7.0 Human Health Effects

This section presents the human health benchmarks used to evaluate human health effects that may result from exposure to constituents modeled for this risk assessment. This includes presentation of the benchmark values used to characterize human health risks and the scientific basis for these values. A summary of the human health benchmarks is presented in Section 7.1. Section 7.2 summarizes epidemiological studies that have addressed possible human health effects associated with the operation of HWC facilities. Section 7.3 contains summaries of the scientific information supporting development of the human health benchmarks by EPA and other agencies. Particulate matter is discussed in Section 7.4.

7.1 Summary of Human Health Benchmarks

Table 7-1 summarizes the benchmark values used for each of the constituents evaluated in this risk assessment. The benchmarks fall into four categories:

- Oral cancer slope factor $(mg/kg\text{-}d)^{-1}$
- Inhalation cancer slope factor $(mg/kg\text{-}d)^{-1}$
- Reference dose (mg/kg-d)
- Reference concentration (mg/m^3).

The oral cancer slope factors, reference doses, and reference concentrations were obtained from IRIS (U.S. EPA, 1998), except for those values footnoted in the table. The inhalation cancer slope factors are not available on IRIS but were calculated for use in this risk assessment based on inhalation unit risk factors (Inhal URFs), which are available from IRIS. Summaries of the health effects data that form the basis for the benchmark values shown in Table 7-1, including unit risk factors that form the basis for the inhalation cancer slope factors, are provided in Section 7.3.

The inhalation cancer slope factors were developed to characterize cancer risks associated with inhalation exposures by adults and children. Because of the assumptions used in the development of the Inhal URFs, the Inhal URFs themselves could not be used directly to evaluate child exposure to human carcinogens. For this risk assessment, the Inhal URFs were converted to Inhal CSFs using the following equation:

$$\text{Inhal CSF } (mg/kg\text{-}d)^{-1} = \text{Inhal (URF) } (\mu g/m^3)^{-1} \bullet 70\ kg \div 20\ m^3/d \bullet 1{,}000\ \mu g/mg \qquad (7\text{-}1)$$

Table 7-1. Health Benchmark Values Used in Modeling

Chemical	Oral Cancer Slope Factor $(mg/kg\text{-}d)^{-1}$	Inhalation Cancer Slope Factor $(mg/kg\text{-}d)^{-1}$	Reference Dose (mg/kg-d)	Reference Concentration (mg/m^3)
Carcinogenic Effects				
Arsenic	1.5E+00	1.5E+01	3.0E-04	NA
Beryllium	NA	8.4E+00	2.0E-03	2.0E-05
Cadmium	NA	6.3E+00	1.0E-03	NA
Chromium VI	NA	4.2E+01	5.0E-03	NA
Nickel	NA	8.4E-01	2.0E-02	NA
2,3,7,8-TCDD	1.56E+05[a]	1.56E+05[a]	NA	NA
Noncancer Effects				
Antimony	NA	NA	4.0E-04	NA
Barium	NA	NA	7.0E-02	5.0E-04[b]
Chlorine	NA	NA	NA	1.0E-03[c]
Chromium III	NA	NA	1.0E+00	NA
Cobalt	NA	NA	6.0E-02	NA
Hydrogen chloride	NA	NA	NA	2.0E-02
Manganese	NA	NA	1.4E-01	5.0E-05
Lead	NA	NA	NA[d]	NA
Elemental mercury	NA	NA	NA	3.0E-04
Inorganic mercury	NA	NA	3.0E-04	NA
Methylmercury	NA	NA	1.0E-04	NA
Selenium	NA	NA	5.0E-03	NA
Silver	NA	NA	5.0E-03	NA
Thallium	NA	NA	8.0E-05	NA

NA = Not available.

