deriving an RfD. Human data do not provide adequate exposure information for deriving an RfD. The principal study gave the highest reported NOAEL, which was used as the basis for the RfD.

The safety factor of 100 includes a factor of 10 for inter-species extrapolation, and a factor of 10 for variability within a sensitive subpopulation. A modifying factor of 5 is used to account for a higher tolerance when given in food (as the principal study did) than when administered in drinking water. The oral route is the only appropriate route to be considered for the RfDo. Confidence in the principal study is medium because it is a lifetime study. Confidence in the database is medium because a small but sufficient number of additional studies support the principal study. Overall confidence in the RfD is, therefore, medium.

Supporting Studies for the EPA Cancer Classification:

There are no available human or animal data by which to evaluate cyanide for carcinogenicity. In vitro studies of genetic effects have been negative except for a marginally positive response in a bacterial mutagenicity test.

Reference:

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

DI(2-ETHYLHEXYL)PHTHALATE (DEHP)

CASRN: 117-81-7
Synonyms: Bis(2-ethylhexyl)phthalate, BEHP

Oral Reference Dose - Chronic (RfDo):	2E-2 (mg/kg)/day
Critical Effect:	Increased liver weight
Safety Factor (SF):	1000
Confidence:	Medium
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	1.4E-2 (mg/kg)/day
Inhalation Cancer Slope Factor:	No data
Inhalation Unit Cancer Risk:	No data
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

Guinea pigs were fed diets containing di(2-ethylhexyl)phthalate for 1 year, and statistically significant increases in liver weights were seen in both groups of treated females. No effects were observed on mortality, body weight, kidney weight, or gross pathology and histopathology of kidney, liver, lung, spleen, or testes. A supporting study in rats showed growth retardation and increased kidney and liver weights. Guinea pigs appear to be more sensitive, with a LOAEL of 19 (mg/kg)/day, and with increased liver weight as the critical effect. The LOAEL was divided by an safety factor of 1000 to derive the RfD. This includes 2 factors of 10 (for interspecies variation and for protection of sensitive human subpopulations). The safety factor also includes another factor of 10 because the guinea pig exposure period was longer than subchronic but less than lifetime and because, while the RfD is derived from a LOAEL, the effect observed was considered to be minimally adverse. Di(2-ethylhexyl)phthalate is a reproductive toxicant in mice of both sexes at higher dietary levels than those used in the guinea pig study. Confidence in the guinea pig study, the database of corroborating studies, and the RfD is medium.

Supporting Studies for the EPA Cancer Classification:

Human carcinogenicity data are inadequate for evidence of a causal association, but animal evidence of carcinogenicity is sufficient. Rats and mice were fed di(2-ethylhexyl)phthalate in the diet for 103 weeks; no clinical signs of toxicity were observed, but a statistically significant increase in hepatocellular carcinomas and carcinomas plus adenomas were seen in female rats and male and female mice. The combined incidence of neoplastic nodules was increased in the high-dose male rats as well. The results from the male mice (hepatocellular adenoma plus carcinoma) were used to derive the slope factor using the linearized ultistage model with extra risk. An adequate number of animals was observed, and a statistically significant increase in liver tumors was seen in both sexes and was dose dependent.

Di(2-ethylhexyl)phthalate is not a direct acting mutagen in several bacterial assays, but the monoester (a metabolite) is positive in two bacterial assays and causes chromosomal aberrations in cultured hamster cells. Di(2-ethylhexyl)phthalate is weakly positive in the thymidine kinase mutation assay and is a potent inducer of hepatic peroxisomal enzyme activity.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

DIBENZ(a,h)ANTHRACENE

CASRN: 53-70-3
Synonyms: 1,2,5,6-Dibenzanthracene, DBA

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Evidence for Classification as to Human Carcinogenicity:

Although there are no human data that specifically link exposure to dibenz(a,h)anthracene to human cancers, it is a component of mixtures that have been associated with human cancer. These include coal tar, soots, coke oven emissions, and cigarette smoke.

There is sufficient evidence of carcinogenicity in animals. Dibenz(a,h)anthracene caused pulmonary adenomas, pulmonary carcinomas, mammary carcinomas, and hemangioendotheliomas in mice given a dibenz(a,h)anthracene emulsion in place of drinking water. This was a short-term experiment and the mice did not tolerate the emulsification well; no statistical analysis was done. In other studies, mammary carcinomas were observed in two strains of female mice that were treated by gavage for 15 weeks with a twice-weekly dose of dibenz(a,h)anthracene. A single dose of dibenz(a,h)anthracene in polyethylene glycol produced forestomach tumors in male mice after 30 weeks.

In mouse skin painting studies, Swiss mice developed skin carcinomas following dermal exposure to dibenz(a,h)anthracene. Numerous studies demonstrate both complete carcinogenic activity and initiating activity.

Subcutaneous injection induced injection site sarcomas in C3H mice, NMRI mice, and C57Bl6 mice; these strains of mice have high aryl hydrocarbon hydroxylase (AHH) activity. Strains low in AHH activity (dibenz(a,h)anthracene and AKR mice) did not form tumors after subcutaneous injection of dibenz(a,h)anthracene. Other positive studies are referenced in the IRIS record.

Dibenz(a,h)anthracene causes DNA damage and mutations in bacteria. In mammalian assays, DNA damage was seen in cultured human cells with and without exogenous metabolic activation. Hamster embryo cells and rat liver cells do not respond to dibenz(a,h)anthracene when cellular oxidative enzymes are not induced. Dibenz(a,h)anthracene causes mutations in Chinese hamster embryo cells and neoplastic transformation in several types of mammalian cells.

Dibenz(a,h)anthracene has a "bay region" structure and is metabolically activated by mixed function oxidases to form mutagenic and carcinogenic dihydrodiols.

Note: The EPA is considering a toxicity equivalency approach to polyaromatic hydrocarbons in which carcinogenic potency is relative to that of benzo(a)pyrene. When these compounds occur in mixtures, this approach may be warranted.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

DIELDRIN

CASRN: 60-57-1
Synonyms: Trade names

Oral Reference Dose - Chronic (RfDo):	5E-5 (mg/kg)/day
Critical Effect:	Liver lesions
Safety Factor (SF):	100
Confidence:	Medium
Inhalation Reference Dose (RfDi):	Not reported
Inhalation Reference Concentration (RfC):	Not reported
Oral Cancer Slope Factor:	1.6E+1 per (mg/kg)/day
Inhalation Cancer Slope Factor:	1.6 E-1 per (mg/kg)/day (HEAST)
Inhalation Unit Cancer Risk:	4.6E-3 per ($\mu g/m^3$)
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

In a 2-year oral exposure study, rats were administered dieldrin (recrystallized, 99% active ingredient) in the diet. Body weight, food intake, and general health remained unaffected throughout the 2-year period, although rats in the high dose group became irritable and exhibited tremors and occasional convulsions. No effects were seen in various hematological and clinical chemistry parameters. At the end of 2 years, females in two of the dose groups had increased liver weights and liver-to-body weight ratios ($p<0.05$). Histopathological examinations revealed liver cell changes. These lesions were considered to be characteristic of exposure to an organochlorine insecticide. The LOAEL was identified as 1.0 ppm (0.005 mg/kg-day) and the NOAEL as 0.1 ppm (0.005 mg/kg-day). At least six other chronic feeding studies were also considered in choosing the critical study and determining the effect levels.

The safety factor of 100 includes a factor of 10 for extrapolation from animals to humans and a factor of 10 for variability among sensitive human subpopulations. Confidence in the critical study is low; the study, however, is relatively complete and supports the critical effect. Confidence in the database is medium due to the number of supporting studies on dieldrin in particular and organochlorine insecticides in general. Overall confidence in the RfD is, therefore, medium.

Supporting Studies for the EPA Cancer Classification:

Human carcinogenicity data for dieldrin are inadequate. Two studies of workers exposed to dieldrin and aldrin were negative but limited in statistical power. In another study, two cases of cancer were observed in pesticide manufacturing workers, but this study also was too limited to draw conclusions. In a retrospective mortality study, no excess cancer was observed in 1155 organochlorine pesticide manufacturing workers; exposures were mixed and not quantitated, and overall results were inconclusive.

Data are sufficient to classify dieldrin as a carcinogen in animals. Dieldrin has been shown to be carcinogenic in various strains of mice of both sexes. At different dose levels the effects range from benign liver tumors to mestatic liver cancer. The Food and Drug Administration conducted a long-term carcinogenesis bioassay for dieldrin, in which dieldrin was administered orally to mice for 2 years. Liver cancer was increased in both males and females. In a follow-up study, the Food and

Drug Administration administered dieldrin orally to mice and again observed a significant increase in liver cancers, but this study was compromised by poor survival. A reevaluation of the histological material of both studies concluded that the hepatomas were malignant and that dieldrin was carcinogenic for male and female mice in both studies. In several subsequent studies of dieldrin in mice of both sexes the incidence of tumors correlated to the number of dose levels and the dose administered. Seven studies in four strains of rats did not produce carcinogenicity; however, only three of these studies were experimentally adequate.

The oral slope factor is the geometric mean of 13 slope factors calculated from liver carcinoma data in both sexes of several strains of mice. The individual slope factors were within a factor of 8 of each other. The inhalation unit risk was calculated from the oral data.

Dieldrin has been reported to cause chromosomal aberrations in cultured mouse and human cells, mutations in cultured hamster cells, and indications of DNA damage in rat and human cells. In bacterial mutagenicity test systems, dieldrin is negative. Five other structurally related organochlorine insecticides have produced liver tumors in mice.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

ETHYLBENZENE

CASRN: 100-41-4
Synonyms: Phenylethane

Oral Reference Dose - Chronic (RfDo):	1E-1 (mg/kg)/day
Critical Effect:	Liver and kidney toxicity in rats
Safety Factor (SF):	1000
Confidence:	Low
Inhalation Reference Dose (RfDi):	3E-1 (mg/kg)/day
Inhalation Reference Concentration (RfC):	1E+0 mg/m^3
Critical Effect:	Developmental toxicity in rats and rabbits
Safety Factor (SF):	300
Confidence:	Low
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The critical study is a 6-month rat oral bioassay; this is considered subchronic. Several behavioral and clinical endpoints were evaluated, and the LOAEL was associated with histopathological changes in the liver and kidney. The safety factor of 1000 reflects factors of 10 for inter- and intraspecies variability and a factor of 10 because a subchronic study was used to derive a chronic RfD. Confidence in this study is low because only female rats were used and because this was not a chronic study. Confidence in the database is low because there are no other reports of oral toxicity. Overall confidence in the RfD is, therefore, low.

Supporting Studies for the Inhalation Reference Concentration (RfC):

The RfC is based on a study in which pregnant rats and rabbits were exposed via inhalation during gestation and sacrificed 1 day before term. In rabbits, maternal and fetal organs were examined, and no maternal or fetal toxicity was found, indicating a NOAEL of 100 ppm. In rats, there was no histological effect on maternal organs, but there was an increase in relative liver, kidney, and spleen weights. There were no effects on any measure of reproductive status, but there was an increase in supernumerary ribs (generally regarded as an indication of fetal toxicity, not teratogenicity). Based on these effects, a LOAEL of 4340 mg/m^3 was established.

These findings are supported by studies in pregnant rats and rabbits. In a subchronic (90-day) inhalation study in rats and mice (not pregnant), animals were necropsied and clinical chemistry was evaluated with the only observed effect being an increase in liver weight. Enlarged lymph nodes were observed in treated rats; however, they were not dose related. Rather, they were attributed to an infectious agent. The mice from this study showed no effects other than increased liver weights. The chronic bioassay that will be a followup to this subchronic study should clarify the significance of the lung lymph node enlargement.

Other supporting studies in rats (various strains), guinea pigs, rabbits, and mice (various strains) have been published. In two occupational studies of workers exposed to ethylbenzene and other substances, no clearcut effects that could be attributed to ethylbenzene were reported. The safety factor

of 300 reflects a factor of 10 to protect unusually sensitive individuals, 3 to adjust for interspecies conversion, and 10 to adjust for the absence of multigeneration reproductive studies. While a variety of effects have been evaluated, a multigeneration reproductive study has not been performed. Therefore, confidence in the critical study, the database, and the overall RfC is low.

Supporting Studies for the EPA Cancer Classification:

There are no data by which to evaluate whether ethylbenzene is a human carcinogen. There are no animal data; the National Toxicology Program plans to proceed with the chronic cancer bioassay. The metabolic pathways for humans and rodents appear to be different. The major metabolites in humans are minor metabolites in rats and rabbits, while the major animal metabolites were not detected in the urine of exposed workers.

Ethylbenzene is not mutagenic in bacterial test systems; however, one report indicates a positive result for ethylbenzene hydroperoxide. In a battery of other short-term tests, ethylbenzene was also negative. One report indicated DNA effects in cultured human lymphocytes.

Reference:

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

ETHYLENE GLYCOL

CASRN: 107-21-1
Synonyms: Ethylene alcohol, Glycol alcohol, Ethylene dihydrate

Oral Reference Dose - Chronic (RfDo):	2E+0 (mg/kg)/day
Critical Effect:	Kidney toxicity
Safety Factor (SF):	100
Confidence:	High
Inhalation Reference Dose (RfDi):	No data
EPA Cancer Classification:	No data available

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

A 2-year dietary study of ethylene glycol in rats was used to derive the RfD. High-dose rats exposed to 1000 (mg/kg)/day via the diet had increased mortality, neutrophil count, and several kidney effects, while female rats showed mild fatty changes in the liver. In the same study, mice were also studied at the same doses but did not show any adverse effects. No adverse effects were seen in any of the mid- and low-dose rats. A second dietary study in rats also noted basically similar effects at roughly similar dose levels. An safety factor of 100 includes a factor of 10 for interspecies variation and 10 for individual human variations in sensitivity.

When monkeys were fed ethylene glycol in the diet for 3 years, no treatment-related toxicity was observed. In a rat teratogenicity study, evidence of toxicity was seen at dietary doses of 1000 (mg/kg)/day. In a three-generation reproductive study, no effects were noted at the same high dose. In rats and mice given ethylene glycol by oral gavage at doses much higher than the previous studies, there was a dose-related increase in malformed fetuses, post-implantation fetal loss, and a decrease in maternal weight gain. EPA concluded that the NOAEL established from the oral toxicity study was also protective of teratogenic and reproductive effects.

Confidence in the critical study is high because it was a well-conducted lifetime study in two species and defined both a LOAEL and NOAEL. Confidence in the database is high because there are studies in rats and monkeys that support the NOAEL and LOAEL of the critical study. Therefore, confidence in the overall RfD is high.

Additional Information:

Ethylene glycol has not been evaluated by EPA for evidence of carcinogenic potential.

Reference:

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

FLUORANTHENE

CASRN: 206-44-0
Synonyms: 1,2-Benzacenaphthene, Benzo(j,k)fluorene

Oral Reference Dose - Chronic (RfDo):	4E-2 (mg/kg)/day
Critical Effect:	Nephropathy, increased liver weights, hematological alterations and clinical effects in mice
Safety Factor (SF):	3000
Confidence:	Low
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The chronic RfDo is based on a subchronic study in which mice were given fluoranthene orally for 13 weeks. A range of clinical and pathological parameters were examined. All treated mice exhibited liver and kidney damage and effects on blood parameters; these effects were dose-related at the higher doses. Microscopic examination of the liver also showed damage. Both a LOAEL and NOAEL were established by this study.

A safety factor of 3000 was used. Factors of 10 were used for inter- and intraspecies variability, a factor of 10 due to use of the subchronic study to derive the chronic RfD, and another factor of 3 due to lack of toxicity information in a second species and lack of developmental and reproductive studies. Three other studies reported in IRIS were inadequate for deriving the RfD. Confidence in the principal study is medium because it was well-designed, identified both a LOAEL and NOAEL, and surveyed a range of effects. Confidence in the database is low due to the lack of information in a second species and lack of developmental and reproductive studies. Therefore, overall confidence in the RfD is low.

Supporting Studies for the EPA Cancer Classification:

There are no human data that evaluate the carcinogenicity of fluoranthene. Animal data are inadequate. Several studies evaluating the complete and initiating carcinogenic activity of fluoranthene in mouse skin painting studies have been consistently negative but fluoranthene is a co-carcinogen with benzo(a)pyrene in mouse skin painting studies. In a short-term lung tumor assay, lung tumors were statistically significantly increased in mice; however, this study by itself was not sufficient to indicate clear carcinogenic activity of fluoranthene. In one study, fluoranthene did not cause injection-site tumors.

Five positive and three negative results in bacterial mutagenicity assays have been reported. One positive and one negative result for chromosomal effects in cultured cells have been reported. Results for causing gene mutations in cultured are also mixed. Overall, evidence for DNA damage and mutation is equivocal.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

FLUORENE

CASRN: 86-73-7
Synonyms: Diphenylenemethane, 2,2'-Methylenebiphenyl

Oral Reference Dose - Chronic (RfDo):	4E-2 (mg/kg)/day
Critical Effect:	Decreased RBC, packed cell volume, and hemoglobin
Safety Factor (SF):	3000
Confidence:	Low
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The chronic RfDo is based on a mouse oral subchronic study in which mice were given fluorene for 13 weeks. A number of clinical and histopathological endpoints were examined. Behavioral and overt clinical signs were seen at the high doses, and a significant decrease in red blood cell count, packed cell volume, and hemoglobin content were noted at mid-doses. Indications of liver toxicity were also seen in the mid doses (12.5 and 250 mg/kg-day) and high dose (500 mg/kg-day), and spleen and kidney effects were also seen. A study of rats given fluorene in the diet for 6 months also noted a range of nonneoplastic responses in several tissues, but these effects were thought to be related to the vehicle or the diet.

A safety factor of 3000 was used. Factors of 10 were used for inter- and intraspecies variability, and 3 for lack of adequate toxicity data in a second species and reproductive and developmental data. The additional factor of 10 was used because the subchronic study was used to derive the chronic RfD. Confidence in the principal study is medium because it was experimentally adequate. Confidence in the supporting database is low due to lack of longer exposures and reproductive and developmental endpoints.

Supporting Studies for the EPA Cancer Classification:

Fluorene has not been examined for human carcinogenicity. Animal bioassay data are inadequate. One study in rats showed no apparent increase in tumor incidence. Skin painting assays for complete or initiating activity of fluorene have been negative or inconclusive. Fluorene has not been positive in bacterial mutagenicity test systems and has been reported as negative in several assays for DNA damage in cultured mammalian cells. One report did state positive results for DNA damage in mouse cells.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

INDENO(1,2,3-cd)PYRENE

CASRN: 193-39-5
Synonyms: o-Phenylenepyrene, 2,3-Phenylenepyrene

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the EPA Cancer Classification:

Although there are no human data that specifically link indeno(1,2,3-cd)pyrene to human cancers, it is a component of mixtures that have been associated with human cancer. These include coal tar, soots, coke oven emissions, and cigarette smoke.

There is sufficient evidence of carcinogenicity in animals. Indeno(1,2,3-cd)pyrene caused a dose-related increase in epidermoid carcinomas in the lung and thorax after implantation into the lungs of Osborne-Mendel rats. One study in which indeno(1,2,3-cd)pyrene was injected intraperitoneally three times into CD-1 mice did not show a significant difference in tumor formation relative to vehicle controls.

In mouse skin painting studies, indeno(1,2,3-cd)pyrene demonstrated cancer initiating and complete carcinogenic activity in several mouse strains. When applied dermally in acetone (but not in dioxane) to female Ha/ICR/Mil mice, indeno(1,2,3-cd)pyrene produced a dose-related increase in skin papillomas and carcinomas. It also demonstrated initiating activity when applied in a two-day period and followed by promotion with croton oil or with tetradecanoyl phorbol. Two metabolites (indeno(1,2,3-cd)pyrene-1,2-diol and -1,2-oxide) demonstrated initiating activity in skin painting assays.

Indeno(1,2,3-cd)pyrene caused mutations in a bacterial test system.

Note: EPA is considering a toxicity equivalency approach to polyaromatic hydrocarbons in which carcinogenic potency is relative to that of benzo(a)pyrene. When these compounds occur in mixtures, this approach may be warranted.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

LEAD, INORGANIC

CASRN: 7439-92-1
Synonyms: Plumbum

Intervention Level in Children:	10 μg/dL blood lead (CDC 1991)
Soil Lead Cleanup Level Guidance:	See below
Oral Reference Dose - Chronic (RfDo):	No recommendation from EPA
Inhalation Reference Dose (RfDi):	No data
Critical Effect:	Effects in the developing brain, nervous system, and other tissues (CDC)
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the Intervention Level:

Lead is a poison that affects virtually every system in the body and no lowest effect level has been identified. It is particularly harmful to the developing brain and nervous system of fetuses and young children. Lead is unique in that a RfD has not been determined. Health studies conducted over many years on children, adults, and workers provide considerable dose-response information about the adverse effects of lead exposure. Lead is ubiquitous in the urban environment; average national background concentrations are approximately 20 ppm. Highest concentrations are found in homes where lead-based paint and lead-soldered water pipes were used, near highways, and near industrial operations that process lead ores and recycled batteries.

Exposure to lead in children occurs primarily via the oral route, but occupational exposure occurs mainly by the inhalation route. Very little absorption occurs through dermal tissues. Lead burden has historically been presented in terms of blood lead levels, or absorbed dose, and not in typical dose terms (mg of lead intake/kg body weight/day).