[a] Provisional value from EPA's Health Effects Assessment for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (U.S. EPA, 1984).
[b] Provisional RfC from EPA's Health Effects Assessment Summary Tables (U.S. EPA, 1997b).
[c] Interim RfC developed for use in this HWC risk assessment.
[d] A lead blood level of 10 μg/dL was used as a benchmark for characterization of human health risks associated with lead exposure.

where

70 kg	=	default adult human body weight
20 m^3/d	=	default adult human daily rate of inhalation
1,000 μg	=	1 mg.

Particulate matter health effects were evaluated using concentration-response relationships that relate reductions in ambient concentrations of PM_{10} and $PM_{2.5}$ to avoided incidence of adverse health effects. The health effects data that form the basis for the PM evaluation are presented in Section 7.4.

7.2 Epidemiology Studies

This section summarizes the results of key epidemiologic studies that have been conducted on the adverse health effects from hazardous waste incinerator emissions. Most of these studies were not designed to examine individual pollutants; instead they investigated incinerator emissions in general.

Often epidemiologic studies of hazardous waste incinerators suffer from a variety of weaknesses. For example, because these studies generally lack exposure estimates for individuals, substantial exposure misclassification can occur due to exposure heterogeneity within the exposed population. Exposure misclassification is especially problematic for studies that use an ecologic study design, because persons who experience the disease outcome of interest may have been completely unexposed (e.g., they may have recently moved to the "exposed" community). Moreover, information on potential confounders (e.g., socioeconomic differences or occupational exposure differences between exposed and unexposed groups) is typically unavailable. For comparisons of chronic disease rates by exposure status, such as the cancer studies by Elliott et al. (1992, 1996), past exposures are more pertinent than are current exposures, but historical measurements are often lacking. Sometimes the facilities have closed so that exposure measurements are not possible. In addition, the small sample sizes associated with many of these studies yield imprecise results, especially for rare outcomes.

Various epidemiologic studies have investigated possible adverse health effects associated with incinerator emissions and environmental pollutants that can be found in incinerator emissions. Because of the problems associated with the interpretation of these epidemiologic studies, firm conclusions about exposure-disease relationships are difficult and often impossible. However, there is some evidence that cancer (especially stomach cancer), respiratory diseases, and reproductive effects may be associated with environmental pollutants from incinerator emissions. Although all of the epidemiologic studies reviewed suffered from some problems and often did not yield definitive results about health risks, these studies do target human populations exposed to environmental pollutants under real-world conditions.

7.2.1 Cancer

Elliot et al. (1992) found no evidence of increased laryngeal and lung cancer in communities in Great Britain exposed to emissions from incinerators of waste solvents and oils. However, the lag periods of 5 and 10 years used for defining the at-risk period may have been

too short to allow for a cancer excess to appear, and the exposure categorization did not take into account stack height, wind patterns, or emissions abatement equipment, so exposure misclassification appears likely. A subsequent study by Elliot et al. (1996) did find evidence of modest cancer excesses (stomach, colorectal, liver, and lung) that reached nominal statistical significance among persons living within 7.5 km of waste incinerators in Great Britain. The authors felt that residual confounding from socioeconomic differences may explain most of the cancer excess. As with the 1992 study, the 1996 study did not take into account stack height, wind patterns, or emissions abatement equipment. The study by Rapiti et al. (1997) also suggested a possible excess of stomach cancer among workers in a municipal waste incinerating plant in Rome who had worked at least 10 years at the facility. The authors noted that the study had low statistical power and that the workers were fairly young, but excess stomach cancer was found nonetheless. They indicated that exposure to bacterial toxins, low socioeconomic status, and nutritional factors may have contributed to the gastric cancer excess.