The following indicate some of the effects caused by lead absorption in the human body. Lead affects heme biosynthesis by inhibiting several enzymes that promote the final stages in the development of red blood cells. As a result, anemia commonly coexists with lead poisoning. Lead exposure is associated with adverse effects in the liver and kidney, and with thyroid function, vitamin D metabolism, juvenile growth, and others. Gastrointestinal effects relate to colic (abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss). In adults, the neurological symptoms resulting from excessive lead absorption are expressed as dizziness, weakness, forgetfulness, irritability, headache, fatigue, impotence, and others. In children, high dose levels cause inflammation and disease of the brain, hyper-irritability, convulsions, stupor, coma, and death. At lower, long-term dose levels (10 to 30 μg lead/dL of blood levels), some children may experience an irreversible decline in IQ levels and lower neuro-psychological performance without signs of lead poisoning (ATSDR 1993). Affected children generally exhibit behavioral problems (inattention and hyperactivity) as blood lead levels increase above 30 to 60 μg/dL levels (ATSDR 1993). When exposed to lead concentrations during reproductive years, women may experience miscarriages and still births.

Numerous well-designed studies have considered both human and animal exposures. As new information has become available, the Centers for Disease Prevention and Control has consistently dropped the intervention blood lead level. Now, 10 μg/dL is the blood lead level above which symptoms of toxicity may be expressed (CDC 1991). However, the onset of lead-induced effects may occur below 10 μg/dL.

The probability of lead toxicity in children (measured as blood lead) is evaluated using EPA's Uptake Biokinetic Model. The Uptake Biokinetic Model estimates blood lead levels from measured lead concentrations in the soil, dust, drinking water, inhaled air, and diet. It evaluates the relative impact from intake by children of these various media. This multimedia model considers (gastrointestinal tract) absorption, distribution within the body (blood, bone, liver, kidney), metabolism and excretion (EPA 1991).

A guidance cleanup level for inorganic lead in soil of 500 to 1000 mg/kg (Clay 1991) has been proposed. Based on the Uptake Biokinetic model using default values, this range projects that 95% of a sensitive population (or of individuals) will maintain blood lead levels at or below 10 μg/dL. However, this model also suggests cleanup levels that are substantially lower when the advice from the EPA Science Advisory Board is followed regarding input and default parameters. During the past several years, the EPA has informally proposed to introduce a lower soil cleanup number or range, but this has not occurred.

Numerous animal studies of rats, mice, guinea pigs, monkeys, and dogs show similar effects to those seen in humans. These studies associate lead dose-response with blood formation and the circulatory system, the liver and kidneys, and with neurological and reproductive functional impairments.

Supporting Studies for the EPA Cancer Classification:

Human evidence is inadequate. However, 10 rat bioassays and 1 mouse assay have shown that kidney tumors increase significantly with exposure to soluble lead compounds in the diet and from subcutaneous injections. These studies have been reproduced by several laboratories and for multiple rat types. Short-term studies show that lead affects the regulation of genetic material (EPA 1994). EPA does not currently recommend numerical estimates for cancer risk from lead.

The occupational association of lead exposure with increased cancer incidence is limited because lead is nearly always found in the presence of arsenic, a class A carcinogen. Small excesses of cancer deaths (due to digestive and urinary tract tumors) in battery plant workers have not been correlated with onset, duration, or level of exposure (EPA 1994). A weak dose-response relationship has been developed between exposure and rectal cancer in workers (EPA 1994). In animals, the kidney is the primary target organ affected by cancer.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). 1993. *Toxicological Profile for Lead.* TD-922, U.S. Department of Health and Human Services, Division of Toxicology, Atlanta, Georgia.

Centers for Disease Control (CDC). 1991. *Preventing Lead Poisoning in Young Children.* U.S. Department of Health and Human Services, U.S. Public Health Service, Atlanta, Georgia.

Clay, D. R. 1991. *Update on OSWER Soil Lead Cleanup Guidance.* Memorandum to EPA Regional Directors, Superfund Branch Chiefs, and Regional Counsels. Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1991. *Technical Support Document on Lead*. Draft, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

MANGANESE

CASRN: 7439-96-5
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	5E-3 (mg/kg)/day (water)
RfDo from food:	1.4E-1 mg/kg-day (food)
Critical Effect:	Central nervous system effects
Safety Factor (SF):	1
Confidence:	Medium (food) and medium-to-low (water)
Inhalation Reference Concentration (RfC):	5E-5 mg/m^3
Critical Effect:	Impairment of neurobehavioral function
Safety Factor (SF):	1000
Confidence:	Medium
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Note: The water RfD is based on the NOAEL described below and assumes a drinking water ingestion rate of 2 L/day by a 70-kg adult and also assumes a separate dietary intake of manganese, because this essential element is found in varying amounts in all diets. Conversely, the dietary RfD assumes a normal range of manganese in the water may be appropriate. Because manganese is more bioavailable from water, separate RfDs for food and water may be appropriate.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The water RfD is based on the NOAEL and LOAEL derived from a study in which manganese levels in drinking water were naturally elevated (range from 3.6 to 2300 $\mu g/L$). A neurologic examination was administered, the score of which represents a composite of the presence and severity of 33 symptoms (e.g., weakness/fatigue, gait disturbances, tremors, dystonia). There was a significant difference in mean neurologic scores between the high and low manganese areas. The arithmetic mean of the range of manganese concentrations for two areas was used to derive the NOAEL and LOAEL. The lack of dietary data is recognized as a source of significant uncertainty in this assessment, but most food was purchased from the market and was thought to be comparable between the areas. Dietary intake of manganese was estimated at 10-15 mg/day due to the high intake of vegetables. One earlier epidemiologic study of a water supply contaminated with manganese and zinc (from buried drycell batteries) noted several cases of manganese poisoning, with the most serious effects in the elderly. Total intakes in this study were much higher than in the critical study described above.

Studies in monkeys support the findings of the two human studies. Several studies of manganese in drinking water have also been done in rodents, but rodents do not exhibit the same neurologic effects that humans do following exposure to manganese. Bioavailability varies with both the diet (fiber and other factors which bind manganese and prevent absorption), and also with the solubility of the manganese salt; one study in mice suggested different organ effects for salts with different solubilities. Relatively little is known about toxicity and speciation.

The World Health Organization studied the manganese levels in adult diets and concluded that 2-3 mg manganese/day is adequate, and 8-9 mg/day is safe, with a vegetarian diet contributing

10 mg/day or more (although the bioavailability of manganese from a vegetarian diet is lower). The National Research Council determined that 2-5 mg/day is adequate and safe, and 10 mg/day is safe as an occasional intake. The RfD for food was based on studies in many large populations for extended time periods and, therefore, uses a safety factor of 1. Dietary intakes in humans reaching toxic levels have not been reported; manganese is not thought to be very toxic via the diet because human physiology keeps body burdens of manganese constant even when there is variation of manganese in the diet.

Information on the susceptibility of children is contradictory. While it has been suggested that children are less susceptible to manganese intoxication and may require slightly higher levels of manganese than do adults, it is also recognized that neonates may be at higher risk because of a higher rate of uptake from the gastrointestinal tract. The relation between gastrointestinal uptake and the developing nervous system has not been investigated.

Supporting Studies for the Inhalation Reference Concentration (RfC):

Many occupational studies on manganese have been performed. The critical study examined workers exposed to manganese dioxide (MnO_2) dust and calculated a respirable dust concentration integrated over the occupational lifetime of the workers. Workers were examined for lung function, neurologic function, and blood parameters. Some blood parameters were consistently in the low-normal range, and several neurologic parameters were significantly altered in exposed workers. A LOAEL was calculated, but the possibility of confounding factors (e.g., educational level) meant that a true threshold could not be determined. Several other occupational studies support neurotoxicity as the critical effect; a wide variety of neurologic effects are seen after various lengths of exposure to various forms of manganese. The inhalation toxicity of manganese is related to particle size and pharmacokinetic events (absorption and delivery to target tissues). Insufficient information is available to determine the relative toxicities of different forms of manganese.

While the critical portal of entry is the lung, the critical target tissue is the brain, with effects including affective symptoms (mood, sleep and appetite patterns, and libido) and neurologic symptoms (balance, coordination, and tremors). There may be a delayed stage affecting the neuromuscular system that may not appear until many years after the onset of exposure. Neuropathology and neuro-chemistry of manganese have been extensively studied. In situations of particulate inhalation, the respiratory system is also a primary target, with numerous reports of manganese pneumonitis and a possible synergism with smoking. One study examined school children near a ferromanganese smelter and found significant correlations between atmospheric manganese levels and respiratory problems, but the dose-response relationship is not clear.

The SF of 1000 includes factors of 10 for protection of sensitive individuals, 10 for the use of the LOAEL to calculate the RfC, and 10 for a combination of less-than-chronic exposures and lack of developmental data. Various studies suggest that children, pregnant women, elderly persons, and those with anemia, iron deficiency, calcium deficiency, and liver impairment may have an increased potential for excessive body burdens of manganese.

Supporting Studies for the EPA Cancer Classification:

Manganese is not classifiable as to carcinogenicity. There are no human data by which to evaluate whether manganese is a carcinogen. The animal data are inadequate. Several studies have examined manganese in various animal cancer test systems, but results were negative, suggestive but inconclusive, or not able to be evaluated.

Reference:

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

MERCURY, INORGANIC

CASRN: 7439-97-6
Synonyms: Quicksilver, Metallic mercury, Colloidal mercury, Mercuric mercury

Oral Reference Dose - Chronic (RfDo):	3E-4 (mg/kg)/day (HEAST)
Critical Effect:	Kidney effects in rats
Safety Factor (SF):	1000
Confidence:	Not available
Inhalation Reference Concentration (RfC):	3E-4 mg/m^3 (HEAST)
Critical Effect:	Neurotoxicity in humans
Safety Factor (SF):	30
Confidence:	Not available
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity.

Note: This profile applies to metallic mercury, elemental mercury, inorganic mercury, and inorganic mercury salts/compounds.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The supporting studies cited in HEAST include several inhalation, oral, and subcutaneous exposure studies in rats. The parenteral study appears to be the study used to develop the RfDo. The toxic effect identified was kidney damage. A risk assessment for mercury is under review by EPA.

Supporting Studies for the Chronic Inhalation Reference Concentration (RfC):

The supporting studies cited in HEAST include several occupational exposure studies. The toxic effect identified was nerve damage. A risk assessment for mercury is under review by EPA.

Supporting Studies for the EPA Cancer Classification:

EPA determined that mercury was unclassifiable as to carcinogenicity because there are no human data and only inadequate animal data. Rats were exposed to metallic mercury for 2 weeks via injection to the abdominal cavity and then observed for their lifetimes. At death, tumors were detected only in tissues which had been in direct contact with the mercury. In a 78-week methyl mercury chloride feeding study of male and female mice, kidney tumors were seen in the exposed male animals, but these results appeared only in a preliminary communication.

Methyl mercury and phenyl mercury (organic mercury forms) administered in the diet of fruit flies have caused chromosome damage. The significance of studies on organic forms of mercury (which show possible carcinogenic action) to inorganic mercury is not known.

References:

U.S. Environmental Protection Agency (EPA). 1990 (September). *Health Effects Assessment Summary Tables*, Table A. PB90-921104, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

METHYLENE CHLORIDE

CASRN: 75-09-2
Synonyms: Dichloromethane, Methane dichloride

Oral Reference Dose - Chronic (RfDo):	6E-2 (mg/kg)/day
Critical Effect:	Liver toxicity
Safety Factor (SF):	100
Confidence:	Medium
Inhalation Reference Dose (RfDi):	Under review by EPA working group
Inhalation Reference Concentration (RfC):	*3E+0 (mg/m^3)
Oral Cancer Slope Factor:	7.5E-3 per (mg/kg)/day
Inhalation Unit Cancer Risk:	4.7E-7 per ($\mu g/m^3$)
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The chosen study was a 24-month chronic toxicity and ocongenicity study of methylene chloride in rats. It used 85 rats/sex at each of four dose groups for 2 years. Many effects were monitored; treatment related histological alterations of the liver were evident at nominal doses of 50 mg/kg-day, or higher. The supporting database is limited. The 100-fold safety factor accounts for expected intra- and interspecies variability to the toxicity of methylene chloride in lieu of specific data.

Supporting Studies for the EPA Carcinogen Classification:

Human carcinogenicity data are considered inadequate for determining whether or not methylene chloride is a human carcinogen. Neither of two studies of chemical factory workers exposed to dichloromethane showed an excess of cancers. One study was too short, and the other provided some suggestion of increased incidence of pancreatic tumors, but did not provide clear evidence.

Animal carcinogenicity data are sufficient. Methylene chloride administered in the drinking water of rats induced a significant increase in liver tumors, and a nonsignificant increase in liver tumors in male mice. Two inhalation studies with dichloromethane have shown an increased incidence of benign mammary tumors in both sexes of two strains of rats; increases in salivary gland tumors and leukemia were seen in single treatment groups, while in mice, both sexes developed liver and lung tumors. In the same 2-year study used to derive the RfDo, female rats showed an increased incidence of liver tumors; male rats did not. In the same study, male mice had an increased incidence of liver tumors that was statistically significant but not dose-related. Female mice did not have increased liver tumor incidence. The EPA regarded this study as suggestive but not conclusive evidence for carcinogenicity of dichloromethane. Two inhalation assays using dogs, rabbits, guinea pigs, and rats showed no tumors but were not conducted for the lifetime of the animals.

Methylene chloride causes mutations in bacterial test systems and causes chromosomal effects in yeast. Results in cultured mammalian cells have generally been negative, but methylene chloride has been shown to transform rat embryo cells and to enhance viral transformation of Syrian hamster embryo cells. Although chlorinated solvents have often been suspected of acting through a nongenotoxic mechanism of cell proliferation, methylene chloride was unable to cause increased cell division in the liver of mice.

The oral slope factor is an arithmetic mean of slope factors derived from the two major studies described above. The inhalation unit risk incorporates information on pharmacokinetics and metabolism. Internal dose estimates were based on the metabolism of dichloromethane by the glutathione-s-transferase pathway. The internal dose was corrected for interspecies differences in sensitivity by using the surface area correction factor. Calculation of a slope factor from the unit risk is inappropriate when pharmacokinetic models are used.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

NAPHTHALENE

CASRN: 91-20-3
Synonyms: Naphthene, Tar camphor

Oral Reference Dose - Chronic (RfDo):	Pending as of 11/1/93
ECAO Provisional RfDo:	4E-3 (mg/kg)/day
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the EPA Cancer Classification:

There are no human data that can be used to determine whether naphthalene is carcinogenic in humans. Animal data are inadequate. The National Toxicology Program is currently evaluating naphthalene for carcinogenicity in mice by the inhalation route; final results are not available. In an early study, rats were given naphthalene in the diet for a short time, and tumors were evaluated as rats died after 2 years; no tumors were found. In a short-term lung tumor assay, mice developed a statistically significant number of lung tumors, but the increase was not dose responsive. In another study in which rats were given naphthalene by gavage in a protocol that looks for pre-neoplastic lesions in the liver, no effect was seen. Intraperitoneal injections of naphthalene in rats also did not cause tumors. The naphthalene fraction of coal tar has showed some carcinogenic effects, but the value of these studies is limited because of potential impurities in the naphthalene.

Naphthalene is negative in bacterial mutagenicity test systems, in DNA damage assays, or in neoplastic transformation assays. A single report of bacterial mutagenicity did not show effects at moderate or high doses.

References:

Poirier, K. A. 1992 (January 23). *Risk Assessment for Polyaromatic Hydrocarbons*. Memorandum to C. Sweeney. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

NICKEL

CASRN: 7440-02-0
Synonyms: Synonyms of nickel refer to different alloys or to different impurities.

Oral Reference Dose - Chronic (RfDo):	2E-2 (mg/kg)/day
Critical Effect:	Decreased body and organ weights
Safety Factor (SF):	300
Confidence:	Low/medium
Inhalation Reference Dose (RfDi):	Not available
EPA Cancer Classification:	Pending

Note: This assessment is for soluble salts of metallic nickel. Other nickel compounds are class A carcinogens; these include nickel refinery dust and nickel subsulfide with inhalation cancer slope factors of 8.4E-1 $((mg/kg)/day)^{-1}$ and 1.7 $((mg/kg)/day)^{-1}$, respectively. The carcinogenic forms of nickel may not be present at Hanford.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The RfD is based on a 2-year drinking water study of rats which resulted in decreased whole body and major organ weights compared to controls. The decreases were seen in both sexes. In another study in rats, changes in blood chemistry were observed in addition to gastrointestinal effects and decreases in liver weight. In the same research, toxic effects were reported in dogs. The toxic effects were to the respiratory system, the gastrointestinal system, the blood, the liver, and the kidney. The weight decrease results of the chronic study are corroborated by a subchronic (90-day) rat feeding experiment. The subchronic study also resulted in pneumonia, ulcers, and microscopic blood chemistry changes. Dose was found to be proportional to toxic response in the test animals (ATSDR 1993).

In a two-generation drinking water study in rats, an increased adverse effect on fetal development was detected at the intermediate and high doses. The results of this study, however, are questionable. In a three-generation drinking water study in rats, exposures resulted in increases in neonatal mortality and other adverse effects in offspring. This study also has several limitations. In another reproductive and fetotoxic effects study in rats exposed to nickel in drinking water, a clear dose-response trend at the lower doses was absent. An increase in mortality among newborns was reported.

Contact dermatitis, which results from dermal exposure to nickel, is the most prevalent effect of nickel in the general human population. Several studies have been performed which examined dermatitis outbreak from oral exposure. The studies indicated that certain humans have a hypersensitivity to nickel; therefore, this fact was considered in developing the RfD. A nutritional requirement for nickel in humans has not been established, but nickel is an essential trace element in several animal species, including rats.

The safety factor of 300 incorporates a factor of 10 each for interspecies and intraspecies variability to toxicity, and a factor of 3 to account for inadequacies in the reproductive study. Confidence in the chronic study, which is the basis of the RfD, is medium because many of the controls died. A medium confidence in the database is recommended by EPA.

Supporting Studies for the EPA Cancer Classification:

Nickel salts are under evaluation for carcinogenicity. As noted previously, nickel subsulfide and nickel refinery dust are carcinogens.

References:

Agency of Toxic Substances Disease Registry (ATSDR). 1993. *Toxicological Profile for Nickel.* TP-92/14, U.S. Department of Health and Human Services, Division of Toxicology, Atlanta, Georgia.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

CASRN: 14797-65-0
Synonyms: Nitrous acid - ion (-1)

Oral Reference Dose - Chronic (RfDo):	1E-1 (mg/kg)/day
Critical Effect:	Blood, methemoglobinemia
Safety Factor (SF):	1
MF:	10
Confidence:	High
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	No data
Inhalation Cancer Slope Factor:	No data
Inhalation Unit Cancer Risk:	No data
EPA Cancer Classification:	No data

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The RfDo for nitrite is derived from an epidemiologic study on the incidence of methemoglobinemia in infants routinely fed formula prepared from nitrate-contaminated water. This study analyzed all known cases of infant methemoglobinemia occurring in 37 states irrespective of date or type of water supply. Nitrate (nitrogen) content ranged from 10 ppm to over 100 ppm. No incidences of methemoglobinemia were found to occur in drinking water containing greater than 10 ppm (10 mg/L) nitrate (nitrogen). A NOEL of 10 mg/L for nitrate (nitrogen) was derived from these studies; other studies support 10 mg/L as the NOAEL.

The NOAEL was divided by a modifying factor of 10 (due to the direct toxicity of nitrite) to calculate a reference dose for a 10-kg child drinking 1 L of water per day as 0.1 mg/kg-day for nitrite. No safety factor was used because the NOEL was based on the critical effect (methemoglobinemia) in the sensitive human population (infants). Confidence in the RfDo is high because the NOEL is determined in the sensitive human population and because the database contains several supporting epidemiologic studies.

Exposure of hemoglobin to nitrite results in the oxidation of the hemoglobin to methemoglobin. Animals do not provide a good model for methemoglobin formation because many species lack nitrate-reducing bacteria. Infants are, however, particularly susceptible due to their high gut content of nitrate-reducing bacteria, their lower enzymatic capacity to reduce methemoglobin to hemoglobin, and to the presence of hemoglobin F, which is more susceptible to oxidation. Methemoglobin formation can cause cyanosis and death in infants, but cyanosis has not been reported to occur in infants using water with 10 mg/L or less of nitrate-nitrogen. While there are some data to the contrary, it is most likely that older children age 1 and above do not respond with increased methemoglobinemia to nitrate in drinking water.

The RfDo for nitrite may change in the near future pending the outcome of a further review being conducted by EPA's reference dose work group.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

PENTACHLOROPHENOL

CASRN: 87-86-5
Synonyms: Trade names

Oral Reference Dose - Chronic (RfDo):	3E-2 (mg/kg)/day
Critical Effect:	Liver and kidney pathology
Safety Factor (SF):	100
Confidence:	Medium
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	1.2E-1 per (mg/kg)/day
Inhalation Cancer Slope Factor:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

When rats were given pentachlorophenol in the diet for 2 years, a reduced rate of body weight gain in females was observed. In both males and females, pigmentation of the liver and kidneys was seen. The dose level of 3 (mg/kg)/day was reported as the NOAEL, and the dose level of 10 (mg/kg)/day was the LOAEL. A study looking at teratogenic effects did not note any teratogenicity. There was fetal and maternal toxicity, but the pentachlorophenol did not cross the placenta, and therefore the observed fetotoxicity was not attributed to the chemical, but may have been a reflection of maternal toxicity. The NOAEL for this effect was the same as for the previous toxicity study.

The safety factor of 100 accounts for intra- and inter-species variability. Confidence in this study is high, and confidence in the database is medium, so the overall confidence in the RfD is also medium.

Supporting Studies for the EPA Cancer Classification:

The carcinogenicity classification is based on inadequate human data and sufficient evidence of carcinogenicity in animals. In one occupational study, workers exposed to undetermined levels of pentachlorophenol and other preservatives excreted pentachlorophenol in their urine (evidence of exposure) but did not show any concurrent clinical conditions. An attempt to reexamine these workers over time was uninformative due to the large number of workers lost to follow-up and other study deficiencies.

Evidence of carcinogenicity in animals is sufficient. Statistically significant increases in the incidence of multiple tumor types (liver, adrenal, blood vessels) in one or both sexes of mice were reported. Two-year bioassays were conducted in mice by adding technical-grade pentachlorophenol in the diet, which did not affect survival, but did cause an increase in adrenal cancer in male mice, a slight but biologically significant increase in liver tumors in female mice, and an increase in vascular tumors in female mice. In the other mouse bioassay, dietary pentachlorophenol caused liver tumors and adrenal tumors in males and females, and vascular tumors in females. Most of the effects in these two studies were dose-related.

In the chronic oral rat study used to derive the RfD, a slight increase in adrenal tumors was noted. Several other studies were judged inadequate for drawing conclusions.

Two assays for DNA and chromosomal effects have been positive.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

PHENANTHRENE

CASRN: 85-01-8
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the EPA Cancer Classification:

There are no human data available for phenanthrene. Animal data are inadequate. A study in rats and a study in mice were both experimentally inadequate. Five studies of cancer-initiating activity in mouse skin painting studies have yielded one positive result in which tumor incidence was reported in treated animals. Four other skin painting studies were negative. Phenanthrene did not cause an increase in treatment-related tumors in other studies when given intraperitoneally or subcutaneously.

Phenanthrene has been negative in several bacterial mutagenicity test systems, in a DNA recombination assay, and in tests for DNA damage in several mammalian cell culture systems. Metabolites of phenanthrene may be weakly mutagenic and weakly carcinogenic. Structural properties of phenanthrene would predict stronger mutagenicity and carcinogenicity than are actually observed; the reason for this inconsistency has not been elucidated.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

POLYCHLORINATED BIPHENYLS (PCBs)

CASRN: 1336-36-3
Synonyms: Aroclor, Aroclor 1221, Aroclor 1232, Aroclor 1242, Aroclor 1248, Aroclor 1254, Aroclor 1260, Aroclor 1262, Aroclor 1268, Aroclor 2565, Aroclor 4465, Aroclor 5442

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	7.7 (mg/kg)/day
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the EPA Cancer Classification:

Human carcinogenicity data are inadequate. Although there are many studies, confounding data or lack of exposure quantification limit their usefulness. Several studies reported either statistically significant or possible increased incidences of melanoma, liver and biliary cancer, blood cancers, or total cancers, but none are definitive. One study reported increases in liver and biliary cancers that were later determined to be not statistically significant because of several confounding factors. In a study of Italian workers, total cancer and deaths due to gastrointestinal tract cancer were increased, but the small number of deaths and other limitations caused the power of the study to be insufficient to detect an increase in tissue-specific cancer. Two occurrences of polychlorinated biphenyl-contaminated rice oil (the Yusho and Yu-cheng incidents) have received wide attention. One follow-up study observed an increase in liver cancers in males and females, but serious shortcomings limit the conclusions that can be drawn.

There is sufficient evidence to classify polychlorinated biphenyls as animal carcinogens. Polychlorinated biphenyl mixtures used in the animal assays were commercial preparations and may not be the same as mixtures of isomers found in the environment. Commercial polychlorinated biphenyl preparations are clearly carcinogenic, but it is not known which of the polychlorinated biphenyl congeners in such preparations are responsible for these effects, or if decomposition products, contaminants, or metabolites are involved in the toxic response.

Early cancer bioassays with rats were experimentally inadequate due to the small number of animals and a short duration of exposure. However, a bioassay with Aroclor 1260 produced a high incidence of liver tumors in female rats, and serial tissue samples over the course of the study showed a progression of liver lesions to liver cancer. A bioassay of Aroclor 1254 in rats showed cellular proliferation in the liver (changes that are potentially pre-neoplastic). A dietary study of Aroclor 1260 in rats caused liver tumors as well as pre-neoplastic changes, which indicate a serial progression of liver lesions to overt cancer. Orally administered polychlorinated biphenyl caused liver tumors in two mouse strains. Additional studies confirm these reports.

Most genotoxicity studies with polychlorinated biphenyls have been negative. It is known that individual polychlorinated biphenyl congeners vary greatly in their potency in producing biological effects. Generally, for the purposes of carcinogenicity assessment, Aroclor 1260 is considered representative of all polychlorinated biphenyl mixtures. There is evidence that mixtures containing more highly chlorinated biphenyls (such as Aroclors 1248, 1254, and 1260) are more potent carcinogens than mixtures containing less chlorine by weight.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

PYRENE

CASRN: 129-00-0
Synonyms: Benzo(d,e,f)phenanthrene

Oral Reference Dose - Chronic:	3E-2 (mg/kg)/day
Critical Effect:	Kidney effects (reneal tubular pathology, decreased kidney weights)
Safety Factor (SF):	3000
Confidence:	Low
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

A 13-week subchronic study, in which mice were given pyrene daily by gavage, was used to derive a subchronic NOAEL of 75 mg/kg-day and a LOAEL of 125 mg/kg-day. Kidney damage was seen in both male and female mice. A safety factor of 3000 reflects 10 each for intra- and interspecies variability, 10 for the use of a subchronic study to determine the chronic RfD, and a factor of 3 to account for the lack of toxicity studies in a second species and lack of reproductive/developmental studies.

Confidence in the critical study is medium, because it was a well-designed study that looked at several toxicological endpoints. Confidence in the database is low due to the lack of supporting subchronic, chronic, and reproductive/developmental studies. Overall confidence in the RfD is, therefore, low.

Supporting Studies for the EPA Cancer Classification:

There is no human data that can be used to determine whether pyrene is a human carcinogen. Animal carcinogenicity data are inadequate. One study examined the effects of injecting pyrene into newborn mice; survival was low and the results of the 1-year short-term study were not considered to be positive because of the lack of a significant incidence of tumors. Several skin-painting studies in mice were either negative or inconclusive. One study in which pyrene was injected subcutaneously did not produce injection site tumors in mice.

Both positive and negative results have been reported in bacterial mutagenicity test systems and in other test systems for DNA damage. Pyrene did not produce chromosome aberrations nor did it cause neoplastic transformation in cultured mammalian cells.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

SELENIUM SULFIDE

CASRN: 7446-34-6
Synonyms: Sulfur selenide, Selsun Blue

Oral Reference Dose - Chronic (RfDo):	No data
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
Inhalation Unit Cancer Risk:	Not available
EPA Cancer Classification:	B2; probable human carcinogen

Supporting Studies for the EPA Cancer Classification:

Human data on the carcinogenicity of selenium sulfide are inadequate. Workers occupationally exposed to excess selenium levels exhibited selenium toxicity (pulmonary irritation, epigastric pain, and dermatitis) but no increase in cancer. These studies generally are limited by low exposures, small sample sizes, and lack of information as to the form (species) of selenium.

Animal carcinogenicity data specifically for selenium sulfide are sufficient. A cancer bioassay conducted by the National Cancer Institute in which rats and mice were given selenium orally showed a dose-related trend in liver tumors in male and female rats, a possible increase in lymphoma and testicular tumors in male rats, an increase in pituitary cancer in female rats, and lung and liver cancer in female mice. Other tissues showed a suggested increase in tumors, but variability and high rates in control animals made a causal and dose-responsive relationship unclear.

Because selenium sulfide is used as an anti-dandruff agent in shampoos, the National Cancer Institute also conducted two dermal cancer studies. In one study, results were judged equivocal; in the other, there was a possible increase in lung tumors.

Selenium sulfide has not been tested for mutagenicity. Selenium sulfide is less soluble in water than sodium selenite or selenate, but the extent to which selenium sulfide is absorbed through the skin or intestinal tract has not been fully elucidated.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

SILVER

CASRN: 7440-22-4
Synonyms: Argentum crede

Oral Reference Dose - Chronic (RfDo):	5E-3 (mg/kg)/day
Critical Effect:	Argyria (see below)
Safety Factor (SF):	3
Confidence:	Low
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Note: This profile does not cover silver cyanide.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The RfD is based on 70 cases of silver poisoning following organic and colloidal silver medication. The clinical syndrome (argyria) is characterized by a benign but permanent bluish-gray discoloration of the skin resulting from deposition of silver in the dermal layer, as well as silver-induced production of melanin. Areas of the skin exposed to the sun become darker due to photoactivated reduction of the metal. Argyria is not associated with adverse health effects, and no pathologic changes or inflammation occurs. Silver has been used for medical treatment of syphilis and as a topical astringent for centuries.

The study on which the RfD is based included intravenous injection of silver (for medical reasons). The amount of discoloration was correlated with the amount of silver deposited in the skin and confirmed by skin biopsies. The total intravenous dose associated with argyria was calculated with an allowance for additional silver that can normally be accumulated in the body over a lifetime. Other case studies of various silver formulations support the clinical finding but are not sufficient for deriving an RfD. The amount of silver in a normal diet has been measured, and dietary studies of silver (as silver nitrate) have been performed in monkeys, rats, mice, and dogs. Argyria can be caused by silver arsphenamine, any silver compound including silver nitrate, silver acetate, and various medicinal formulations.

A safety factor of 3 was used to account for minimal effects in an apparently sensitive subpopulation. The RfD is based on the most sensitive patient whose dose could be confirmed; other case reports did not indicate an observable effect at doses which were 5 times higher. The clinical effect is cosmetic with no associated adverse health effects. No safety factor for subchronic to chronic duration is needed because the dose has been apportioned over a lifetime of 70 years. Confidence in the critical human study is medium; the patients receiving higher doses of silver that did not develop argyria were not described, and the particular patient who developed argyria was being treated for syphilis and may have been of compromised health. Confidence in the human database is low because only case reports appear in the literature and because an intravenous study was used to calculate an RfDo.

Another condition, argyrosis, results from silver deposition in the eye, generally from the use of eye drops or cosmetics. Toxic effects of silver have also been reported for the cardiovascular system and the liver. In the latter case, liver damage was seen in rats deficient in selenium or vitamin E.

Supporting Studies for the EPA Cancer Classification:

No evidence of cancer in humans has been reported despite frequent therapeutic use of silver over many years.

Animal data are inadequate. Local tumors have been induced after subcutaneous implantation of foils and discs of silver and other noble metals (as well as plastics and ivory). However, the tumors may be due to the solid objects rather than to their composition. Two other studies of silver have been negative. In one study, colloidal silver was injected intravenously and subcutaneously into rats, and tumors were noted but were not reported as statistically increased. In another study, silver powder suspended in an emulsifier was injected intramuscularly, with no development of injection site tumors.

Silver has not been well tested for mutagenicity or chromosomal effects, but two studies in bacterial mutagenicity test systems were negative.

Reference:

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

STRONTIUM

CASRN: 7440-24-6
Synonyms: Stable strontium

Oral Reference Dose - Chronic (RfDo):	0.6 (mg/kg)/day
Critical Effects:	Strontium rickets
Safety Factor (SF):	300
Confidence:	Medium
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	No data
Inhalation Cancer Slope Factor:	No data
EPA Carcinogen Classification:	No data, and D not classifiable as to human carcinogenicity

Note: This assessment evaluates only the chemical effects of strontium. For information on radiotoxicity, see the strontium-90 profile.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The three supporting studies for the RfDo were performed in rats. In one study, both young and adult female rats were given various doses of strontium carbonate in their diets. Changes to bone mineralization and cartilage were examined. Young rats were found to be more susceptible to lower doses than adult rats. Adverse effects to bone and cartilage were observed to increase with dose administered. In another study, stable strontium was administered to weanling male rats. The authors concluded that a threshold dose exists below which adverse effects on body growth or bone mineralization did not occur. The third study examined rickets in male rats given strontium chloride in drinking water for 3 months, 3 years, and three generations. An increase in bone and soft tissue levels of strontium was observed in the treated animals, but toxic effects on tissues (including bone tissues) were not observed.

Strontium causes adverse effects on bones by substituting for calcium in the bone matrix. The toxic effect of strontium is worsened by inadequate calcium levels in the diet. These findings have been confirmed in dogs administered oral doses of strontium phosphate in conjunction with low levels of dietary calcium. Relatively little information is available regarding the potential for developmental toxicity resulting from exposure to strontium. There is not enough data to derive an RfDo. based on the toxicity of stable strontium in humans. Strontium has been used as a nonstandard medical treatment.

The safety factor of 300 includes a factor of 10 to extrapolate from animals to humans, 10 from an incomplete database, and 3 to protect sensitive subpopulations. The confidence in the RfD is medium, reflecting the confidence in the study and the database. The limitations of these studies include an incomplete report of experimental details, the lack of a second species, and little available information on reproductive and developmental effects.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables*. EPA 540-R-93-058, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

TETRACHLOROETHYLENE

CASRN: 127-18-4
Synonyms: Perchloroethylene, PCE

Oral Reference Dose - Chronic (RfDo):	1E-2 (mg/kg)/day
Critical Effect:	Liver toxicity
Safety Factor (SF):	1000
Confidence:	Medium
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	Not available (see below)
ECAO Suggested Slope Factor:	5.2E-2 per mg/kg-day
Inhalation Cancer Slope Factor:	Not available (see below)
ECAO Suggested Slope Factor:	2.0E-3 per mg/kg-day
Inhalation Unit Cancer Risk:	Not available (see below)
ECAO Suggested Unit Risk:	5.8E-7 per $\mu g/m^3$
EPA Carcinogen Classification:	Pending as of 7/1/93

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

Mice exposed to tetrachloroethylene by gavage for 6 weeks exhibited increased liver triglycerides, increased liver weight, decreased liver DNA content, increased SGPT, decreased levels of glucose-6-phosphate, hepatocellular necrosis, and polyploidy. A NOAEL of 14 mg/kg-day was established by a study of rats given tetrachloroethylene in drinking water. The RfD incorporates a safety factor of 1000, which results from factors of 10 for intraspecies variability, interspecies variability, and extrapolation of a subchronic effect to its chronic equivalent.

Other studies support the findings of the principal studies. Mice and rats exposed by gavage for 11 days exhibited hepatotoxicity. Inhalation studies support the use of a factor of 10 for extrapolating from a subchronic to chronic exposure. Several chronic inhalation studies have been performed, and none are inconsistent with the NOAEL of 14 mg/kg-day. Confidence in the principal study is low due to incomplete histopathology; confidence in the database for tetrachloroethylene is medium, and confidence in the RfD is medium. While no one study combines the features desired for deriving a RfD, the database as a whole is relatively complete. Reproductive and teratology studies are lacking.

Additional Information:

Tetrachloroethylene was classified as a class C (possible human carcinogen) by EPA in 1985. In 1987, the classification was changed to class B2 (probable human carcinogen). EPA's Science Advisory Board suggests that the weight-of-evidence is on the C-B2 continuum. At the present time, EPA has not adopted a final position on which class tetrachloroethylene belongs in. EPA's Environmental Criteria and Assessment Office (ECAO) suggests an oral cancer slope factor of 5.2E-2 per mg/kg-day (since the animal studies are adequate for deriving a slope factor) and an inhalation unit risk of 5.8E-7 per $\mu g/m^3$, which is the geometric mean of slope factors calculated from different animal inhalation studies.

References:

Dollarhide, J. S. 1993. *Carcinogenicity Information for Tetrachloroethylene (CASRN 127-18-4) and Trichloroethylene (CASRN 79-01-6).* Memorandum to C. Sweeney, U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio (February 26).

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

THALLIUM COMPOUNDS

CASRN: 7446-18-6
Synonyms: Thallium sulfate

Oral Reference Dose - Chronic (RfDo):	8E-5 (mg/kg)/day
Critical Effect:	No adverse effects at the NOAEL; increased liver enzymes at higher levels
Safety Factor (SF):	3000
Confidence:	Low
NOAEL:	0.25 mg/kg-day
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable

Note: This profile applies to the following compounds: thallium acetate (CASRN 563-68-8), thallium nitrate (CASRN 7446-18-6), thallium carbonate (CASRN 6533-73-9), and thallium chloride (CASRN 7791-12-0). The oral reference dose (RfDo) for thallic oxide (CASRN 1314-32-5) and thallium selenite (CASRN 12039-52-0) have been withdrawn from IRIS.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

Using the results of a rat oral subchronic study with thallium sulfate, reference doses were calculated for thallium acetate, thallium carbonate, thallium nitrate, and thallium chloride. In this study, rats were treated orally with thallium sulfate for 90 days. Several dose-related toxic effects were seen, and the NOAEL was based on moderate dose-related changes in blood chemistry parameters. A NOAEL cannot be calculated from the anecdotal human data. The safety factor of 3000 includes factors of 10 to extrapolate from subchronic to chronic data, 10 for intraspecies extrapolation, and 10 for intraspecies variability. An additional safety factor of 3 was used due to a lack of reproductive and chronic toxicity data. Confidence in the critical study is low because of uncertainties in the results. Confidence in the supporting database was low because of the paucity of animal data and the anecdotal nature of human data. Overall confidence in the RfD is, therefore, low.

Supporting Studies for the EPA Cancer Classification:

Human data are inadequate. Two occupational studies on workers exposed to thallium (form unspecified) have been reported and form the basis for classification of all thallium compounds. In one study, medical records of 86 workers exposed to thallium, matched to records of 79 unexposed workers, did not indicate an increase in cancer; this study has significant biological and statistical limitations. In another study, health effects in 128 men exposed to thallium for various lengths of time indicated elevated urinary thallium levels but no indication of thallium poisoning. However, the study was inadequate to determine whether cancer was elevated or not.

There is no animal data with respect to carcinogenicity of thallium compounds. In in vitro test systems for bacterial mutagenicity and DNA damage, results are generally negative. Positive results have been seen for DNA damage in at least two different assay systems.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

TOLUENE

CASRN: 108-88-3
Synonyms: Methyl benzene, Methylbenzol, Phenyl-methane

Oral Reference Dose - Chronic (RfDo):	2E-1 (mg/kg)/day
Critical Effect:	Changes in liver and kidney weights in rats
Safety Factor (SF):	1000
Confidence:	Medium
Inhalation Reference Dose (RfDi):	1E-1 (mg/kg)/day
Inhalation Reference Concentration (RfC):	4E-1 mg/m^3
Critical Effects:	Neurological effects in occupational studies Degeneration of nasal epithelium - rat inhalation study
Safety Factor (SF):	300
Confidence:	Medium
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The critical study was a subchronic study in which rats were given toluene orally for 13 weeks. Several toxic effects were noted at the higher doses, including prostration, hypoactivity, lacrimation, salivation, tremors, and other behaviors. None of these effects were seen at intermediate doses. There were no hematological effects at any dose. Changes in liver serum enzymes were noted at the highest surviving dose but were not considered biologically significant. Several pathologic and organ weight changes were noted at the intermediate doses; the most sensitive changes were kidney and liver weight changes at a dose that did not cause cellular changes. This dose was chosen as the LOAEL; a lower dose was chosen as the NOAEL.

Supporting studies include a parallel study in mice; the mice appeared to be somewhat less sensitive than rats. Several subchronic and chronic inhalation studies in rats and mice have been performed but are not considered suitable for deriving an RfDo. One study reported an increase in embryo lethality in mice given toluene orally, but only at higher doses than the NOAEL.

Confidence in the critical study is high. Confidence in the supporting database is only medium because there is no adequate reproductive study and because the critical study was a subchronic rather than chronic study. Overall confidence in the RfD is, therefore, medium.

Supporting Studies for the Inhalation Reference Concentration (RfC):

Both occupational and animal data provided the basis for the RfC. In humans, toluene is a respiratory irritant with central nervous system (CNS) effects. An occupational study of female workers, which included personal sampling dosimetry, evaluated neurobehavioral effects and observed dose-related decrements in function. Because irritant effects and other clinical symptoms were not evaluated, this study serves as supporting evidence only for the neurobehavioral effects. Several other occupational studies support these results. Numerous chronic, subchronic, and acute exposure studies have demonstrated CNS effects typical of solvent exposure. Severity correlates well with concentration, including instances of inhalation abuse and at lower occupational exposure levels.

A 2-year inhalation cancer bioassay in rats did not result in neoplasia but provided evidence of degeneration of the olfactory and respiratory epithelium at all doses; therefore, the lowest dose was chosen as the LOAEL. No other clinical signs were noted in any treatment group.

The safety factor of 300 includes factors of 10 for interspecies variability, 10 because a LOAEL rather than a NOAEL was used, and a factor of 3 due to database deficiencies.

Toluene has been suspected of causing congenital defects in humans and has documented fetal effects in situations of toluene abuse. This has been confirmed in rats and mice. Fetotoxicity has also been documented in rats, mice, and rabbits. LOAELs or NOAELs have been established for several other effects in various species.

Confidence in the critical human study is medium due to the small sample size, and confidence in the rat study was medium because it did not establish a NOAEL. Confidence in the database is medium due to the lack of chronic human neurotoxicity or irritation studies.

Supporting Studies for the EPA Cancer Classification:

There are no human data suitable for evaluation whether toluene is a human carcinogen. Animal data are inadequate. A 2-year inhalation cancer bioassay in rats was considered inadequate due to the low concentration used. Several studies have examined toluene carcinogenicity, after dermal application, with negative results.

Toluene is not mutagenic in bacterial test systems, does not cause chromosomal effects in yeast, does not appear to cause chromosome damage in workers or in cultured mammalian cells, and does not cause chromosomal damage in bone marrow cells of rats or mice. One Russian study reported chromosome effects in rat bone marrow cells; however, this has not been confirmed in other studies.