7.2.2 Respiratory Disease

Feigley et al. (1994) found evidence of increased respiratory symptoms among persons living near a hazardous waste incinerator, including a symptom (morning cough) reported in a similar study by Shy et al. (1995). Persons who expressed concern about health effects from hazardous waste incineration were more likely to report symptoms than were persons with less concern, so a reporting bias may have contributed to the difference between communities. Shy et al. (1995) found a small excess of some respiratory symptoms, but most symptoms showed no excess in the exposed population. Marth et al. (1995) presented fairly persuasive evidence that municipal and hospital waste incineration in Cairo may compromise certain types of immune system function that could increase the risk of bacterial and viral infections; there was also an increase in pulmonary allergic reactions among exposed children. However, that paper included no information about how the children were selected, and there is no information about the participation rate among children/families who were asked to participate, so possible selection bias is a concern.

7.2.3 Reproductive Effects

Using retrospective estimates of air pollution levels from two incineration plants, Williams et al. (1992) found that the only district with a statistically significant different sex ratio compared to the Scottish average was the district identified a priori as having the highest exposure level. Computer mapping of the sex ratios showed aberrations where pollution levels were expected to be relatively high. Lloyd et al. (1988) found evidence that community exposure to municipal waste and/or chemical waste incinerator emissions may increase the proportion of twin births in humans and cattle. However, there were no exposure measurements available for any members of the study population, and thus there is no assurance that persons living in the high-exposure areas actually were the ones who experienced the highest exposures or that mothers of twins on average had relatively high exposures.

In addition to the above problems, studies of incinerator emissions usually cannot ascertain possible health effects associated with the individual pollutants emitted from facilities because the study population is usually exposed to several pollutants simultaneously. This aspect of incinerator studies is not necessarily a weakness in that exposure-disease associations can be

estimated for the pollutant mixture, but attempts to identify safe levels for any given pollutant are difficult at best with these studies. On the other hand, multiple pollutants could have synergistic effects with regard to adverse health effects, and studies of individual pollutants at similar exposure levels could fail to detect hazards that are present in populations exposed to a pollutant mixture.

7.3 Constituent Health Effects

This section presents (in alphabetical order) health benchmarks and supporting information on 20 of the constituents evaluated in this risk assessment. Particulate matter is discussed separately in Section 7.4.

7.3.1 Antimony

7.3.1.1 Introduction. Antimony is found at very low levels throughout the environment. Soil usually contains very low concentrations of antimony (less than 1 ppm). However, higher concentrations have been detected at hazardous waste sites and at antimony processing sites. Food contains small amounts of antimony: the average concentration of antimony in meats, vegetables, and seafood is 0.2 to 1.1 ppb. There are many different antimony compounds that occur naturally or are manufactured chemicals. Antimony trioxide is one example; it is found naturally in the environment and may also be produced by oxidizing antimony sulfide ore or antimony metal in air at 600° to 800° C. The most common industrial use of antimony compounds is to produce antimony trioxide for fire retardation. Persons who work in industries that process antimony ore and metal or manufacture antimony trioxide may be exposed to antimony by breathing dust or by skin contact (ATSDR, 1992a).

7.3.1.2 Cancer Effects. Limited data are available on the carcinogenic effects of antimony. One study in humans did not report an increased incidence of cancer in workers exposed to antimony oxide in the workplace for 9 to 31 years. Animal studies have shown conflicting results. Several studies have reported an increase in lung tumors in rats exposed by inhalation to antimony trioxide and antimony trisulfide, while other studies did not report an increase in these tumors (ATSDR, 1992a).

EPA has not classified antimony or antimony trioxide for carcinogenicity and has not calculated a unit risk estimate for antimony (U.S. EPA, 1998).

7.3.1.3 Noncancer Effects. The primary effects from chronic (long-term) inhalation exposure to antimony in humans are respiratory effects that include antimony pneumoconiosis (inflammation of the lungs due to irritation caused by the inhalation of dust), alterations in pulmonary function, chronic bronchitis, chronic emphysema, inactive tuberculosis, pleural adhesions, and irritation. Other effects noted in humans chronically exposed to antimony by inhalation are cardiovascular effects (increased blood pressure, altered EKG readings, and heart muscle damage) and gastrointestinal disorders (ATSDR, 1992a).