Reference:

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

TRIBUTYL PHOSPHATE

CASRN: 126-73-8
Synonyms: TBP, Butyl phosphate, Phosphoric acid tributyl ester, Tri-n-butyl phosphate, Tributoxyphosphine oxide

Oral Reference Dose - Chronic (RfDo):	5E-3 (mg/kg)/day (provisional)
Critical Effect:	Urinary bladder hyperplasia in rats
Safety Factor (SF):	3000
Confidence:	Low
Source:	EPA: Environmental Criteria & Assessment Office
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	Not available
Inhalation Cancer Slope Factor:	Not available
EPA Cancer Classification:	Study underway
ECAO Recommendation:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

EPA's Environmental Criteria and Assessment Office (ECAO) has developed a provisional RfDo based on a review of available toxicity databases and a search of the published research literature.

Several studies in rats and mice have been performed. In a subchronic study, rats were administered tributyl phosphate in the diet for 13 weeks and screened for a wide range of toxic effects. Effects were noted in various dose groups: a decrease in the rate of body weight gain, prolonged blood clotting time, increased serum liver enzymes, and alterations in other blood chemistry parameters. Urinary bladder cellular proliferation was used as the basis for both a LOAEL and a NOAEL.

Neurotoxicity is a particular concern with tributyl phosphate due to structural similarity to tri-ortho-cresyl phosphate, which causes delayed neurotoxicity in hens, the sensitive species. Slight neurotoxicity was observed in a 2-week oral rat study, but a 13-week study at slightly lower daily doses did not report neurotoxic effects. No neurotoxicity was evident in workers with long occupational exposures (to mixed substances at generally undocumented concentrations).

Developmental toxicity has also been examined in one rat study in which slight developmental toxicity was observed at the lowest administered dose, which was higher than the NOAEL for bladder effects.

A safety factor of 3000 was used with 10 each for inter- and intraspecies variability, 10 for the use of a subchronic study to derive a chronic RfD, and 3 because no chronic or multigenerational studies have been done. Confidence in the principal study is high; it was a well-designed and conducted subchronic study which identified both a LOAEL and NOAEL. Confidence in the database is low because no chronic oral studies were located. Overall confidence in the RfDo is, therefore, low.

Supporting Studies for the EPA Cancer Classification:

A cancer bioassay begun in 1992 is currently underway. Tributyl phosphate is negative in bacterial mutagenicity test systems, in cultured cell mutagenicity test systems, and in mammalian test systems for chromosome damage in vivo and in vitro.

References:

Dollarhide, J. S. 1992. *Toxicology and Carcinogenicity Information for Tris (2)-ethylhexyl)phosphate (CAS# 78-42-2) and Tributyl Phosphate (CAS# 126-73-8)*. Memorandum to C. Sweeney. U.S. Environmental Protection Agency, Region X, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

Patty, F., ed. 1963. *Toxicology*. 2nd ed. Volume II of *Industrial Hygiene and Toxicology*. Cited in *CHRIS* (Volume 21 of TOMES) [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

TRICHLOROETHYLENE

CASRN: 79-01-6
Synonyms: Acetylene trichloride, Ethylene trichloride, TCE, TRI

Oral Reference Dose - Chronic (RfDo):	Under review by EPA working group
Provisional Chronic Reference Dose (P-RfD):	6E-3 (mg/kg)/day
Confidence:	Low
Safety Factor (SF):	3000
Source:	ECAO
Inhalation Reference Dose (RfDi):	Under review by EPA working group (IRIS)
Oral Cancer Slope Factor:	New carcinogen summary in preparation by CRAVE (IRIS)
[Old Withdrawn IRIS Oral Cancer Slope Factor =	1.1E-2 kg-day/mg]
Inhalation Cancer Slope Factor:	New carcinogen summary in preparation by CRAVE (IRIS)
[Old Withdrawn IRIS Inhalation Slope Factor =	2E-3 kg-day/mg]
EPA Cancer Classification:	New carcinogen summary in preparation by CRAVE (IRIS)
[Old Withdrawn IRIS Cancer Classification =	B2; probable human carcinogen]

Provisional Information on Trichloroethylene:

An oral reference dose (RfDo) is not available for trichloroethylene on IRIS or HEAST. The IRIS record states that the RfD is under review.

Two chronic and subchronic mouse and rat gavage bioassays identify the kidney (in mice and rats) and the liver (in mice) as target organs for trichloroethylene-induced nonneoplastic effects; however, the data are not suitable for deriving an RfD. Also, the lowest doses in the chronic studies reduced survival, and, therefore, cannot be used to derive an RfD. While one of the bioassays is suitable for consideration as a basis for the RfD, the 6-month drinking water study of mice described above provides a better basis because it identified both NOAELs and LOAELs for the responses of the liver and kidney to orally administered trichloroethylene. The threshold for liver toxicity (relative liver weight) was lower than that for renal effects (elevated levels of protein and ketones). Although the study did not include histological examinations of the liver and kidney, a more comprehensive examination of hepatotoxicity in mice orally exposed to trichloroethylene for 6 weeks showed that liver weight increases were attributable to hypertrophy of the liver cells and that the hepatic response progressed to degenerative changes at higher doses.

The provisional chronic reference dose (P-RfD) is derived from the mouse NOAEL by a safety factor of 3000 (10 for interspecies extrapolation, 10 for intraspecies variation, 10 for extrapolation to chronic duration, and 3 for weakness of the database).

Confidence in the principal study is low. Adequate numbers of animals were exposed by a relevant route and were evaluated for several endpoints. However, histological examinations were not conducted on the tissues, and the duration of exposure was only one-quarter of a lifetime. Confidence in the database is low. Several subchronic toxicity studies in rats and mice are available, as are studies

of reproductive performance in rats and mice. However, chronic oral bioassays do not adequately describe dose-response relationships for chronic oral exposure to low doses of trichloroethylene, and comprehensive developmental toxicity studies are not available. Reflecting low confidence in the principal study and the database, confidence in the provisional RfD for trichloroethylene is low.

The Agency of Toxic Substances Disease Registry has prepared two Toxicological Profiles on trichloroethylene, each with a different minimum response level. Occupational exposure to trichloroethylene in air has been associated with effects on the central nervous system (e.g., nausea, headache, reduced cognitive performance, sleep disturbances), the heart, and other organs but not on the kidney or liver. Data regarding effects in humans repeatedly exposed to trichloroethylene in drinking water are confounded by concurrent exposure to other chemicals.

References:

Dollarhide, J. S. 1992. *Risk Assessment Issue Paper for: Provisional Oral RfD for Trichloroethylene (CAS #79-01-6)*. Memorandum to P. Cirone. U.S. Environmental Protection Agency, Region X, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

URANIUM, SOLUBLE SALTS

CASRN: None
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	3E-3 mg U/kg-day
Critical Effect:	Kidney toxicity (rabbits)
Safety Factor (SF):	1000
Confidence:	Medium
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	No data
Inhalation Cancer Slope Factor:	No data
EPA Carcinogen Classification:	No data

Note: "Natural Uranium" (CASRN: 7440-61-1) has a separate IRIS record, but there is no information on the reference dose (RfD) or carcinogenicity therein. This profile is for "uranium, soluble salts," which has no CASRN. All uranium is radioactive; however, the radiotoxicity of uranium is addressed in profiles for the individual isotopes. For information on the chemical toxicity of individual uranium salts, the Superfund Health Risk Technical Support Center (513/569-7300) may be contacted directly.

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

Uranium is a classic nephrotoxin. The toxicity of uranium to humans has been of interest since the 1800s when it was used as a homeopathic cure for diabetes mellitus. Early reports demonstrate the susceptibility of humans to the nephrotoxicity of ingested uranium but provide an inadequate basis for estimating the threshold dose for toxic effects. Experiments in which human volunteers were injected intravenously with uranium have provided some information on biochemical parameters of kidney function in humans.

Rabbits, rats, and dogs were given uranium in their diet for 30 days. The experimental results for uranyl nitrate hexahydrate in rabbits, the most sensitive species, are the supporting study for the RfD. A dose response relationship was detected for weight loss and kidney damage, and the lowest dose tested in rabbits (2.8 mg U/kg/day) was established as the LOAEL. Note that the dose has been corrected for the percentage of the molecular weight of the salt that is uranium. Another oral study with rabbits yielded inconclusive results. Water-soluble uranium compounds are thought to be more toxic than insoluble compounds.

The safety factor of 1000 is based on intraspecies (factor of 10) and interspecies (factor of 10) variability to the toxicity and use of the LOAEL rather than the NOAEL (factor of 10). Confidence in the study, database, and RfD is medium because the critical study is believed to be well designed but used a small number of test animals, and because the effects of uranium in several species have been studied.

In a reproductive study of 2-years duration, test animals (species unspecified; probably rats) fed uranium nitrate experienced a decrease in food consumption and declines in weight gain. Decreases in the numbers of litters born and litter size were consistent with the nutritional status of the animals. A second study by the same people exposed rats via the diet for 1 day. In this study, decreases in number of offspring were observed with treatment.

There are numerous reports of the toxicity of uranium salts to people. Data are currently inadequate to determine a threshold for uranium levels in the kidney which cause toxic effects.

Supporting Studies for the EPA Cancer Classification:

Chemical action of uranium has not been evaluated for carcinogenicity.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables*. EPA 540-R-93-058, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

VANADIUM

CASRN: 7440-62-2
Synonyms: Elemental vanadium

Oral Reference Dose - Chronic and Subchronic (RfDo):	7E-3 (mg/kg)/day
Critical Effect:	Not reported
Safety Factor (SF):	100
Confidence:	Not reported
Source:	HEAST
Inhalation Reference Dose:	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Unit Risk:	Not available
EPA Cancer Classification:	Not available

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The RfDo is based on a NOAEL of 5 ppm reported for a lifetime oral drinking water study in rats.

Note: A risk assessment for vanadium has been performed and is under review by an EPA work group.

Reference:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

VANADIUM PENTOXIDE

CASRN: 1314-62-1
Synonyms: Vanadic anhydride, Vanadium oxide

Oral Reference Dose - Chronic (RfDo):	9E-3 (mg/kg)/day
Critical Effect:	Decreased hair cystine
Safety Factor (SF):	100
Confidence:	Low
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	Not available

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The RfD is based on an unpublished study in which rats were fed diets with one of two different vanadium levels for 2.5 years (lifetime). Growth rate and survival were not significantly affected, but a significant increase was reported in the hair cystine content of exposed animals. The IRIS record indicates that other chronic and subchronic studies with vanadium have been reported, but none were more suitable than the critical study for calculating a NOAEL. In another subchronic feeding study, the effect on hair cystine was confirmed, as well as the effects on hemoglobin and erythrocytes at higher doses. Several epidemiologic studies have been conducted on workers. None of these contained sufficient exposure measurements for calculating a RfD based directly on human exposure.

The RfDo for a 70-kg adult was calculated by assuming that rats eat feed equivalent to 5% of their body weight per day and by applying a safety factor of 100 (10 for interspecies extrapolation and 10 for added protection of unusually sensitive individuals). Confidence in the critical study is low because of a lack of reported experimental detail. Confidence in the database is low because of the paucity of data for vanadium pentoxide.

Reference:

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

VANADIUM SULFATE

CASRN: 36907-42-3
Synonyms: None

Oral Reference Dose - Chronic and Subchronic (RfDo):	2E-2 (mg/kg)/day
Critical Effect:	Not reported
Safety Factor (SF):	100
Confidence:	Not reported
Source:	HEAST
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification	Not available

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

The RfD is based on a NOAEL of 2.24 mg/kg-day reported for a lifetime oral drinking water study in rats.

Reference:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables: FY-1994 Annual*. EPA 540-R-94-020, U.S. Environmental Protection Agency, Washington, D.C.

VINYL CHLORIDE

CASRN: 75-01-4
Synonyms: Chlorethene, Chlorethylene, Chloroethene, Chloroethylene, Ethylene monochloride, VC

Oral Reference Dose - Chronic (RfDo):	Not available
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	1.9E+0 per (mg/kg)/day
Limitation: use of these values are on an interim basis as validated by CRAVE (04/05/90)	
Inhalation Slope Factor	3.0E-1 per (mg/kg)/day
Inhalation Unit Cancer Risk:	8.4E-5 per ($\mu g/m^3$)
Limitation: use of these values are on an interim basis as validated by CRAVE (04/05/90)	
EPA Cancer Classification:	A; human carcinogen

Supporting Studies for the EPA Cancer Classification:

Maltoni et al. (1981), as cited in HEAST (EPA 1993), observed the LOAEL for liver cancer in exposed rats at 4 hr/5 day/52 week to be 1 ppm of vinyl chloride. The LOAEL for 6 rats exposed by oil gavage at 5 times per week for 52 weeks was 0.3 (mg/kg)/day. The observed LOAEL for carcinogenicity for 8 rats oil chlorgavaged for 52 weeks at 5 times per week was 16.65 (mg/kg)/day. This study forms the basis for the cancer slope factors presented in HEAST.

A large number of studies of workers exposed to vinyl chloride have identified a wide range of target organs that may be affected by chronic inhalation. Twenty-six studies give supporting evidence for human carcinogenicity, seven studies show carcinogenicity after inhalation in animals, and three studies show carcinogenicity in animals after oral exposure. Human data on oral exposures are lacking and confounded by the volatility of vinyl chloride, which would predict inhalation exposure during ingestion.

The Agency for Toxic Substances and Disease Registry states there are substantial data on chromosome damage in humans exposed to vinyl chloride. These studies are supported by both animal studies and in vitro studies that show positive effects in a variety of microbial mutagenicity systems, in cultured mammalian cells, and other tests for DNA damage.

Reference:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables*. EPA 540-R-93-058, U.S. Environmental Protection Agency, Washington, D.C.

XYLENES

CASRN: 1330-20-7
Synonyms: Dimethylbenzene, o-Xylene, m-Xylene, p-Xylene, Mixed xylenes

Oral Reference Dose - Chronic (RfDo):	2E+0 (mg/kg)/day
Critical Effect:	Hyperactivity, decreased body weight and increased mortality in male rats
Safety Factor (SF):	100
Confidence:	Medium
Inhalation Reference Dose (RfDi):	Not available
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

Rats and mice were given xylenes orally for 2 years during a cancer bioassay and were observed for clinical signs of toxicity and mortality. Comprehensive histologic examinations were made at the end of the study. There was a dose-related increased mortality in male rats that was significant at the high-dose group but was not significant in the low-dose group. Mice given the high dose exhibited hyperactivity, a central nervous system effect. There was no evidence of histopathologic effect in any of the treated rats or mice. The low dose was, therefore, chosen as the NOAEL. A safety factor of 100 was used to account for inter- and intraspecies variability.

A RfD was previously derived from a 6-month dietary study in rats with many experimental limitations. An inhalation study in guinea pigs, rats, dogs, and monkeys observed indications of toxicity but was insufficient for estimating an inhalation RfD. Xylene is fetotoxic and teratogenic in mice at high oral doses, but the EPA considers the RfD, as calculated, to be protective of these effects.

Confidence in the critical study is medium; it was well-designed and exposed two species for their lifetimes. It also included extensive histological examinations, but did not include clinical chemistry, blood enzymes, or urinalysis. Confidence in the database is medium because there are supporting studies in other species, and a study of teratogenicity and fetotoxicity, but a LOAEL was not defined. Overall confidence in the RfD is, therefore, medium.

Supporting Studies for the EPA Cancer Classification:

There are no data by which to evaluate whether xylene is carcinogenic in humans.

Animal carcinogenicity data are inadequate. In a 2-year cancer bioassay, rats and mice were treated by gavage with a mixture of xylenes and ethylbenzene in a National Toxicology Program study. No significant changes in the incidence of neoplasia or nonneoplastic lesions occurred that could be considered related to the xylene treatment. One other study reported an increased incidence of malignant tumors in rats treated by gavage with xylene for 2 years but did not report specific tumor types or survival rates.

In a study of chromosomal effects in workers occupationally exposed to xylene, no significant effects were noted. Xylene does not cause chromosome effects in cultured cells, does not cause

mutations in bacterial test systems, and does not cause chromosome aberrations in bone marrow cells of rats exposed by inhalation. There is one report of weak mutagenic activity in a fruit fly mutation assay.

Reference:

U.S. Environmental Protection Agency (EPA). 1994 (January 1). *IRIS: Integrated Risk Information System* (Volume 21), [CD-ROM], expires July 31, 1994. Available from Micromedex, Inc., Denver, Colorado.

ZINC AND COMPOUNDS

CASRN: 7440-66-6
Synonyms: None

Oral Reference Dose - Chronic (RfDo):	3E-1 (mg/kg)/day
Critical Effect:	Decrease in erythrocyte superoxide dismutase concentration in humans
Safety Factor (SF):	3
Confidence:	Medium
Inhalation Reference Dose (RfDi):	No data
Oral Cancer Slope Factor:	Not applicable
Inhalation Cancer Slope Factor:	Not applicable
Inhalation Unit Cancer Risk:	Not applicable
EPA Cancer Classification:	D; not classifiable as to human carcinogenicity

Supporting Studies for the Chronic Oral Reference Dose (RfDo):

Zinc is an essential nutrient with Recommended Daily Allowance values ranging from 5 to 15 mg/day for different age and sex categories. The RfDo is based on a clinical study which investigated the effects of excess oral zinc supplements on copper and iron balance. In a 10-week study, healthy women given 50 mg zinc/day showed a statistically significant decrease in erythrocyte superoxide dismutase activity. This change in enzyme activity is considered a better indicator of altered copper status than a measure of metal concentration in tissue or plasma. This finding has also been documented by studies in rats fed copper-deficient or high-zinc diets. There was also a significant decline in serum ferritin and hematocrit values at 10 weeks. Such a decrease could pose a significant risk to the iron status of women. A LOAEL of 1.0 (mg/kg)/day was calculated from the sum of the baseline dietary estimate for zinc plus the supplemental zinc dose.

The principal study is supported by several other studies which indicate that zinc supplementation can alter copper balance. The effects on copper and iron biochemistry are considered of concern because long-term iron or copper deficiency could result in significant adverse effects, such as copper deficiency anemia. Excess levels of zinc have also been reported to cause decreases in high-density lipoprotein (HDL) levels, which may be significant because a sustained decrease in HDL concentrations may be associated with increased risk of coronary artery disease.

A safety factor of 3 was used, based on a minimal LOAEL from a moderate-duration study of the most sensitive humans and the consideration that zinc is an essential dietary nutrient. The level of confidence in the studies is medium because they are well-conducted clinical studies with many biochemical parameters investigated but only few numbers of humans were tested. The confidence in the overall database is medium because these studies are all of short duration.

Supporting Studies for the EPA Cancer Classification:

There are no reports on the possible carcinogenicity of zinc and compounds per se in humans. Case studies have been used to evaluate the effects of zinc administered for therapeutic reasons. There are reports which compare zinc levels in normal and cancerous tissue. Studies of occupational exposure to zinc compounds have also been conducted, and no evidence of cancer has been noted.

However, these studies have limited value because they do not correlate exposure with cancer risk and were designed to evaluate other endpoints. Numerous animal studies to ascertain carcinogenicity have been performed and are similarly inconclusive.

References:

U.S. Environmental Protection Agency (EPA). 1993. *Health Effects Assessment Summary Tables*. EPA 540-R-93-058, U.S. Environmental Protection Agency, Washington, D.C.

U.S. Environmental Protection Agency (EPA). 1993 (October 1). *IRIS: Integrated Risk Information System* (Volume 20), [CD-ROM], expires April 30, 1994. Available from Micromedex, Inc., Denver, Colorado.

3.0 General Discussion of Radionuclide Slope Factors

This section presents information on radionuclides and the radionuclide slope factors that are common to all radionuclides (Table 3.1). A summary of radionuclide slope factors is given in Table 3.1.

3.1 Weight of Evidence Classification

The U.S. Environmental Protection Agency (EPA) considers all radionuclides to be Group A (known human) carcinogens because all radionuclides emit ionizing radiation known to cause cancer in humans based on evidence at high dose levels (i.e., above 10 rads) (ICRP 1991).

Table 3.1 indicates the known types of cancer related to intakes of radionuclides by humans and indicates the organ that represents the highest risk of developing cancer. Few radionuclides have positive evidence relating exposure to cancer incidence in particular organs. In the Type of Cancer column in Table 3.1, the entries without parentheses indicate that radionuclide studies exist to support occurrence of cancer in humans in the organ listed. When such evidence is not available, the organs having the highest risk of cancer based solely on calculations of committed effective dose equivalent in each organ are listed in parentheses. The organ listed in parentheses is the organ for which the committed dose equivalent multiplied by the organ weighting factor (ICRP 1979) is the highest. The first organ listed is for the inhalation route and the second is for the ingestion route.

The organ dose values are based on those given in Federal Guidance Report No. 11 (Eckerman et al. 1988). Special calculations were performed for several radionuclides when data in Federal Guidance Report No. 11 indicated that the highest risk organ was "Remainder." For these radionuclides, the committed effective dose equivalents were calculated using the CINDY software program (Strenge et al. 1992), which uses the same models and data as the Federal Guidance Report No. 11. Special calculations were necessary for the ingestion intake route for radionuclides with listed organs of lower large intestine and stomach. Radionuclides that are fairly uniformly distributed throughout all organs of the body will have gonads listed as the organ having the most risk (e.g., cesium-137). This is because all organs will have approximately the same dose and the gonad risk factor is highest. Note, however, the gonad risk is related more to incidence of serious genetic effects than to cancer.