Animal studies have reported lung, cardiovascular, liver, and kidney damage from exposure to high levels of antimony by inhalation. Exposure to lower levels has resulted in eye irritation, hair loss, lung damage, and cardiovascular effects (changes in EKGs). Reproductive

effects, including failure to conceive, were reported in rats exposed to antimony trioxide by inhalation (ATSDR, 1992a).

Reference Dose. The RfD for antimony is 4.0E-04 mg/kg-d, based on a LOAEL of 0.35 mg/kg-d, an uncertainty factor of 1,000, and a modifying factor of 1. The RfD was based on a study in which 50 male and 50 female rats were administered 5 ppm potassium antimony tartrate in water (Schroeder et al., 1970, as cited in U.S. EPA, 1998). Over the period of the study, growth rates of treated animals were not affected, but male rats survived 106 and females survived 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 and no increase in tumors was seen as a result of treatment. Since there was only one level of antimony administered, a NOAEL could not be established in the study. The concentration of 5 ppm antimony was expressed as an exposure of 0.35 mg/kg-d by the authors.

An uncertainty factor of 1000 was applied based on a tenfold factor for interspecies conversion, a tenfold factor to protect sensitive individuals, and an additional tenfold factor because the effect level was a LOAEL, and a NOAEL was not established (U.S. EPA, 1998).

EPA has low confidence in the study on which the RfD was based because only one species and one dose level were used, a NOAEL was not determined, and gross pathology and histopathology were not well described; low confidence in the database due to lack of adequate oral exposure investigations; and, consequently, low confidence in the RfD (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for antimony (U.S. EPA 1998). However, EPA has established an RfC for antimony trioxide of 2.0E-04 mg/m^3 based on a benchmark concentration (adjusted) of 0.074 mg/m^3, an uncertainty factor of 300, and a modifying factor of 1. This RfC was based on a study in which groups of 65 rats /sex/group were exposed to actual concentrations of 0, 0.06, 0.51, or 4.50 mg/m^3 antimony trioxide for 6 h/d, 5 d/wk for 1 year (Newton et al., 1994, as cited in U.S. EPA, 1998). No significant changes in hematological parameters were observed that were concentration related. An increase in cataracts was noted but a dose-response relationship was not observed. Microscopic lesions of the lungs revealed interstitial inflammation in control and exposure groups at the end of 6, 12, 18, and 24 months. This incidence was analyzed to determine a benchmark concentration. The concentrations associated with 1, 5, and 10 percent relative increases in the probability of response were estimated using both the Weibull and linear models. The lower 95 percent confidence limit for the 10 percent relative increase in probability of response was determined to be 0.87 mg/m^3 and a human equivalent concentration of 0.074 mg/m^3 was calculated (U.S. EPA, 1998).

An uncertainty factor of 300 was applied based on a tenfold factor for the protection of sensitive human subpopulations, a threefold factor for interspecies extrapolation because the dosimetric adjustments account for part of this area of uncertainty, a threefold uncertainty factor for lack of reproductive and developmental bioassays, and an additional threefold uncertainty factor to account for less-than-lifetime exposure duration, since there is no evidence that, at the lowest exposure level tested in the Newton et al. (1994) study, the levels of antimony in the rat reached a steady-state concentration (U.S. EPA, 1998).

EPA has medium confidence in the study on which the RfC was based because it was not a chronic, lifetime study; medium confidence in the database because no adequate developmental or reproductive studies are available, and consequently, medium confidence in the RfC (U.S. EPA, 1998).

Note: Risks from antimony trioxide were not evaluated in the model because HWCs are not expected to emit significant quantities of antimony trioxide based on thermodynamic considerations.