3.2 Slope Factor Evaluation

The slope factors are the risk per unit intake or exposure for an individual in a stationary population with an expected lifetime of about 70 years (U.S. average in 1970). The risk estimates are based on age- and organ-specific cancer incidence risk coefficients (NAS 1990), combined with the dose received in corresponding age intervals. The risk is characterized as the best estimate (median) of the age-averaged lifetime total excess cancer-incidence risk per unit intake or exposure. The internal dosimetry is based on models and data presented by the International Commission on Radiological Protection (ICRP) (1979-1988). All dose estimates are for the 70-kg Reference Man (ICRP 1973). Age-specific dosimetry considerations were not used in the dosimetry analyses because of uncertainty in definition of age-dependent parameters.

Table 3.1. Summary of Radionuclide Parameters

Contaminant	Weight of Evidence Classification	Type of Cancer (highest risk organ inhalation/ingestion)	Oral Slope Factor $(pCi)^{-1}$	Inhalation Slope Factor $(pCi)^{-1}$	External Slope Factor $(pCi\text{-}yr/g)^{-1}$	Half-life
Americium-241	A	(bone surface/bone surface)	3.28E-10	3.85E-08	4.59E-09	4.32E+02 yr
Antimony-125	A	(lung/gonad)	2.97E-12	5.20E-12	1.34E-06	2.77E+00 yr
Barium-140	A	(lung/lower large intestine)	1.18E-11	3.17E-12	6.00E-07	1.28E+01 d
Beryllium-7	A	(lung/gonad)	8.64E-14	1.78E-13	1.73E-07	5.33E+01 d
Carbon-14	A	(gonad/gonad)	1.03E-12	6.99E-15	0.0E+00	5.73E+03 yr
Cerium-141	A	(lung/lower large intestine)	3.91E-12	4.32E-12	1.41E-07	3.25E+01 d
Cerium-144	A	(lung/lower large intestine)	2.96E-11	1.08E-10	2.58E-08	2.84E+02 d
Cesium-134	A	(gonad/gonad)	4.73E-11	2.89E-11	5.88E-6	2.06E+00 yr
Cesium-137+D	A	(gonad/gonad)	3.16E-11	1.91E-11	2.09E-06	3.00E+01 yr
Chromium-51	A	(lung/gonad)	1.38E-13	1.74E-13	1.02E-07	2.77E+01 d
Cobalt-57	A	(lung/gonad)	9.71E-13	2.88E-12	2.07E-07	2.71E+02 d
Cobalt-58	A	(lung/gonad)	2.82E-12	5.17E-12	3.73E-06	7.08E+01 d
Cobalt-60	A	(lung/gonad)	1.89E-11	6.88E-11	9.76E-06	5.27E+00 yr
Europium-152	A	(red marrow/gonad)	5.73E-12	7.91E-11	4.08E-06	1.33E+01 yr
Europium-154	A	(bone surface/lower large intestine)	9.37E-12	9.15E-11	4.65E-06	8.80E+00 yr
Europium-155	A	(bone surface/lower large intestine)	1.65E-12	9.60E-12	6.08E-08	4.96E+00 yr
Hydrogen-3	A	(gonad/gonad)	7.15E-14	9.59E-14	0.0E+00	1.24E+01 yr
Iodine-129	A	(thyroid/thyroid)	1.84E-10	1.22E-10	2.69E-09	1.57E+07 yr
Iron-59	A	(lung/gonad)	5.87E-12	7.08E-12	4.63E-06	4.45E+01 d
Lead-210+D	A	(bone surface)	1.01E-9	3.86E-09	1.45E-10	2.23E+01 yr
Manganese-54	A	(lung/gonad)	1.96E-12	3.69E-12	3.26E-06	3.13E+02 d

Table 3.1. (contd)

Contaminant	Weight of Evidence Classification	Type of Cancer (highest risk organ inhalation/ingestion)	Oral Slope Factor $(pCi)^{-1}$	Inhalation Slope Factor $(pCi)^{-1}$	External Slope Factor $(pCi\text{-}yr/g)^{-1}$	Half-life
Nickel-63	A	(lung/gonad)	5.50E-13	1.01E-12	0.0E+00	9.60E+01 yr
Plutonium-238	A	(lung/bone surface)	2.95E-10	2.74E-08	1.94E-11	8.77E+01 yr
Plutonium-239	A	(lung/bone surface)	3.16E-10	2.78E-08	1.26E-11	2.41E+04 yr
Plutonium-240	A	(lung/bone surface)	3.15E-10	2.78E-08	1.87E-11	6.54E+03 yr
Plutonium-241	A	(bone surface/bone surface)	5.20E-12	2.81E-10	0.0E+00	1.44E+01 yr
Potassium-40	A	(gonad/gonad)	1.25E-11	7.46E-12	6.11E-07	1.28E+09 yr
Promethium-147	A	(lung/lower large intestine)	1.41E-12	7.49E-12	6.35E-12	2.62E+00 yr
Radium-226+D	A	bone (lung/bone surface)	2.96E-10	2.75E-09	6.74E-06	1.60E+03 yr
Radium-228+D	A	bone (lung/bone surface)	2.48E-10	9.94E-10	3.28E-06	5.75E+00 yr
Ruthenium-103	A	(lung/gonad)	3.32E-12	4.59E-12	1.70E-06	3.93E+01 d
Ruthenium-106+D	A	(lung/lower large intestine)	3.45E-11	1.15E-10	7.57E-07	3.68E+02 d
Sodium-22	A	(gonad/gonad)	8.02E-12	4.88E-12	8.18E-06	2.60E+00 yr
Strontium-90+D	A	(red marrow//red marrow)	5.59E-11	6.93E-11	0.0E+00	2.91E+01 yr
Technetium-99	A	(lung/stomach)	1.40E-12	2.89E-12	6.19E-13	2.13E+05 yr
Thorium-228+D	A	liver, lung, blood (lung/bone surface)	2.31E-10	9.68E-08	6.24E-06	1.91E+00 yr
Thorium-232	A	liver, lung, blood (bone surface/bone surface)	3.28E-11	1.93E-08	1.97E-11	1.41E+10 yr
Uranium-234	A	(lung/bone surface)	4.44E-11	1.40E-08	2.14E-11	2.44E+05 yr
Uranium-235+D	A	(lung/bone surface)	4.70E-11	1.30E-08	2.65E-07	7.04E+08 yr
Uranium-238+D	A	(lung/bone surface)	6.20E-11	1.24E-08	5.46E-08	4.47E+09 yr
Zinc-65	A	(lung/gonad)	9.93E-12	9.98E-12	2.27E-06	2.44E+02 d
Zirconium-95	A	(lung/gonad)	3.92E-12	6.48E-12	2.81E-06	6.40E+01 d

Source of slope factors information:

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2.* EPA 540-R-94-114. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

Source of half-life values:

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

The inhalation and ingestion slope factors represent best estimates of the age-averaged, lifetime excess cancer incidence (fatal and nonfatal cancer) risk per unit intake of activity. These slope factors are expressed as risk per picocurie (pCi) intake.

The slope factors for external exposure are best estimates of the lifetime excess cancer incidence risk for each year of exposure to external radiation from photon-emitting radionuclides distributed uniformly in a thick layer of soil. Radionuclides with no gamma or X-ray emissions will not have significant external-exposure slope factors. The dose received by organs of the body is nearly uniform for higher energy photons. For low-energy photons, significantly lower dose rates may exist for organs and tissues deeper inside the body, being shielded by outer organs and tissues.

The exposure point for the external-exposure slope factors is taken to be 1 m above ground level. These slope factors are expressed as risk/year of exposure per pCi/g of soil for contamination covering an infinite area in a thick layer. The "thick layer of soil" represents a thickness such that additional depth would not increase the risk factor (because of shielding by the soil). Federal Guidance Report No. 12 (Eckerman and Ryman 1993) presents dose-rate factors for exposure to monoenergetic photons as a function of depth of contamination in soil. Results were presented for depths of 1 cm, 5 cm, 15 cm, and "infinite" (represented by a depth 4 mean free path lengths for the particular photon energy). The results indicate that a 1-cm depth is equivalent to an infinite soil depth for photons of energy 0.02 MeV and less, 5 cm is equivalent for photons of 0.05 MeV and less, and 15 cm is equivalent for photons of 0.2 MeV and less. For photons of energy 5 MeV, the 15-cm dose rate value is 70% of the infinite value, indicating that even for high-energy photons the effective infinite thickness is probably within 1 m.

The external-exposure slope factors are applicable to areas that are less than infinite in extent. The approximation of infinite area depends on the radiations emitted by the particular radionuclide. For radionuclides that emit relatively high-energy photons (gamma energies greater than about 0.1 MeV), the area approximating an infinite source is much larger than for radionuclides that emit only low-energy radiations. Napier et al. (1984) performed a sensitivity study on the area required to represent an "infinite" source for external exposure to a plane source. Their results indicate that external dose-rate factors for high-energy gamma emitters are not increased once the radius of contamination has reached about 20 m. Also, 50% of the dose is received within a source radius of about 6 m. These conclusions are applicable to cobalt-58, cobalt-60, cerium-141, cerium-144, cesium-137, ruthenium-103, zinc-65, and other high-energy photon emitters, as discussed in the specific radionuclide profiles.

The EPA's *Health Effects Assessment Summary Tables* (HEAST) external slope factors include contributions from penetrating radiation emitted by the radionuclide. The contribution from bremsstrahlung radiation generated by beta particles and electrons emitted from radionuclides is not included in the slope factor calculation. This contribution is generally small compared to the penetrating radiation contributions. However, for a few radionuclides (those emitting no penetrating radiations), the bremsstrahlung dose represents the only source of external radiation. External dose rate factors presented in Federal Guidance Report Number 12 (Eckerman and Ryman 1993) allow approximation of slope factors that include bremsstrahlung contributions. These estimated slope factors are discussed in the specific radionuclide sections for carbon-14, plutonium-241, strontium-90, and ruthenium-106.

3.3 Uptake, Distribution, and Retention

The internal dosimetry for inhalation and ingestion slope factors is based primarily on recommendations of the ICRP (1979-1988). Details of uptake, distribution, and retention are provided in the specific radionuclide profiles. The parameters describing the metabolic models for the various radionuclides are based on animal and human data. Most of the parameter values recommended by the ICRP have a significant level of uncertainty. While the profiles present the point values recommended by the ICRP, the reader is cautioned that radiation doses calculated from these models also include a significant level of uncertainty. The ICRP models are defined to represent a 70-kg Reference Man and do not consider differences for younger age groups. Some differences for women are included in application of the models. As stated previously, the generation of slope factors for inhalation and ingestion also do not include dosimetric differences as a function of age.

3.4 Occurrence of Radionuclides

When the information in this report is used to perform risk analyses, the analyst must carefully review the radionuclides stated to be present in the inventory. Types of radionuclides likely to be present include those related to the initial fuel (uranium), radionuclides produced by neutron absorption reactions within the reactor, fission products, and activation products (radionuclides produced by activation of structural material). Radionuclides with half lives of less than approximately 6 months are not likely to be present (i.e., be major contributors to risk) in Hanford wastes, unless they are decay products of a longer-lived parent radionclide. A review of the list of radionuclides for which toxicity profiles are provided indicates that the following radionuclides are not likely to be present in Hanford wastes: antimony-125 (2.77 year half-life), barium-140 (12.7 day half-life), beryllium-7 (53.3 day half-life), cerium-141 (32.5 day half-life), chromium-51 (27.7 day half-life), cobalt-58 (70.8 day half-life), iron-59 (44.5 day half-life), ruthenium-103 (39.3 day half-life), and zirconium-95 (64.0 day half-life). Should these radionuclides be listed as present, the analyst should review the age of the material and possibly question the information source.

3.5 Evidence of Cancer for Specific Radionuclides and Elements

The limited experimental evidence available on cancer types in humans is summarized for specific elements and radionuclides.

Americium

Animal studies indicate that the carcinogenicity of americium-241 in bone is similar to that of plutonium (Sanders and Kathren 1983).

Cesium

Beagle dog studies involving single intravenous injections of cesium-137 were reviewed by the National Council on Radiation Protection and Measurements (NCRP) (1977). A variety of malignant tumors were observed. It was concluded that for the relatively high doses received by the animals in

the studies, "life shortening and an increased incidence of malignant tumors may be anticipated." Because cesium behaves similarly to potassium with distribution throughout the soft tissues of the body, the observation of a variety of malignant tumors is not surprising.

Curium

Animal studies indicate that the carcinogenicity of curium-244 in bone and lungs is similar to that of plutonium (Sanders and Kathren 1983).

Iodine

Iodine is transferred primarily to the thyroid gland after intake (ICRP 1979). Data on thyroid exposure of humans to iodine-131 have been summarized by the NCRP (1985). The conclusion is that "iodine-131 has not been shown to be carcinogenic in people," and that "iodine-131 appears less carcinogenic in people on a rad-for-rad basis than external radiation." In a brief discussion of iodine-129, the conclusion that "iodine-129 does not pose a meaningful threat of thyroid carcinogenesis in people" was also drawn. Although a lack of experimental evidence exists for induction of thyroid cancer in humans, the metabolism and dosimetry used for iodine predict that the organ having the highest risk of cancer incidence is the thyroid, as indicated in Table 3.1.

Neptunium

In a review of the aspects of neptunium relevant to radiation protection guidelines, the NCRP (1988) cites Soviet literature involving experiments with rats which indicate that bone cancer is the predominant long-term effect of low-level injections of neptunium-237, and both lung and bone cancer incidences are elevated following inhalation exposure.

Plutonium

Animal experiments involving plutonium have resulted in increased incidence of lung cancer from inhalation and bone cancer following ingestion (Sanders and Kathren 1983). A study of workers exposed to plutonium via inhalation has not shown a statistically significant occurrence of lung cancer (Tietjen 1987).

Radium

Significant human exposures to radium have occurred (e.g., ingestion of radium by dial painters), and studies of these exposures form the basis for estimates of risk from internal deposition of radium isotopes (NCRP 1991). Observed skeletal cancers in humans from radium include bone sarcomas and head sinus carcinomas (Mays et al. 1985). The primary radioisotope involved in radium doses has been radium-226 with a smaller contribution from radium-228. In Germany, between 1944 and 1951, patients treated with injections of radium-224 for tuberculosis and ankylosing spondylitis were observed to develop bone tumors and leukemia (Sanders and Kathren 1983).

Strontium

The NCRP report on strontium radiobiology (NCRP 1991) states that "there have been no cases of human exposure to strontium-90 on record which would provide direct guidance concerning the kinds of effects to be expected or their frequency." They also state "the observations that bone sarcomas

have been produced by skeletally-deposited radium...and that leukemias have been produced by exposure to x-rays...and atom-bomb radiation...suggests that significant skeletal doses from strontium-90 could also produce bone sarcomas and leukemias in people." The risk of cancer (as presented by the NCRP) is based on a comparison of observed effects in humans from exposure to radium and effects in animals for strontium-90 relative to radium. Animal experiments have shown an increased incidence of bone tumor and leukemias from strontium-90 (Sanders and Kathren 1983).

Thorium

Olsen et al. (1990) recently reported results of a study on patients who received radioactive Thorotrast (thorium dioxide) during cerebral angiography and other procedures in the 1930s and 1940s. They found that Thorotrast patients were at a high risk of developing cancer of the liver, lung, and blood (leukemia).

Uranium

No direct information exists on cancer induction by uranium in people (Mays et al. 1985).

3.6 Radionuclides Included in This Document

The following radionuclides are discussed:

Americium-241
Antimony-125
Barium-140
Beryllium-7
Carbon-14
Cerium-141
Cerium-144
Cesium-134
Cesium-137+D
Chromium-51
Cobalt-57
Cobalt-58
Cobalt-60
Europium-152
Europium-154
Europium-155
Hydrogen-3
Iodine-129
Iron-59
Lead-210(+D)
Manganese-54
Nickel-63
Plutonium-238
Plutonium-239
Plutonium-240
Plutonium-241
Potassium-40
Promethium-147
Radium-226(+D)
Radium-228(+D)
Ruthenium-103
Ruthenium-106(+D)
Sodium-22
Strontium-90(+D)
Technetium-99
Thorium-228(+D)
Thorium-232
Uranium-234
Uranium-235(+D)
Uranium-238(+D)
Zinc-65
Zirconium-95

3.7 References

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AMERICIUM-241

CASRN: 14596-10-2
Synonyms: None

Oral Slope Factor:	3.28E-10 risk/pCi ingested
Inhalation Slope Factor:	3.85E-8 risk/pCi inhaled
External Slope Factor:	4.59E-9 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Americium-241 undergoes alpha decay (432.2 year half-life) with emission of gamma rays, X-rays, and electrons. The gamma radiations are all under 0.1 MeV but are significant enough to potentially produce external exposure. The primary radiation causing internal dose is the alpha radiation. Americium-241 decays to neptunium-237 (2.14E+6 year half-life) which in turn undergoes alpha decay to protactinium-233 (27 day half-life). The neptunium decay product of americium-241 is generally not included in risk analyses because of the much longer half-life (and, therefore, less relative dose contribution).

Uptake, Distribution, and Retention in the Body (ICRP 1979, 1986):

Americium is not taken up readily in the gastrointestinal tract, and the International Commission on Radiological Protection (ICRP) recommends an absorption fraction of 0.001. The ICRP also recommends that all compounds of americium be assigned to lung inhalation class W. The HEAST (1994) slope factors are based on inhalation class W and an absorption fraction of 0.001. The absorbed activity is assumed to be distributed to the skeletal bone (45%), liver (45%), and gonads (0.035% for testes and 0.011% for ovaries). Material not transferred to organs is assumed to be excreted. Retention in skeleton is described by a 50 year biological half-life and retention in liver by a 20 year biological half-life. Material in the gonads is assumed to be retained indefinitely. All isotopes of americium are considered to be uniformly distributed over bone surfaces at all times following their deposition in the skeleton.

Significant Exposure Routes:

Both inhalation and ingestion of americium-241 may result in a significant exposure. The low-energy gamma and X-ray radiations result in a moderate external-exposure slope factor. The external pathway is likely to cause less risk than internal exposures (depending, of course, on the exposure scenario).

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

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ANTIMONY-125

CASRN: 14234-35-6
Synonyms: None

Oral Slope Factor:	2.97E-12 risk/pCi ingested
Inhalation Slope Factor:	5.20E-12 risk/pCi inhaled
External Slope Factor:	1.34E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Antimony-125 undergoes beta decay (2.77 year half-life) to radioactive tellurium-125m (yield 22.8%, 58 day half-life) and to stable tellurium-125 (yield 77.2%). Gamma rays and X-rays are emitted of energy between 0.0036 and 0.67 MeV, with the most significant radiations at 0.60, 0.61, and 0.64 MeV. The beta particle emissions range from 0.025 to 0.22 MeV (average energy). The HEAST (1994) slope factors do not include the radiations from tellurium-125m. Including these radiations would increase the ingestion slope factor to 3.54E-12 (about 19%) and the inhalation slope factor to 5.86E-12 (about 13%), with an insignificant increase in the other external slope factor.

Uptake, Distribution, and Retention in the Body (ICRP 1981):

The gastrointestinal uptake fraction for antimony is set to 0.1 for ingestion of tartar emetic and to 0.01 for other compounds of antimony. The inhalation class for antimony oxides, hydroxides, halides, sulfides, sulfates, and nitrates is set to class W, and to class D for all other compounds of antimony. The HEAST (1994) slope factors are based on inhalation class W and an uptake fraction of 0.1. Antimony leaving the blood is assumed to be translocated to excreta (0.2%), to liver (0.1%), to mineral bone (0.2%), and uniformly throughout all other organs and tissues (0.5%). Antimony retention is described for all tissues and organs by a two-compartment model. A fraction of 0.95 is retained with a biological half-life of 5 days, and the remainder (0.05) is retained with a biological half-life of 100 days.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides, and the inhalation and ingestion slope factors are moderate. External exposures are likely to be significant, while ingestion and inhalation risks are likely to be less important, depending on the media concentrations and the exposure scenarios.

References:

International Commission on Radiological Protection (ICRP). 1981. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 3). *Annals of the ICRP*, Vol. 6, No. 2/3, Pergamon Press, New York, New York.

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BARIUM-140

CASRN: 14798-08-4
Synonyms: None

Oral Slope Factor:	1.18E-11 risk/pCi ingested
Inhalation Slope Factor:	3.17E-12 risk/pCi inhaled
External Slope Factor:	6.00E-7 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Barium-140 undergoes beta decay (12.74 day half-life) with emission of significant beta particles, gamma rays, and X-rays. The primary gamma rays contributing to dose are between 0.16 and 0.54 MeV. The beta particle average energies are between 0.14 and 0.36 MeV. The decay product lanthanum-140 is radioactive (40.27 hour half-life) and decays to cerium-140 which is stable. Lanthanum-140 also has significant beta and gamma emissions. Barium-140 has a relatively short half-life and would not be expected to be present in reactor materials that have been out of a reactor for greater than 1 year. See comments in the general section on "Occurrence of Radionuclides" regarding review of radionuclide inventory information containing short-lived radionuclides.

Uptake, Distribution, and Retention in the Body (ICRP 1972, 1980):

The fractional absorption of barium in the gastrointestinal tract is assumed to be 0.1. Based on experiments on dogs with $BaSO_4$ and $BaCl_2$, barium is assigned inhalation class D (clearance from the lungs on the order of days). The HEAST (EPA 1994) slope factors are based on inhalation class D and an absorption fraction of 0.1. The distribution and retention of barium radionuclides is described by the model developed by the Task Group on Alkaline Earth Metabolism in Adult Man (ICRP 1972). This model used various time-dependent functions to describe the distribution and retention of alkaline earth elements in blood, bone surface, compact bone (old and new), cancellous bone (old and new), bone volume, and soft tissue compartments. Parameter values are defined for these functions for each alkaline earth element (calcium, strontium, barium, and radium). For purposes of bone dosimetry, barium-140 is assumed to be distributed uniformly over bone surfaces (ICRP 1980).

Significant Exposure Routes:

The slope factors are moderate compared to other radionuclides and may result in a significant risk. Although not addressed in the HEAST (1994) slope factors, ingrowth of the decay product lanthanum-140 should be included in exposure assessments. This should be done because internal slope factors for lanthanum-140 are similar to those for barium-140 and the external-exposure slope factor for lanthanum-140 is about 15 times higher than the external-exposure slope factor for barium-140. This will result in doubling the internal dose and increasing the external dose rate by about 15 after just a few days.

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BERYLLIUM-7

CASRN: 13966-2-4
Synonyms: None

Oral Slope Factor:	8.64E-14 risk/pCi ingested
Inhalation Slope Factor:	1.78E-13 risk/pCi inhaled
External Slope Factor:	1.73E-7 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Beryllium-7 decays by electron capture (53.3 day half-life) to the stable isotope lithium-7. The primary emissions are gamma rays of energy 0.478 MeV.

Uptake, Distribution, and Retention in the Body (ICRP 1981):

The absorption of beryllium in the gastrointestinal track is set to 0.005 based on experiments in several mammalian species. An inhalation class of Y is assigned to oxides, halides, and nitrates of beryllium; all other compounds are assigned to inhalation class W. The HEAST (1994) slope factors are based on an inhalation class of Y. The material entering the blood is assumed to translocate to mineral bone (0.4), other organs and tissues (0.2), and directly to excretion (0.4). The biological retention half-life for mineral bone and all organs is set to 1,500 days. A two-compartment model is used to describe retention in other tissues and organs, with a fraction of 0.8 retained with a biological half-life of 15 days and a fraction of 0.2 retained with a biological half-life of 1,500 days. Beryllium-7 is assumed to be uniformly distributed throughout bone volume following transfer to the bone.

Significant Exposure Routes:

The external-exposure slope factor is moderate relative to many other radionuclide indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides (partly because of the lack of beta or alpha radiations), indicating these pathways may not be a significant source of exposure, depending on the exposure scenario considered.

References:

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CASRN: 14762-75-5
Synonyms: None

Oral Slope Factor:	1.03E-12 risk/pCi ingested
Inhalation Slope Factor:	6.99E-15 risk/pCi inhaled
External Slope Factor:	0.0 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Carbon-14 has a radiological half-life of 5,730 years. Carbon-14 undergoes beta decay to the stable isotope nitrogen-14 (0.0495 MeV average energy). No penetrating radiations are emitted by carbon-14; however, bremsstrahlung radiation generated by beta particles cause a low level of extreme exposure equivalent to a slope factor of approximately 1E-11.

Uptake, Distribution, and Retention in the Body (ICRP 1981):

The dosimetry presented for ingestion of carbon-14 is based on ingestion of labelled organic compounds, which are assumed to be completely absorbed into the blood from the gastrointestinal tract. Inhalation of carbon-14 in the form of carbon monoxide gas, carbon dioxide gas, and organic labelled compounds is considered. For carbon monoxide, 0.4 of the inhaled carbon-14 becomes instantaneously bound to hemoglobin and 0.6 is exhaled. The bound activity is assumed to be uniformly distributed throughout all organs and tissues and is retained with a biological half-life of 200 minutes. All carbon dioxide inhaled is assumed to be absorbed and transferred to blood. The retention of carbon dioxide activity is assumed to be described by a three-compartment model with 1% retained with a half-life of 60,000 minutes, 81% with a half-life of 60 minutes, and 18% with a half-life of 5 minutes. Carbon-14 in the form of labelled organic compounds is uniformly distributed (for inhalation and ingestion intake) and is assumed to be retained with a biological half-life of 40 days. The HEAST (EPA 1994) slope factors are based on inhalation of carbon-14 as carbon dioxide and on ingestion of carbon-14 as organic compounds.

Significant Exposure Routes:

The inhalation and ingestion slope factors for carbon-14 are small compared to many other radionuclides and may not result in a significant exposure, depending on the activity involved. There is no threat from external radiation exposure to carbon-14. The slope factor for ingestion can be used to estimate the dermal exposure risk when the form of the contaminant is labelled organic compounds. This is true because of the complete absorption and uniform distribution within the body for carbon-14.

References:

International Commission on Radiological Protection (ICRP). 1981. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 3). *Annals of the ICRP*, Vol. 6, No. 2/3, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

CERIUM-141

CASRN: 13967-74-3
Synonyms: None

Oral Slope Factor:	3.91E-12 risk/pCi ingested
Inhalation Slope Factor:	4.32E-12 risk/pCi inhaled
External Slope Factor:	1.41E-7 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Cerium-141 has a radiological half-life of 32.50 days and undergoes beta decay to the stable isotope praseodymium-141. There are several gamma ray emissions between 0.10 and 0.15 MeV, plus two beta-particle emissions of 0.13 and 0.18 MeV (average energy).

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The absorption of cerium in the gastrointestinal track is believed to be very small and is represented by an absorption fraction of 3.0E-4. An inhalation class of Y is assigned to oxides, hydroxides, and fluorides of cerium; all other compounds are assigned to inhalation class W. The HEAST (1994) slope factors are based on an inhalation class of Y and an absorption fraction of 3.0E-4. The material entering the blood is assumed to translocate to liver (0.6), to spleen (0.05), and to bone (0.2). The remainder is assumed to be deposited in all other organs (0.15). The biological retention half-life is set to 3,500 days for all organs. All isotopes of cerium are assumed to be uniformly distributed over bone surfaces following transfer to the bone.

Significant Exposure Routes:

The external-exposure slope factor is moderate relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides (partly because of the relatively short half-life of cerium-141), but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2.* EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

CERIUM-144

CASRN: 14762-78-8
Synonyms: None

Oral Slope Factor:	2.96E-11 risk/pCi ingested
Inhalation Slope Factor:	1.08E-10 risk/pCi inhaled
External Slope Factor:	2.58E-8 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Cerium-144 has a radiological half-life of 284.3 days and undergoes beta decay to two isotopes. Praseodymium-144m (7.2 minute half-life) is produced with a yield of 1.78%, and praseodymium-144 (17.28 minute half-life) is produced with a yield of 98.22%. Praseodymium-144m decays by internal transition to praseodymium-144 (99.9%) and by beta decay to the stable isotope neodymium-144 (0.1%). Praseodymium-144 also undergoes beta decay to the stable isotope neodymium-144. There are several gamma ray emissions between 0.01 and 0.13 MeV, with the primary emission at 0.13. The two primary beta-particle emissions are at 0.049 and 0.090 MeV (average energy). The HEAST (1994) slope factors for cerium-144 do not include contributions from equilibrium amounts of the praseodymium isotopes. If included, the oral and inhalation slope factors would be unchanged, but the external exposure slope factor (for cerium-144+D) would increase to 1.59E-7.

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The metabolic models for cerium-144 are the same as described for cerium-141.

Significant Exposure Routes:

The external-exposure slope factor is low relative to many other radionuclides indicating external exposure is not likely to represent a significant exposure pathway. However, if praseodymium-144 is allowed to be in equilibrium with the cerium-144 parent, the slope factor is higher and the estimated risk would be higher. The internal slope factors are not as high as many other radionuclides, but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

CESIUM-134

CASRN: 13967-70-9
Synonyms: None

Oral Slope Factor:	4.73E-11 risk/pCi ingested
Inhalation Slope Factor:	2.89E-11 risk/pCi inhaled
External Slope Factor:	5.88E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

The primary decay mode for cesium-134 is beta particle emission (2.062 year half-life) to stable barium-134. Several gamma rays are emitted of energy between 0.48 and 1.37 MeV. The primary beta particle emission is at an average energy of 0.21 MeV.

Uptake, Distribution, and Retention in the Body (ICRP 1979):

Based on evidence for cesium chloride and other commonly occurring compounds of cesium, the International Commission on Radiological Protection (ICRP) considers radionuclides of cesium to be rapidly and completely absorbed from the gastrointestinal tract to the blood (uptake fraction, $f_1 = 1.0$). Cesium is also considered to be absorbed rapidly in the lung. All cesium radionuclides are assigned inhalation class D (clearance times from the lung on the order of days). Material in the blood is transferred uniformly throughout the body, and its retention is described by a two-compartment model. Ten percent is retained with a half-life of 2 days, and the remainder is retained with a half-life of 110 days. Because of the uniform distribution of cesium throughout the body, the radiation received by all organs is approximately equal for inhalation and ingestion. The HEAST (EPA 1994) on inhalation class D and an absorption fraction of 0.95.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides; but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPA 540-R-94-114, Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency, Washington, D.C.

CESIUM-137+D

CASRN: 10045-97-3(+D)
Synonyms: None

Oral Slope Factor:	3.16E-11 risk/pCi ingested
Inhalation Slope Factor:	1.91E-11 risk/pCi inhaled
External Slope Factor:	2.09E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Cesium-137 has a radiological half-life of 30.0 years. Cesium-137 undergoes beta decay by two modes: 5.4% to the stable isotope barium-137 (average beta particle energy of 0.17 MeV) and 94.6% to the radioactive isotope barium-137m (average beta particle energy of 0.42 MeV). Barium-137m decays (half-life 2.52 minutes) by isomeric transition to stable barium-137 with the release of a 0.66-MeV gamma ray. Contributions to risk from the cesium-137 decay product barium-137m are included in the listed slope factor values.

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The uptake, distribution, and retention of cesium-137+D in the body is as described for cesium-134.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides; but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

CHROMIUM-51

CASRN: 14392-02-0
Synonyms: None

Oral Slope Factor:	1.38E-13 risk/pCi ingested
Inhalation Slope Factor:	1.74E-13 risk/pCi inhaled
External Slope Factor:	1.02E-7 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Chromium-51 decays by electron capture (27.70 day half-life) to stable vanadium-51. The primary radiation is a 0.32-MeV gamma ray.

Uptake, Distribution, and Retention in the Body (ICRP 1980):

The absorption fraction for trivalent chromium compounds is set to 0.01 and for hexavalent compounds to 0.1. The HEAST (1994) slope factors are based on an absorption fraction of 0.1. This value is used for ingested material and for material entering the gastrointestinal tract after inhalation. Chromium oxides and hydroxides are assigned a lung class of Y, and halides and nitrates are assigned class W, and all other compounds are assigned class D. The HEAST (1994) slope factors are based on a lung class of Y. The material entering the blood is assumed to translocate (retention half-life of 0.5 days) to bone (0.05), other organs and tissues (0.65), and directly to excretion (0.3). The retention half-life for material in bone is assumed to be 1,000 days. Of the 0.65 to other organs and tissues, 0.4 is retained with a biological half-life of 6 days and the other 0.25 is retained with a biological half-life of 80 days.

Significant Exposure Routes:

The external-exposure slope factor is moderate relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are lower than for most radionuclides, but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1980. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 2). *Annals of the ICRP*, Vol. 4, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2.* EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

COBALT-57

CASRN: 13981-50-5
Synonyms: None

Oral Slope Factor:	9.71E-13 risk/pCi ingested
Inhalation Slope Factor:	2.88E-12 risk/pCi inhaled
External Slope Factor:	2.07E-7 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Cobalt-57 has a radiological half-life of 270.9 days. Cobalt-57 undergoes electron capture decay to the stable isotope iron-57 with emission of electron radiation (several emissions of 0.14 MeV and less, average energy) and one primary low-energy gamma ray (0.12 MeV).

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The absorption fraction is set at 0.3 for organically complexed cobalt compounds and all inorganic compounds (except oxides and hydroxides). For oxides and hydroxides of cobalt and all other inorganic compounds ingested in tracer quantities, the absorption fraction is set at 0.05, representing a less available form. The oral slope factor is based on the more highly absorbed form, which will result in a higher estimate of risk. Inhaled cobalt is assigned inhalation classes Y (oxides, hydroxides, halides, and nitrates) and W (other compounds). Also, material translocated from the lungs to the gastrointestinal tract is poorly absorbed in the gastrointestinal tract, and an absorption fraction of 0.05 is used. The inhalation slope factor is based on the higher retention inhalation class Y, resulting in a higher estimate of risk. The absorbed material is assumed to be retained in the blood with a half-life of 0.5 days. Half of the absorbed material (0.5) goes directly to excretion, 0.05 goes to the liver, and the remainder (0.45) is uniformly distributed throughout the other organs and tissues of the body. Retention of cobalt in any organ (liver and other tissues) is described by a three-compartment model with deposition fractions of 0.6, 0.2, and 0.2, and half-lives of 6, 60, and 800 days, respectively.

Significant Exposure Routes:

The external-exposure slope factor is moderate relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are lower than many other radionuclides and represent less potential for risk, depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

COBALT-58

CASRN: 1381-38-9
Synonyms: None

Oral Slope Factor:	2.82E-12 risk/pCi ingested
Inhalation Slope Factor:	5.17E-12 risk/pCi inhaled
External Slope Factor:	3.73E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Cobalt-58 has a radiological half-life of 70.80 days. Cobalt-58 undergoes electron capture and beta-plus decay to the stable isotope iron-58 with emission of beta-plus radiation (0.20 MeV average energy) and two primary gamma rays (0.51 and 0.81 MeV).

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The metabolic models for cobalt-58 are the same as described for cobalt-57.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides (partly because of the relatively short half-life of cobalt-58), but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

COBALT-60

CASRN: 10198-40-0
Synonyms: None

Oral Slope Factor:	1.89E-11 risk/pCi ingested
Inhalation Slope Factor:	6.88E-11 risk/pCi inhaled
External Slope Factor:	9.76E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Cobalt-60 has a radiological half-life of 5.271 years. Cobalt-60 undergoes beta decay to the stable isotope nickel-60 with emission of beta radiation (0.096 MeV average energy) and two high-energy gamma rays of 1.17 and 1.33 MeV (both at 100% yield).

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The metabolic models for cobalt-60 are the same as described for cobalt-57.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

EUROPIUM-152

CASRN: 14683-23-9
Synonyms: None

Oral Slope Factor:	5.73E-12 risk/pCi ingested
Inhalation Slope Factor:	7.91E-11 risk/pCi inhaled
External Slope Factor:	4.08E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Europium-152 has a radiological half-life of 13.33 years. Europium-152 undergoes beta decay to gadolinium-152 (yield 0.2792, very long lived) and electron capture decay to the stable isotope samarium-152 (yield 0.7208). Gadolinium-152 is very long lived, and its radiations are not included in dosimetric calculations. Europium-152 radiations include gamma rays, X-rays, beta particles, and Auger electrons. The gamma radiations include a spectrum of energies with primary contributors to external dose at (in decreasing order of contribution) 1.408 MeV (21% yield), 1.112 MeV (13.6% yield), 1.09 MeV (10.2% yield), 0.96 MeV (14.5% yield), 0.78 MeV (10.1% yield), and 0.34 MeV (27% yield).

Uptake, Distribution, and Retention in the Body (ICRP 1981):

The absorption fraction from the gastrointestinal tract for all compounds of europium is set to 0.001. Inhaled compounds of europium are assigned to inhalation class W, based on data on two healthy adult males who accidentally inhaled europium oxide. The material entering the blood is deposited in the liver (0.4), the mineral bone (0.4), and the kidneys (0.06). The remainder goes directly to excretion. The biological half-lives for retention of europium are 3,500 days for liver and bone, and 10 days for kidneys. Europium deposited in mineral bone is assumed to be uniformly distributed over bone surfaces.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides, but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1981. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 3). *Annals of the ICRP*, Vol. 6, No. 2/3, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

EUROPIUM-154

CASRN: 15585-10-1
Synonyms: None

Oral Slope Factor:	9.37E-12 risk/pCi ingested
Inhalation Slope Factor:	9.15E-11 risk/pCi inhaled
External Slope Factor:	4.65E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Europium-154 has a radiological half-life of 8.8 years. Europium-154 undergoes beta decay to the stable isotope gadolinium-154 (yield 0.9998) and electron capture decay to the stable isotope samarium-154 (yield 0.0002). Europium-154 radiations include gamma rays, X-rays, beta particles, and Auger electrons. The gamma radiations include a spectrum of energies up to 1.6 MeV, with a primary gamma to 1.27 MeV (36% yield).

Uptake, Distribution, and Retention in the Body (ICRP 1981):

The metabolic models for europium-154 are the same as for europium-152.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides, but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1981. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 3). *Annals of the ICRP*, Vol. 6, No. 2/3, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

EUROPIUM-155

CASRN: 14391-16-3
Synonyms: None

Oral Slope Factor:	1.65E-12 risk/pCi ingested
Inhalation Slope Factor:	9.60E-12 risk/pCi inhaled
External Slope Factor:	6.08E-8 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Europium-155 has a radiological half-life of 4.96 years. Europium-155 undergoes beta decay to the stable isotope gadolinium-155. Europium-155 radiations include gamma rays, X-rays, beta particles, and Auger electrons. The gamma radiations include a spectrum of low energies up to 0.15 MeV, with primary radiations at 0.105 MeV (21% yield) and 0.086 MeV (31% yield). Internal exposures result primarily from beta particles and gamma radiations.

Uptake, Distribution, and Retention in the Body (ICRP 1981):

The metabolic models for europium-155 are the same as for europium-152.

Significant Exposure Routes:

The external-exposure slope factor is moderate relative to other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides, but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1981. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 3). *Annals of the ICRP*, Vol. 6, No. 2/3, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

HYDROGEN-3

CASRN: 10028-17-8
Synonyms: Tritium

Oral Slope Factor:	7.15E-14 risk/pCi ingested
Inhalation Slope Factor:	9.59E-14 risk/pCi inhaled
External Slope Factor:	0.0E-0 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Hydrogen-3 has a radiological half-life of 12.35 years. Hydrogen-3 undergoes beta decay to the stable isotope helium-3 (0.0057 MeV average energy). There are no penetrating radiation emissions from hydrogen-3.

Uptake, Distribution, and Retention in the Body (ICRP 1979):

Ingested tritiated water is assumed to be completely absorbed and rapidly mixed uniformly with the total body water. Exposure to atmospheric tritiated water vapor results in inhalation intake and absorption through the skin. The fraction absorbed is estimated as 50% of the amount inhaled. The absorbed and inhaled hydrogen-3 is assumed to be rapidly mixed uniformly with the total body water. Data on humans indicate that hydrogen-3 retention in the body is described by a single exponential with a half-life of 10 days. Because of the uniform distribution throughout the body, the radiation received by all organs is approximately equal for inhalation and ingestion.

Significant Exposure Routes:

Both inhalation and ingestion of hydrogen-3 could result in a significant exposure. No threat exists from external radiation exposure to hydrogen-3 because the weak beta-radiation emissions are not able to penetrate soil or air. Dermal contact with waterborne hydrogen-3 could also result in significant exposure, particularly if other exposure routes are excluded. The slope factor for ingestion exposure can be used to estimate the dermal exposure risk. This is true because of the complete absorption and uniform distribution within the body for hydrogen-3.

Other Information (ICRP 1979):

When organic compounds labelled with hydrogen-3 are ingested, the dosimetry may differ considerably from that for tritiated water. Of particular interest is ingestion of tritiated thymidine that may be incorporated into DNA. Even though much of the ingested tritiated thymidine will be broken down in the gastrointestinal tract (producing tritiated water), some will be incorporated into DNA, thus posing a significantly higher radiation risk than for ingestion of tritiated water. The dosimetry for exposure to atmospheric elemental hydrogen-3 is limited to consideration of dose received from hydrogen-3 contained in the lung air. Elemental hydrogen-3 is not considered to be absorbed by the lung, and the dose is estimated to be about four orders of magnitude less that for exposure to equal activity of tritiated water vapor.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

IODINE-129

CASRN: 15046-84-1
Synonyms: None

Oral Slope Factor:	1.84E-10 risk/pCi ingested
Inhalation Slope Factor:	1.22E-10 risk/pCi inhaled
External Slope Factor:	2.69E-9 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Iodine-129 undergoes beta decay (1.57E+7 year half-life) with production of stable xenon-129. The primary emissions are a beta particle of 0.049 MeV average energy, several Auger electrons (average energies less than 0.03 MeV), several gamma rays (less than 0:04 MeV), and several X-rays (less than 0.035 MeV).

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The gastrointestinal uptake of iodine is assumed to be 1.0 for all commonly occurring iodine compounds. Based on experimental data on mice, rats, dogs, and sheep, the International Commission on Radiological Protection (ICRP) recommends lung inhalation class D. The HEAST slope factors are based on an adsorption fraction of 0.95 and lung inhalation class D. Distribution and retention of iodine in the body is described by a simple three-compartment model that involves transfer of iodine initially to the thyroid, with subsequent transfer of iodine in organic form to other organs and tissues. Of the iodine reaching the blood, 70% is assumed to be excreted, and the remainder is transferred to the thyroid as inorganic iodine. The iodine in the thyroid is lost from the thyroid as organic iodine and is assumed to be uniformly distributed among all other organs (other than the thyroid). Part (10%) of the organic iodine is assumed to be excreted, and the remainder (90%) is assumed to be returned to the blood. Inorganic iodine in the thyroid is assumed to be retained with a biological half-life of 120 days, and organic iodine in all other organs is assumed to be retained with a biological half-life of 12 days.