7.3.2 Arsenic

7.3.2.1 Introduction. Arsenic is a naturally occurring element in the earth's crust that is usually found combined with other elements. Arsenic combined with elements such as oxygen, chlorine, and sulfur is referred to as inorganic arsenic; arsenic combined with carbon and hydrogen is referred to as organic arsenic. In this health effects summary, arsenic refers to inorganic arsenic and its associated compounds. Organic arsenic compounds, such as arsine gas, are not discussed.

7.3.2.2 Cancer Effects. There is clear evidence that chronic exposure to inorganic arsenic in humans increases the risk of cancer. Studies have reported that inhalation of arsenic results in an increased risk of lung cancer. In addition, ingestion of arsenic has been associated with an increased risk of nonmelanoma skin cancer and bladder, liver, kidney, and lung cancer. No information is available on the risk of cancer in humans from dermal exposure to arsenic (U.S. EPA, 1998).

Animal studies have not clearly associated arsenic exposure, via ingestion exposure, with cancer. No studies have investigated the risk of cancer in animals as a result of inhalation or dermal exposure (U.S. EPA, 1998).

EPA has classified inorganic arsenic in Group A - Known Human Carcinogen. For arsenic, the Group A classification was based on the increased incidence in humans of lung cancer through inhalation exposure and the increased risk of skin, bladder, liver, kidney, and lung cancer through drinking water exposure (U.S. EPA, 1998).

An expert panel on arsenic carcinogenicity was convened by EPA in May 1997. They concluded that, “it is clear from epidemiological studies that arsenic is a human carcinogen via the oral and inhalation routes.” They also concluded that “one important mode of action is unlikely to be operative for arsenic” and that “the dose-response for arsenic at very low doses would likely be truly nonlinear, i.e., with a decreasing slope as the dose decreased. However, at very low doses such a curve might be linear with a very shallow slope, probably indistinguishable from a threshold” (U.S. EPA, 1998).

Inhalation Cancer Risk. EPA used the absolute-risk linear extrapolation model to estimate the inhalation unit risk for inorganic arsenic. Five studies on arsenic-exposed copper smelter workers were modeled for excess cancer risk (Brown and Chu, 1982, 1983a, 1983b; Enterline and Marsh, 1982; Higgins et al., 1982; Lee-Feldstein 1983; Welch et al., 1982). All five studies showed excess risks of lung cancer that were related to the intensity and duration of

exposure and the duration of the latency period. The estimates of unit risk obtained from the five studies were in reasonably good agreement, ranging from 1.25×10^{-3} to 7.6×10^{-3} $(\mu g/m^3)^{-1}$. Using the geometric mean of these data, EPA calculated an inhalation unit risk estimate of 4.3E-03 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1998).

EPA did not rank their confidence in the arsenic cancer risk estimate for inhalation exposure. However, EPA stated that the studies examined a large number of people, the exposure assessments included air measurements and urinary arsenic measurements, lung cancer incidence was significantly increased over expected values, and the range of the estimates from two different exposure areas was within a factor of 6 (U.S. EPA, 1998).

Oral Cancer Risk. To estimate the risks posed by ingestion of arsenic, EPA used the data that Tseng (1977) obtained in Taiwan concerning skin cancer incidence, age, and level of exposure via drinking water. In 37 villages that had obtained drinking water for 45 years from artesian wells with various elevated levels of arsenic, 40,421 individuals were examined for hyperpigmentation, keratosis, skin cancer, and blackfoot disease (gangrene of the extremities caused by injury to the peripheral vasculature). The local well waters were analyzed for arsenic, and the age-specific cancer prevalence rates were found to be correlated with both local arsenic concentrations and age (duration of exposure). EPA used these data to calculate a unit risk estimate for arsenic. It was assumed that Taiwanese persons had a constant exposure from birth and that males consumed 3.5 liters of drinking water per day and females consumed 2.0 liters per day. Doses were converted to equivalent doses for U.S. males and females based on differences in body weights and differences in water consumption, and it was assumed that skin cancer risk in the U.S. population would be similar to that in the Taiwanese population. The multistage model with time was used to predict dose-specific and age-specific skin cancer prevalence rates associated with ingestion of inorganic arsenic. EPA calculated an oral cancer slope factor of 1.5 E+00 $(mg/kg\text{-}d)^{-1}$ with a corresponding unit risk estimate of 5.0E-05 $(\mu g/L)^{-1}$ from oral exposure to arsenic in drinking water (U.S. EPA, 1998).