Significant Exposure Routes:

The internal slope factors are moderate to high compared to other radionuclides, while the external-exposure slope factor is lower than for most radionuclides. Internal exposure routes could result in significant risk depending on the contamination level in the media of exposure, while external exposures are less likely to result in significant risk.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

IRON-59

CASRN: 14596-12-4
Synonyms: None

Oral Slope Factor:	5.87E-12 risk/pCi ingested
Inhalation Slope Factor:	7.08E-12 risk/pCi inhaled
External Slope Factor:	4.63E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Iron-59 undergoes beta decay (44.53 day half-life) to stable cobalt-59. The radiation emissions are high-energy gamma rays (0.14 to 1.29 MeV) and beta particles of average energy from 0.036 to 0.64 MeV.

Uptake, Distribution, and Retention in the Body (ICRP 1980):

The absorption fraction for iron in the gastrointestinal tract is set to 0.1. Inhalation of iron hydroxides and halides are assigned to class W, and all other commonly occurring compounds are assigned to class D. The HEAST (1994) slope factors are based on a lung class of W. Material entering the blood is assumed to be transferred to the liver (0.08) and the spleen (0.013), with the remainder uniformly distributed in all other organs and tissues. The retention in all organs is described by a biological half-life of 2,000 days.

Significant Exposure Routes:

The external-exposure slope factor is high, and the internal slope factors are moderate relative to those for other radionuclides. A significant risk could be obtained from all pathways depending on the contamination level in the medium of exposure and the exposure situation.

References:

International Commission on Radiological Protection (ICRP). 1980. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 2). *Annals of the ICRP*, Vol. 4, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPA 540-R-94 114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

LEAD-210(+D)

CASRN: 14255-04-0(+D)
Synonyms: Radium D

Oral Slope Factor:	1.01E-9 risk/pCi ingested
Inhalation Slope Factor:	3.86E-9 risk/pCi inhaled
External Slope Factor:	1.45E-10 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Lead-210 undergoes beta decay (22.3 year half-life) to the radioactive isotope bismuth-210 (5.01 day half-life). Bismuth-210 undergoes beta decay to radioactive polonium-210 (1.384 day half-life), which undergoes alpha decay to stable lead-206. The slope factors for lead-210(+D) include the radiations from all of these radionuclides in secular equilibrium with lead-210. The radiations from lead-210 are low-energy beta particles, Auger electrons, and gamma rays. Bismuth-210 emits a beta particle of 0.39 MeV average energy, and polonium-210 emits alpha particles and several relatively high-energy gamma rays (about 0.8 MeV) of low yield (about 0.001%). The internal dose comes mainly from the alpha particle emissions of polonium-210 (from polonium-210 produced after intake of lead-210). The external dose is mainly from the low-energy lead-210 gamma and X-rays. The slope factors for lead-210(+D) include contributions from lead-210, bismuth-210, and polonium-210 in secular equilibrium, with the lead-210 and polonium-210 values providing the majority of the risk.

Uptake, Distribution, and Retention in the Body (ICRP 1980):

The gastrointestinal absorption fraction for compounds of lead is set to 0.2. The inhalation class for all commonly occurring compounds of lead are assigned an inhalation class of D. The lead entering the blood is assumed to be translocated to the skeleton (0.55), the liver (0.25), the kidneys (0.02), and to all other organs and tissues (0.18). A three-compartment model is used to describe the retention in all organs. For skeleton, the three compartments are represented by deposition fractions of 0.6, 0.2, and 0.2, with corresponding biological half-lives of 12, 180, and 10,000 days. For all other organs, the three compartments are represented by deposition fractions of 0.8, 0.18, and 0.02, with corresponding biological half-lives of 12, 180, and 10,000 days. For purposes of bone dosimetry, lead-210 is assumed to be uniformly distributed throughout bone volume at all times after intake.

Significant Exposure Routes:

The internal slope factors are high compared to most other radionuclides, and the external-exposure slope factor is low. The internal exposure pathways may result in a significant risk, depending on the concentration of lead-210 in the media. The external exposure pathway is less likely to result in significant exposures.

References:

International Commission on Radiological Protection (ICRP). 1980. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 2). *Annals of the ICRP*, Vol. 4, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

MANGANESE-54

CASRN: 13966-31-9
Synonyms: None

Oral Slope Factor:	1.96E-12 risk/pCi ingested
Inhalation Slope Factor:	3.69E-12 risk/pCi inhaled
External Slope Factor:	3.26E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Manganese-54 undergoes electron capture decay (312.5 days half-life) to the stable isotope chromium-54, with emission of gamma radiation (0.83 MeV) and low-energy Auger electron radiation (several emissions of less than 0.006 MeV average energy).

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The absorption fraction is set at 0.1 for all compounds of manganese. For oxides, hydroxides, halides, and nitrates of manganese, a lung class of W is assigned, and for all other compounds a class of D is assigned. The HEAST (1994) slope factors are based on a lung class of W. The material entering the blood is assumed to be transferred to the bone (0.35), the liver (0.25), and all other organs and tissues (0.4). The material entering the bone is retained with a biological half-life of 40 days. The retention of material in liver and all other organs and tissues is described using two-compartment models. For liver 0.1 (of the 0.25) is retained with a biological half-life of 4 days, and the other 0.15 is retained with a biological half-life of 40 days. For all other organs and tissues, 0.2 (of the 0.4) is retained with a biological half-life of 4 days, and the other 0.2 is retained with a biological half-life of 40 days.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are lower than many other radionuclides and represent less potential for risk, depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

NICKEL-63

CASRN: 13981-37-8
Synonyms: None

Oral Slope Factor:	5.50E-13 risk/pCi ingested
Inhalation Slope Factor:	1.01E-12 risk/pCi inhaled
External Slope Factor:	0.0 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Nickel-63 has a radiological half-life of 96 years. Nickel-63 undergoes beta decay to the stable isotope copper-63. The primary radiation is a 0.017 MeV (average energy) beta ray.

Uptake, Distribution, and Retention in the Body (ICRP 1981):

The uptake of nickel from the gastrointestinal tract is set at 0.05 for all compounds of nickel. Oxides, hydroxides, and carbides of nickel are assigned an inhalation class of W, and all other compounds (except nickel carbonyl) are assigned class D. The inhalation slope factor in HEAST (1994) for nickel-63 is based on inhalation class W. Inhaled nickel carbonyl is assumed to be completely absorbed in the lung and transferred from the lung to the blood with a biological half-life of 0.1 days. The nickel reaching the blood is assumed to be deposited in the kidneys (2%), uniformly in all organs (30%), and the remainder is excreted directly (68%). The nickel reaching the kidneys is retained with a biological half-life of 0.2 days, and the material in the other organs is retained with a biological half-life of 1,200 days.

Significant Exposure Routes:

Both the inhalation and ingestion slope factors are low relative to other radionuclides and are less likely to result in a significant exposure. The external-exposure slope factor is zero because there are no gamma or X-ray radiation emitted by nickel-63; therefore, this pathway does not represent a source of risk.

References:

International Commission on Radiological Protection (ICRP). 1981. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 3). *Annals of the ICRP*, Vol. 6, No. 2/3, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2.* EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

PLUTONIUM-238

CASRN: 13981-16-3
Synonyms: None

Oral Slope Factor:	2.95E-10 risk/pCi ingested
Inhalation Slope Factor:	2.74E-8 risk/pCi inhaled
External Slope Factor:	1.94E-11 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Plutonium-238 undergoes alpha decay (87.74 year half-life) with emission of gamma rays, X-rays, and Auger electrons. The gamma and X-ray radiations are all under 0.1 MeV and are less significant than those from many other radionuclides. The primary radiation causing internal dose is the alpha radiation. Plutonium-238 decays to uranium-234 (2.445E+5 year half-life) which in turn undergoes alpha decay to thorium-230 (7.7E+4 year half-life). The uranium-234 and thorium-230 produced from decay of plutonium-238 is generally not included in risk analyses because of the long half-life of uranium-234.

Uptake, Distribution, and Retention in the Body (ICRP 1979, 1986):

Plutonium is not taken up readily in the gastrointestinal tract, and the International Commission on Radiological Protection (ICRP) recommends an absorption fraction of $1x10^{-3}$. The absorbed activity is assumed to be distributed to the skeletal bone (45%), the liver (45%), and the gonads (0.035% for testes and 0.011% for ovaries). Material not transferred to organs is assumed to be excreted. Retention in skeleton is described by a 50-year biological half-life and retention in liver by a 20-year biological half-life. Material in the gonads is assumed to be retained indefinitely. All isotopes of plutonium are considered to be uniformly distributed over bone surfaces at all times following their deposition in the skeleton. Inhalation dose factors used in determining the inhalation slope factors are based on ICRP lung class Y (clearance times from the lung on the order of years).

Significant Exposure Routes:

Both inhalation and ingestion of plutonium-238 may result in a significant exposure. The low-energy gamma and X-ray radiations result in a relatively low external-exposure slope factor. The external pathway is likely to cause less risk than internal exposures (depending on the exposure scenario).

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1986. "The Metabolism of Plutonium and Related Elements." (ICRP Publication 48). *Annals of the ICRP*, Vol. 16, No. 2/3, Pergamon Press, New York, New York.

PLUTONIUM-239

CASRN: 15117-48-3
Synonyms: None

Oral Slope Factor:	3.16E-10 risk/pCi ingested
Inhalation Slope Factor:	2.78E-8 risk/pCi inhaled
External Slope Factor:	1.26E-11 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Plutonium-239 undergoes alpha decay (24,065 year half-life) with emission of gamma rays, X-rays, and Auger electrons. While some of the gamma radiations are of moderate energy (under 0.5 MeV), their abundance is small and external dose rates are less significant than those from many other radionuclides. The primary X-rays are under 0.1 MeV. The primary radiation causing internal dose is the alpha radiation. Plutonium-239 decays to uranium-235 (7.038E+8 year half-life) which in turn undergoes alpha decay to thorium-231 (25.52 hour half-life). The radiations from the uranium-235 and its decay products are generally not included in risk analyses because of the long half-life of uranium-235.

Uptake, Distribution, and Retention in the Body (ICRP 1979, 1986):

The metabolic models for plutonium-239 are the same as described for plutonium-238.

Significant Exposure Routes:

Both inhalation and ingestion of plutonium-239 may result in a significant exposure. The low-energy gamma and X-ray radiations result in a relatively low external-exposure slope factor. Therefore, the external pathway is likely to cause less risk than internal exposures (depending on the exposure scenario).

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1986. "The Metabolism of Plutonium and Related Elements." (ICRP Publication 48). *Annals of the ICRP*, Vol. 16, No. 2/3, Pergamon Press, New York, New York.

PLUTONIUM-240

CASRN: 14119-33-6
Synonyms: None

Oral Slope Factor:	3.15E-10 risk/pCi ingested
Inhalation Slope Factor:	2.78E-8 risk/pCi inhaled
External Slope Factor:	1.87E-11 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Plutonium-240 undergoes alpha decay (6,537 year half-life) with emission of gamma rays, X-rays, and Auger electrons. The gamma and X-ray radiations are all under 0.1 MeV and are less significant than those from many other radionuclides. The primary radiation causing internal dose is the alpha radiation. Plutonium-240 decays to uranium-236 (2.342E+7 year half-life) which in turn undergoes alpha decay to thorium-232 (1.405E+10 year half-life). The radiations from both of these decay products are generally not included in risk analyses because of their long half-lives.

Uptake, Distribution, and Retention in the Body (ICRP 1979, 1986):

The metabolic models for plutonium-239 are the same as described for plutonium-238.

Significant Exposure Routes:

Both inhalation and ingestion of plutonium-240 may result in a significant exposure. The low-energy gamma and X-ray radiations result in a relatively low external-exposure slope factor. Therefore, the external exposure pathway is likely to cause less risk than internal exposures (depending on the exposure scenario).

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

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International Commission on Radiological Protection (ICRP). 1986. "The Metabolism of Plutonium and Related Elements." (ICRP Publication 48). *Annals of the ICRP*, Vol. 16, No. 2/3, Pergamon Press, New York, New York.

PLUTONIUM-241

CASRN: 14119-32-5
Synonyms: None

Oral Slope Factor:	5.20E-12 risk/pCi ingested
Inhalation Slope Factor:	2.81E-10 risk/pCi inhaled
External Slope Factor:	0.0 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Plutonium-241 undergoes alpha and beta decay (14.4 year half-life) with emission of alpha particles, beta particles, gamma rays, X-rays, and Auger electrons. The primary plutonium-241 decay mode is beta decay to americium-241 (432.2 year half-life), which occurs with a yield of 99.997%, and produces beta particles with an average energy of 0.005 MeV. The gamma and X-ray radiations are all under 0.2 MeV and are less frequent and less significant than those from many other radionuclides. Therefore, the external-exposure slope factor is set to zero in HEAST (EPA 1994); however, bremsstrahlung radiation generated by beta particles causes a low level of external exposure equivalent to a slope factor of approximately 4.5E-12. The alpha radiation is produced in conjunction with decay to uranium-237 (6.75 day half-life) but occurs for just 0.00245% of all transition events. The HEAST external slope factor ignores the uranium-237 contribution of 3.36E-12. Slope factors for americium-241 are provided (see the americium-241 toxicity profile) and must be used in conjunction with an estimate of the americium-241 present during the time period of interest for the risk analysis.

Uptake, Distribution, and Retention in the Body (ICRP 1979, 1986):

The metabolic models for plutonium-241 are the same as described for plutonium-238.

Significant Exposure Routes:

The inhalation and ingestion slope factors are moderate compared to other radionuclides and may result in a significant exposure. The zero external-exposure slope factor (and the low estimated contributions from uranium-237 and bremsstrahlung) indicates this pathway will not be an important source of risk. However, the age of the plutonium-241 is very important because the americium-241 decay product activity will increase with time and could represent a significant source of external radiation.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1986. "The Metabolism of Plutonium and Related Elements." (ICRP Publication 48). *Annals of the ICRP*, Vol. 16, No. 2/3, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2.* EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

POTASSIUM-40

CASRN: 13966-00-2
Synonyms: None

Oral Slope Factor:	1.25E-11 risk/pCi ingested
Inhalation Slope Factor:	7.46E-12 risk/pCi inhaled
External Slope Factor:	6.11E-7 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Potassium-40 undergoes electron capture and beta decay with a half-life of 1.28+E9 years, with production of stable argon-40 (89.3% yield) and stable calcium-40 (10.7% yield), by the two decay modes, respectively. The primary emissions are a beta particle of 0.585 MeV average energy (yield 89.3%) and a gamma ray of 1.46 MeV (yield 10.7%).

Uptake, Distribution, and Retention in the Body (ICRP 1980):

Most compounds of potassium are very soluble, and the International Commission on Radiological Protection (ICRP) recommends an absorption fraction of 1.0 and a lung inhalation class of D. The HEAST slope factors are based on an absorption fraction of 0.95. Potassium entering the blood is assumed to be uniformly distributed to all organs and tissues. The material is retained in organs and tissues with a biological half-life of 30 days.

Significant Exposure Routes:

The slope factors are moderate compared to other radionuclides, and significant risks could result from all three exposure routes, depending on the contamination level in the medium of exposure. Potassium-40 is a naturally occurring radionuclide and is not produced in significant amounts from reactor operations. Therefore, risks evaluated for potassium-40 should be considered as part of background radiation.

References:

International Commission on Radiological Protection (ICRP). 1980. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 2). *Annals of the ICRP*, Vol. 4, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

PROMETHIUM-147

CASRN: 14380-75-7
Synonyms: None

Oral Slope Factor:	1.41E-12 risk/pCi ingested
Inhalation Slope Factor:	7.49E-12 risk/pCi inhaled
External Slope Factor:	6.35E-12 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Promethium-147 undergoes beta decay (2.623 year half-life) to the extremely long-lived radioactive isotope samarium-147 (1.06E+11 year half-life). Several low-intensity gamma and X-rays are emitted of energy between 0.0063 and 0.12 MeV. The beta particle emission is at an average energy of 0.062 MeV.

Uptake, Distribution, and Retention in the Body (ICRP 1981):

The gastrointestinal uptake fraction for promethium is set to 3.0E-4 in conformity with the value for cerium. The inhalation class for oxides, hydroxides, carbides, and fluorides of promethium is set to Y, and for all other compounds of promethium to class W. The HEAST (1994) slope factors are based on inhalation class Y. Promethium leaving the blood is assumed to be translocated to the liver (0.45) and the skeleton (0.45), with the remainder going directly to excretion (0.1). Promethium is retained in liver and skeleton with a biological half-life of 3,500 days. Promethium translocated to skeleton is assumed to be uniformly distributed over bone surfaces.

Significant Exposure Routes:

The inhalation slope factor is moderate relative to many other radionuclides indicating inhalation exposure could represent a significant exposure pathway. The external and ingestion slope factors are low compared to those for many other radionuclides indicating a significant risk is less likely to occur.

References:

International Commission on Radiological Protection (ICRP). 1981. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 3). *Annals of the ICRP*, Vol. 6, No. 2/3, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPAEPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

RADIUM-226(+D)

CASRN: 13982-63-3(+D)
Synonyms: None

Oral Slope Factor:	2.96E-10 risk/pCi ingested
Inhalation Slope Factor:	2.75E-9 risk/pCi inhaled
External Slope Factor:	6.74E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Radium-226 undergoes alpha decay (1,600 year half-life) to the radioactive isotope radon-222 (3.824 day half-life). Radon-222 decays through several radioactive isotopes, all with half-lives less than a few minutes, to radioactive isotope lead-210 (22.3 year half-life). The primary radiations that cause internal risk are the alpha particles from radium-226 and the short-lived progeny. The external exposure risk is from gamma radiations emitted by lead-214 and bismuth-214.

The HEAST (1994) slope factors for radium-226(+D) include contributions from the progeny (radon-222, polonium-218, lead-214, bismuth-214, and polonium-214). For ingestion and external-exposure slope factors, these progeny are assumed to be in secular equilibrium with the parent radium-226. For the inhalation slope factor, the progeny are assumed to be at 50% of the secular equilibrium concentration.

Uptake, Distribution, and Retention in the Body (ICRP 1973, 1979):

The fractional absorption of radium in the gastrointestinal tract is assumed to be 0.2. All chemical compounds of radium are assigned an inhalation class of W (clearance from the lungs on the order of weeks). The distribution and retention of radium radionuclides is described by the model developed by the Task Group on Alkaline Earth Metabolism in Adult Man (ICRP 1973). This model used various time dependent functions to describe the distribution and retention of alkaline earth elements in blood, bone surface, compact bone (old and new), cancellous bone (old and new), bone volume, and soft tissue compartments. Parameter values are defined for these functions for each alkaline earth element (calcium, strontium, barium, and radium). For purposes of bone dosimetry, radium-226 is assumed to be distributed uniformly throughout the volume of mineral bone. The radon-222 produced in soft tissue is assumed to escape the body without decaying. For radon-222 produced in mineral bone, a fraction of 0.3 is estimated to remain in the bone and decay.

Significant Exposure Routes:

The slope factors are high compared to most other radionuclides and may result in a significant exposure from all pathways.

References:

International Commission on Radiological Protection (ICRP). 1973. "Alkaline Earth Metabolism in Adult Man." (ICRP Publication 20). *Annals of the ICRP*, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

RADIUM-228(+D)

CASRN: 15262-20-1(+D)
Synonyms: None

Oral Slope Factor:	2.48E-10 risk/pCi ingested
Inhalation Slope Factor:	9.94E-10 risk/pCi inhaled
External Slope Factor:	3.28E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Radium-228 undergoes beta decay (5.75 year half-life) to the radioactive isotope actinium-228 (6.13 hour half-life). Actinium-228 undergoes beta decay to radioactive thorium-228 (1.913 year half-life). The radiations from radium-228 are low-energy beta particles, Auger electrons, and gamma rays. The primary radiations for internal and external risk are the radiations from the short-lived actinium-228 decay product, which are included in the HEAST (1994) slope factors. Radium-228 and several of its decay products undergo alpha decay and also represent a significant contribution to internal dose (as activity produced after intake). Radiations from thorium-228 and its progeny are not included in the external-exposure slope factor for radium-228(+D).

Uptake, Distribution, and Retention in the Body (ICRP 1973, 1979):

The uptake, distribution, and retention of radium in the body is as described for radium-226(+D).

Significant Exposure Routes:

The slope factors are high compared to most other radionuclides and may result in a significant exposure from all pathways.

References:

International Commission on Radiological Protection (ICRP). 1973. "Alkaline Earth Metabolism in Adult Man." (ICRP Publication 20). *Annals of the ICRP*, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

RUTHENIUM-103

CASRN: 13968-53-1
Synonyms: None

Oral Slope Factor:	3.32E-12 risk/pCi ingested
Inhalation Slope Factor:	4.59E-12 risk/pCi inhaled
External Slope Factor:	1.70E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Ruthenium-103 undergoes beta decay with a half-life of 39.28 days. The beta emissions range from 0.02 to 0.24 MeV (average energy), and the significant gamma ray emissions range from 0.3 to 0.61 MeV. The decay products of ruthenium-103 are the stable isotope rhodium-103 (yield 0.3%) and the radioactive isotope rhodium-103m (yield 99.7%). Rhodium-103m (half-life 56.12 minutes) decays by isomeric transition with emission of low-energy X-rays, gamma rays, and Auger electrons. The contributions to dose from the rhodium-103m decay product are small compared to the ruthenium-103 emissions.

Uptake, Distribution, and Retention in the Body (ICRP 1980):

The absorption fraction from the gastrointestinal tract is set to 0.05 for all compounds of ruthenium. Oxides and hydroxides of ruthenium are assigned a lung class of Y, halides to class W, and all other compounds to class D. The HEAST (1994) slope factors are based on lung class Y. Ruthenium is assumed to be retained in the blood with a biological half-life of 0.3 days. Of the material leaving the blood, 0.15 goes directly to excretion and the rest is deposited uniformly in all other organs and tissues. A three-compartment model is used to describe retention of ruthenium in all other organs and tissues. A fraction of 0.35 (of the 0.85) is retained with a biological half-life of 8 days, 0.3 is retained with a biological half-life of 35 days, and 0.2 is retained with a biological half-life of 1,000 days.

Significant Exposure Routes:

The inhalation and ingestion slope factors for ruthenium-103 are moderate compared to other radionuclides, and the external-exposure slope factor is high. Significant risks could result from all three exposure routes, depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1980. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 2). *Annals of the ICRP*, Vol. 4, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

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RUTHENIUM-106(+D)

CASRN: 13967-48-1
Synonyms: None

Oral Slope Factor:	3.45E-11 risk/pCi ingested
Inhalation Slope Factor:	1.15E-10 risk/pCi inhaled
External Slope Factor:	7.57E-7 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Ruthenium-106 undergoes beta decay with a half-life of 368.2 days. The beta emission has an average energy of 0.01 MeV. There are no other radiation emissions. The decay product of ruthenium-106 is the radioactive isotope rhodium-106. Rhodium-106 (half-life 29.9 seconds) undergoes beta decay to the stable isotope palladium-106. Rhodium-106 has significant gamma and beta emissions. The HEAST (1994) slope factors include contributions from rhodium-106.

Uptake, Distribution, and Retention in the Body (ICRP 1980):

The metabolic models for ruthenium-106 are the same as described for ruthenium-103.

Significant Exposure Routes:

The internal slope factors for ruthenium-106 are moderate to high compared to other radionuclides. Significant risks could result from internal exposure routes, depending on the contamination level in the medium of exposure. The external-exposure slope factor for ruthenium-106 is moderate compared to other radionuclides and may result in significant risk.

References:

International Commission on Radiological Protection (ICRP). 1980. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 2). *Annals of the ICRP*, Vol. 4, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

SODIUM-22

CASRN: 13966-32-0
Synonyms: None

Oral Slope Factor:	8.02E-12 risk/pCi ingested
Inhalation Slope Factor:	4.88E-12 risk/pCi inhaled
External Slope Factor:	8.18E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Sodium-22 undergoes electron capture and beta-plus decay with a half-life of 2.602 years. The primary beta-plus emission is 0.215 MeV (average energy), and the significant gamma ray emissions are 0.51 and 1.3 MeV. The decay product from sodium-22 is the stable isotope neon-22.

Uptake, Distribution, and Retention in the Body (ICRP 1980):

Most compounds of sodium are very soluble, and the International Commission on Radiological Protection (ICRP) recommends an absorption fraction of 1.0 and a lung clearance class of D (clearance times from the lung on the order of days). The HEAST slope factors are based on an absorption fraction of 0.95. Thirty percent of the absorbed activity is assumed to be distributed to the skeletal bone with the remainder distributed uniformly throughout all other organs and tissues of the body. Sodium deposited in the bone is assumed to be uniformly distributed throughout the bone volume at all times following deposition. Retention in skeleton is described by a two-compartment model with biological half-lives of 10 days (99% of activity in bone or about 29.7% of activity reaching the blood) and 500 days (1% of activity in bone or about 0.3% of activity reaching the blood). Retention in other organs and tissues is described by a biological half-life of 10 days.

Significant Exposure Routes:

The inhalation and ingestion slope factors are moderate compared to other radionuclides and the external-exposure slope factor is high. The high-energy gamma radiations result in one of the highest external-exposure slope factors for any radionuclide. Significant risks could result from all three exposure routes, depending on the contamination level in the medium of exposure. The relatively short half-life for sodium-22 indicates that it may only be important for reactors that have operated in the past 10 (or so) years.

References:

International Commission on Radiological Protection (ICRP). 1980. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 2). *Annals of the ICRP*, Vol. 4, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

STRONTIUM-90(+D)

CASRN: 10098-97-2(+D)
Synonyms: None

Oral Slope Factor:	5.59E-11 risk/pCi ingested
Inhalation Slope Factor:	6.93E-11 risk/pCi inhaled
External Slope Factor:	0.0 risk/yr per pCi/g soil

Note: Chemical toxicity for strontium is addressed in a separate profile.

Radionuclide Decay Information (ICRP 1983):

Strontium-90 undergoes beta decay (29.12 year half-life) with emission of a 0.2 MeV average energy beta particle. The decay product is radioactive yttrium-90 (64.0 hour half-life), which undergoes beta decay to the stable isotope zirconium-90. Yttrium-90 emits a beta particle of average energy 0.93 MeV which contributes to internal radiation risk. Neither strontium-90 nor yttrium-90 have sufficient X-ray emissions to result in significant external exposure risk. The radiations from yttrium-90 are included in the internal slope factors for strontium-90(+D). The bremsstrahlung generated by beta particles (from strontium-90 and yttrium-90) cause a low level of external exposure equivalent to a slope factor of approximately 2E-8.

Uptake, Distribution, and Retention in the Body (ICRP 1973, 1979):

The fractional absorption of strontium in the gastrointestinal tract is assumed to be 0.3 for soluble salts of strontium and to 0.01 for strontium titanate. For inhalation, soluble salts of strontium are assigned to inhalation class D and strontium titanate is assigned to inhalation class Y. The HEAST (1994) slope factors for inhalation and ingestion are based on inhalation class D and a gastrointestinal absorption fraction of 0.3. The distribution and retention of strontium radionuclides is described by the model developed by the Task Group on Alkaline Earth Metabolism in Adult Man (ICRP 1972). This model uses various time-dependent functions to describe the distribution and retention of alkaline earth elements in blood, bone surface, compact bone (old and new), cancellous bone (old and new), bone volume, and soft tissue compartments. Parameter values are defined for these functions for each alkaline earth element (calcium, strontium, barium, and radium). For purposes of bone dosimetry, strontium-90 is assumed to be distributed uniformly throughout the volume of mineral bone (ICRP 1979). Strontium is known to be a bone-seeking element (similar to calcium). The bone surface is the organ receiving the highest committed dose equivalent for both inhalation and ingestion intake routes.

Significant Exposure Routes:

The ingestion slope factor is high compared to many other radionuclides, and the inhalation slope factor is moderate. Each of these pathways could result in a significant exposure. The external exposure pathway is not of concern because of the lack of emissions of penetrating radiation from strontium-90 and yttrium-90.

References:

International Commission on Radiological Protection (ICRP). 1972. "Alkaline Earth Metabolism in Adult Man." (ICRP Publication 20). *Annals of the ICRP*, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1973. "Alkaline Earth Metabolism in Adult Man." (ICRP Publication 20). *Annals of the ICRP*, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2.* EPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

TECHNETIUM-99

CASRN: 14133-76-7
Synonyms: None

Oral Slope Factor:	1.40E-12 risk/pCi ingested
Inhalation Slope Factor:	2.89E-12 risk/pCi inhaled
External Slope Factor:	6.19E-13 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Technetium-99 undergoes beta decay (2.13E+5 year half-life) to the stable isotope ruthenium-99. The beta particle emission average energy is 0.10 MeV. There are no gamma or X-ray radiations listed.

Uptake, Distribution, and Retention in the Body (ICRP 1980):

The gastrointestinal uptake fraction for technetium is set to 0.8 for all compounds. The inhalation class for technetium oxides, hydroxides, halides, and nitrates is set to W, and for all other compounds to class D. The HEAST (1994) slope factors are based on inhalation class W and an uptake fraction of 0.8. Technetium leaving the blood is assumed to be translocated to the thyroid (0.04), to the liver (0.03), to the stomach wall (0.1), and uniformly throughout all other organs and tissues (0.83). Technetium retention in the thyroid is described by a biological half-life of 0.5 days. For all other tissues and organs, retention is described by a three-compartment model. A fraction of 0.75 is retained with a biological half-life of 1.6 days, a fraction of 0.2 is retained with a biological half-life of 3.7 days, and the remainder (0.05) is retained with a biological half-life of 22 days.

Significant Exposure Routes:

The external-exposure slope factor is very low relative to many other radionuclides, and the ingestion and inhalation slope factors are moderate. External exposures risks are likely to be insignificant, while internal exposure risks may be significant, depending on the media concentrations and the exposure scenarios.

References:

International Commission on Radiological Protection (ICRP). 1980. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 2). *Annals of the ICRP*, Vol. 4, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

U.S. Environmental Protection Agency (EPA). 1994. *Health Effects Assessment Summary Tables FY 1994: Supplement Number 2*. EPAEPA 540-R-94-114, U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, D.C.

THORIUM-228(+D)

CASRN: 14274-82-9(+D)
Synonyms: None

Oral Slope Factor:	2.31E-11 risk/pCi ingested
Inhalation Slope Factor:	9.68E-8 risk/pCi inhaled
External Slope Factor:	6.24E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Thorium-228 undergoes alpha decay (1.913 year half-life) to the radioactive isotope radium-224 (3.66 day half-life). Radium-224 undergoes decay through a series for short-lived radionuclides ending in the stable isotope lead-208. Radiations from all of these radionuclides (thorium-228, radium-224, radon-220, polonium-216, lead-212, bismuth-212, polonium-212, and thallium-208) are included in the slope factors for thorium-228(+D). The radiations from the series include several alpha particle emissions that contribute to the internal dose factors, and several gamma and X-rays that result in the high external-exposure slope factor.

Uptake, Distribution, and Retention in the Body (ICRP 1972, 1979):

The gastrointestinal absorption fraction for all compounds of thorium is set to 2E-4. The inhalation class for thorium oxides and hydroxides is set to Y, and for all other compounds to class W. The HEAST (1994) slope factors are based on inhalation class Y and an uptake fraction of 2E-4. Thorium is translocated from the blood to the bone (0.7), the liver (0.04), all other organs and tissues (0.16), and directly to excretion (0.1). Thorium is retained in bone with a biological half-life of 8,000 days, and in liver and all other organs and tissues with a biological half-life of 700 days. The blood is cleared with a biological half-life of 0.5 days.

Significant Exposure Routes:

All of the thorium-228(+D) slope factors are high compared to most other radionuclides and may result in a significant exposure from all pathways.

References:

International Commission on Radiological Protection (ICRP). 1972. "Alkaline Earth Metabolism in Adult Man." (ICRP Publication 20). *Annals of the ICRP*, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

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THORIUM-232

CASRN: 07440-29-1
Synonyms: None

Oral Slope Factor:	3.28E-11 risk/pCi ingested
Inhalation Slope Factor:	1.93E-8 risk/pCi inhaled
External Slope Factor:	1.97E-11 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Thorium-232 undergoes alpha decay (1.405E+10 year half-life) to the radioactive isotope radium-228 (5.75 year half-life). Decay of radium-228 is described in the radium-228(+D) profile. The decay of thorium-232 releases alpha, Auger electrons, conversion electrons, gamma rays, and X-rays. The alpha radiation is the primary source of dose from inhalation and ingestion exposures. The gamma and X-rays are of low energy and intensity and do not result in a significant external exposure slope factor.

Uptake, Distribution, and Retention in the Body (ICRP 1972, 1979):

The uptake, distribution, and retention of thorium in the body is as described for thorium-228(+D).

Significant Exposure Routes:

The internal slope factors are high compared to most other radionuclides, and the external-exposure slope factor is lower than for most radionuclides. The inhalation and ingestion pathways may result in a significant exposure, while the external exposure pathway is less likely to cause significant exposures.

References:

International Commission on Radiological Protection (ICRP). 1972. "Alkaline Earth Metabolism in Adult Man." (ICRP Publication 20). *Annals of the ICRP*, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

URANIUM-234

CASRN: 13966-29-5
Synonyms: None

Oral Slope Factor:	4.44E-11 risk/pCi ingested
Inhalation Slope Factor:	1.40E-8 risk/pCi inhaled
External Slope Factor:	2.14E-11 risk/yr per pCi/g soil

Note: Chemical toxicity for uranium is addressed in a separate profile.

Radionuclide Decay Information (ICRP 1983):

Uranium-234 undergoes alpha decay (2.445E+5 year half-life) with emission of alpha particles, gamma rays, X-rays, and Auger electrons. The gamma and X-ray radiations are all under 0.12 MeV and are less significant than those from many other radionuclides. The primary radiation causing internal dose is the alpha radiation. Uranium-234 decays to thorium-230 (7.7E+4 year half-life). Thorium-230 undergoes alpha decay (with radiations similar to uranium-234) to radium-226 (half-life 1,600 years). The contributions from radium-226 and its decay products are generally not included in risk analyses because of the long half-life of the intermediate radionuclide thorium-230. The exception is for material in which secular equilibrium is assumed to occur, in which case contributions from all decay products are included. Because the half-life of thorium-230 is on the order of the half-life for uranium-234, entries for uranium-234+D are not generated in HEAST (1994).

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The absorption fraction in the gastrointestinal tract is set to 0.05 for water-soluble inorganic hexavalent uranium compounds, and to 0.002 for other compounds such as UF_4, UO_2, and U_3O_8 which usually involve tetravalent uranium. Inhalation class D is assigned to soluble compounds (UF_6, UO_2F_2, and $UO_2(NO_3)_2$), class W is assigned to less soluble compounds (UO_3, UF_4, and UCl_4) and class Y to highly insoluble uranium oxides. The HEAST (1994) slope factors were based on an absorption fraction of 0.05 and an inhalation class of Y. Retention of uranium in organs of the body is described by two-compartment models. Of the material entering the blood, 0.2 is transferred to mineral bone and retained with a biological half-life of 20 days, and 0.023 is transferred to mineral bone and retained with a biological half-life of 5,000 days. For transfer to kidneys, 0.12 is retained with a biological half-life of 6 days, and 0.00052 is retained with a biological half-life of 1,500 days. For material uniformly distributed to all other tissues, 0.12 is retained with a biological half-life of 6 days, and 0.00052 is retained with a biological half-life of 1,500 days. The remainder of uranium leaving the blood is assumed to be directly excreted. Long-lived uranium isotopes (uranium-232, uranium-233, uranium-234, uranium-235, uranium-236, and uranium-238) are assumed to be uniformly distributed throughout the volume of mineral bone following their deposition.

Significant Exposure Routes:

Both inhalation and ingestion of uranium-234 may result in a significant exposure. The external-exposure slope factor is low relative to other radionuclides and is likely to cause less risk than internal exposures (depending on the exposure scenario).

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

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URANIUM-235(+D)

CASRN: 15117-96-1(+D)
Synonyms: None

Oral Slope Factor:	4.70E-11 risk/pCi ingested
Inhalation Slope Factor:	1.30E-8 risk/pCi inhaled
External Slope Factor:	2.65E-7 risk/yr per pCi/g soil

Note: Chemical toxicity for uranium is addressed in a separate profile.

Radionuclide Decay Information (ICRP 1983):

Uranium-235 undergoes alpha decay (7.038E+8 year half-life) with emission of alpha particles, gamma rays, X-rays, and Auger electrons. The gamma and X-ray radiations are all under 0.24 MeV. The primary radiation causing internal dose is the alpha radiation. Uranium-235 decays to thorium-231 (25.52 hour half-life). Thorium-231 undergoes beta decay to protactinium-231 (half-life 3.276E+4 years). Protactinium-231 decays to actinium-227 (half-life 21.77 years) which decays to a series of short-lived radionuclides. The contributions from thorium-231 are included in the slope factors for uranium-235(+D), but contributions from other decay products are not included.

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The metabolic models for uranium-235 are the same as described for uranium-234.

Significant Exposure Routes:

The external-exposure slope factor for uranium-235(+D) is moderate, and the inhalation and ingestion slope factors are high relative to values for other radionuclides. The risk from these pathways could be significant depending on the exposure scenario.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

URANIUM-238(+D)

CASRN: 7440-61-1(+D)
Synonyms: None

Oral Slope Factor:	6.20E-11 risk/pCi ingested
Inhalation Slope Factor:	1.24E-8 risk/pCi inhaled
External Slope Factor:	5.46E-8 risk/yr per pCi/g soil

Note: Chemical toxicity for uranium is addressed in a separate profile.

Radionuclide Decay Information (ICRP 1983):

Uranium-238 undergoes alpha decay (4.468E+9 year half-life) with emission of alpha particles, gamma rays, X-rays, and Auger electrons. The gamma and X-ray radiations are all under 0.05 MeV. The primary radiation causing internal dose is the alpha radiation. Uranium-238 decays to thorium-234 (24.10 day half-life). Thorium-234 undergoes beta decay to protactinium-234m (yield 99.8%, half-life 1.17 minutes) and to protactinium-234 (yield 0.2%, half-life 6.7 hours). Protactinium-234m decays to uranium-234 (yield 99.8%, half-life 2.445E+5 years) and to protactinium-234 (yield 01.3%). Uranium-234 decays to a series of radionuclides as described in the uranium-234 profile. Protactinium-234 also decays to uranium-234. The contributions from thorium-234, protactinium-234m, and protactinium-234 are included in the slope factors for uranium-238(+D), but contributions from other decay products are not included.

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The metabolic models for uranium-238 are the same as described for uranium-234.

Significant Exposure Routes:

The external-exposure slope factor for uranium-238(+D) is moderate, and the inhalation and ingestion slope factors are high relative to values for other radionuclides. The risk from these pathways could be significant depending on the exposure scenario.

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

ZINC-65

CASRN: 13982-39-3
Synonyms: None

Oral Slope Factor:	9.93E-12 risk/pCi ingested
Inhalation Slope Factor:	9.98E-12 risk/pCi inhaled
External Slope Factor:	2.27E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Zinc-65 has a radiological half-life of 243.9 days and undergoes electron capture and positron decay (beta plus) to the stable isotope copper-65. The primary radiations are a 1.12-MeV gamma ray, a 0.143-MeV (average energy) positron, and several Auger electrons of average energy below 0.007 MeV.

Uptake, Distribution, and Retention in the Body (ICRP 1980):

The gastrointestinal absorption fraction is set to 0.5 for all compounds of zinc. The inhalation class is set to Y for all compounds of zinc. Based on studies of zinc retention in mice, rats, dogs, and man, zinc leaving the blood is translocated to the skeleton (0.2) and to all other organs and tissues (0.8, uniformly). Material deposited in the skeleton is retained with a biological half-life of 400 days. A two-compartment model is used to describe retention in other organs and tissues. A fraction of 0.3 is retained with a biological half-life of 20 days and 0.7 with a biological half-life of 400 days.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides, but a significant risk could be obtained depending on the contamination level in the medium of exposure.

References:

International Commission on Radiological Protection (ICRP). 1980. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 2). *Annals of the ICRP*, Vol. 4, No. 3/4, Pergamon Press, New York, New York.

International Commission on Radiological Protection (ICRP). 1983. "Radionuclide Transformations: Energy and Intensity of Emissions." (ICRP Publication 38). *Annals of the ICRP*, Pergamon Press, New York, New York.

ZIRCONIUM-95

CASRN: 13967-71-0
Synonyms: None

Oral Slope Factor:	3.92E-12 risk/pCi ingested
Inhalation Slope Factor:	6.48E-12 risk/pCi inhaled
External Slope Factor:	2.81E-6 risk/yr per pCi/g soil

Radionuclide Decay Information (ICRP 1983):

Zirconium-95 has a radiological half-life of 63.98 days and undergoes beta decay to the radioactive isotopes niobium-95m (yield 0.00698) and niobium-95 (yield 0.993). Niobium-95m (86.6 hour half-life) decays by isomeric transition to niobium-95. Niobium-95 (35.15 day half-life) decays to the stable isotope molybdenum-95. The primary radiations from zirconium-95 are gamma rays of 0.72 and 0.76 MeV, and beta particles of average energy 0.11 and 0.12 MeV. Radiations from the radioactive niobium progeny will contribute to internal dose risk following intake of zirconium-95. The beta emissions from niobium-95 (average energy 0.043 MeV) and Auger electron emissions from niobium-95m (average energy less than 0.014 MeV) contribute slightly less to internal dose than the zirconium beta radiation. The HEAST (1994) slope factors for zirconium-95 do not account for the transient equilibrium contributions of niobium-95m or niobium-95.

Uptake, Distribution, and Retention in the Body (ICRP 1979):

The gastrointestinal absorption fraction is set to 0.002 for all compounds of zirconium. The inhalation class is set to Y for zirconium carbide, to class W for oxides, hydroxides, halides, and nitrates of zirconium, and to class D for all other compounds of zirconium. The HEAST (1994) slope factor for inhalation is based on inhalation class W. Zirconium entering the blood is assumed to be translocated to the skeleton (0.5) and to all other organs and tissues (0.5, uniformly). Material deposited in the skeleton is retained with a biological half-life of 8,000 days. Material in other organs and tissues is retained with a biological half-life of 7 days. Zirconium in the skeleton is assumed to be uniformly distributed over bone surfaces at all times following deposition.

Significant Exposure Routes:

The external-exposure slope factor is high relative to many other radionuclides indicating external exposure could represent a significant exposure pathway. The internal slope factors are not as high as many other radionuclides but a significant risk could be obtained depending on the contamination level in the medium of exposure. External exposure risk calculations should account for the ingrowth of progeny (niobium-95m and niobium-95) with time because these radionuclides contribute significantly to external dose following decay of the parent (over periods of several weeks or more).

References:

International Commission on Radiological Protection (ICRP). 1979. "Limits for Intakes of Radionuclides by Workers." (ICRP Publication 30, Part 1). *Annals of the ICRP*, Vol. 2, No. 3/4, Pergamon Press, New York, New York.

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