The Tseng (1977) cancer data have the following limitations: (1) total arsenic exposure was uncertain because of intake from the diet and other sources, (2) there was uncertainty as to the amount of water consumed per day by Taiwanese males, (3) temporal variability of arsenic concentrations in specific wells was not known, (4) there was uncertainty concerning exposure durations, and (5) fluorescent substances were found in the water that are possible confounders or could cause synergistic effects (U.S. EPA, 1998).

7.3.2.3 Noncancer Effects. The primary effect noted in humans from chronic exposure to arsenic, through both inhalation and oral exposure, are effects on the skin. The inhalation route has resulted primarily in irritation of the skin and mucous membranes (dermatitis, conjunctivitis, pharyngitis, and rhinitis), while chronic oral exposure has resulted in a pattern of skin changes that includes the formation of warts or corns on the palms and soles, along with areas of darkened skin on the face, neck, and back. Other effects noted from chronic oral exposure include peripheral neuropathy, cardiovascular disorders, liver and kidney disorders, and blackfoot disease. No information is available on effects in humans from chronic low-level dermal exposure to arsenic (ATSDR, 1993a).

No studies are available on the chronic noncancer effects of arsenic in animals, from inhalation or dermal exposure. Oral animal studies have noted effects on the kidney and liver (ATSDR, 1993a).

Reference Dose. EPA has established an RfD for inorganic arsenic of 3.0E-04 mg/kg-d, based on a NOAEL (adjusted to include arsenic exposure from food) of 0.0008 mg/kg-d, an uncertainty factor of 3, and a modifying factor of 1 (U.S. EPA, 1998). This was based on two studies (Tseng et al., 1968, and Tseng, 1977, as cited in U.S. EPA, 1998) that showed that the prevalence of blackfoot disease increased with both age and dose for individuals exposed to high levels of arsenic in drinking water. This same population also displayed a greater incidence of hyperpigmentation and skin lesions. Other human studies support these findings, with several studies noting an increase in skin lesions from chronic exposure to arsenic through the drinking water (Cebrian et al., 1983; Hindmarsh et al., 1977; Southwick et al., 1983, as cited in U.S. EPA, 1998).

An uncertainty factor of 3 was applied to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals (U.S. EPA, 1998).

EPA has medium confidence in the studies on which the RfD was based, in the database, and in the RfD. The key studies were extensive epidemiologic reports that examined effects in a large number of people. However, doses were not well-characterized, other contaminants were present, and potential exposure from food or other sources was not examined. The supporting studies suffer from other limitations, primarily the small populations studied. However, the general database on arsenic does support the findings in the key studies; this was the basis for EPA's "medium confidence" ranking of the RfD (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for inorganic arsenic (U.S. EPA, 1998).

7.3.3 Barium

7.3.3.1 Introduction. Barium is a naturally occurring element that is found in the earth's crust. Barium enters the environment primarily through the weathering of rocks and minerals. The general population is exposed to barium usually at low levels, through consumption of drinking water and foods. Barium and its compounds are used in automotive paints, stabilizers for plastics, and jet fuel (ATSDR, 1990a).

7.3.3.2 Cancer Effects. Limited human data are available on the carcinogenicity of barium. The only available studies involve a single topical application of barium chloride to the cervix of one woman. These studies reported a number of cell transformations in the cervix; however, 1 to 2 weeks after the application, these cellular alterations were no longer observed (U.S. EPA, 1998).

Two chronic oral animal studies evaluated the carcinogenicity of barium in rats and mice. No statistically significant increases in the incidences of tumors were observed in the barium-exposed rats (U.S. EPA, 1998).

EPA has classified barium in Group D - Not Classifiable as to Human Carcinogenicity. This was based on the availability of adequate chronic oral studies in rats and mice that have not demonstrated carcinogenic effects but a lack of adequate inhalation studies (U.S. EPA, 1998).

EPA has not calculated a unit risk estimate for barium (U.S. EPA, 1998).

7.3.3.3 Noncancer Effects. Hypertension has been noted in humans who ingested high doses of barium and workers who inhaled dusts of barium ores and barium carbonate (U.S. EPA, 1998). Other effects noted in humans from chronic exposure include musculoskeletal effects, such as progressive muscle weakness, and neurological effects, including numbness and tingling around the mouth and neck (ATSDR, 1990a).

Chronic, oral exposure to barium in experimental animals has resulted in increases in blood pressure and kidney effects (ATSDR, 1990a; U.S. EPA, 1998).

Reference Dose. EPA has calculated an RfD for barium of 7.0E-02 mg/kg-d based on a NOAEL (adjusted) of 0.21 mg/kg-d, an uncertainty factor of 3, and a modifying factor of 1. This was based on several epidemiological studies that investigated the effects of elevated levels of barium in drinking water (Brenniman and Levy, 1984; Wones et al., 1990, as cited in U.S. EPA, 1998). Wones et al. (1990) found no increases in systolic or diastolic blood pressure in subjects who consumed drinking water containing barium at levels ranging from 0 to 10 mg/L for 10 weeks. Brenniman and Levy (1984) conducted a retrospective epidemiology study that compared 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 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 or use of water softeners or medication. In addition, several rat studies that reported increased kidney weights in rats exposed to barium in drinking water for 13 weeks or 2 years were considered (NTP, 1994, as cited in U.S. EPA, 1998). NOAELs of 45 and 65 mg/kg-d were selected from these studies (U.S. EPA, 1998).

An uncertainty factor of 3 was applied to account for potential differences between adults and children and the existence of adequate developmental toxicity studies (U.S. EPA, 1998).

EPA has medium confidence in the principal studies used as the basis for the RfD because LOAELs for cardiovascular and kidney disease were not identified in the human studies. However, the animal studies provided information regarding NOAELs and LOAELs for kidney effects of barium, but cardiovascular effects did not occur in these studies. EPA has medium confidence in the database because of the existence of subchronic and chronic human studies, suchronic and chronic animal studies in more than one species, and a reproductive/developmental study in rats and mice. EPA has medium confidence in the RfD as well (U.S. EPA, 1998).

Reference Concentration. EPA has not calculated an RfC for barium (U.S. EPA, 1998). However, EPA has calculated a provisional RfC of 5.0E-04 mg/m^3 for barium (U.S. EPA, 1997b). This was based on a 4-month reproductive study in rats in which a NOAEL of 0.8 mg/m^3 was selected (Tarasenko et al. 1977, as cited in U.S. EPA, 1997b).

7.3.4 Beryllium

7.3.4.1 Introduction. Pure beryllium is a hard gray metal that does not occur naturally but does occur as a chemical component of certain kinds of rocks, coal and oil, soil, and volcanic dust. Two kinds of mineral rocks, bertrandite and beryl, are mined commercially for the recovery of beryllium. Beryllium is also found combined with other elements such as fluoride, chlorine, sulfur, oxygen, and phosphorus (ATSDR, 1993b).

7.3.4.2 Cancer Effects. Several human epidemiological studies have shown increases in lung cancer in beryllium-processing workers (U.S. EPA, 1998).

Beryllium compounds have been shown to cause lung cancer in rats and monkeys from inhalation exposure and lung tumors in rats exposed by intratracheal instillation. Osteosarcomas have been produced in rabbits and in mice by intravenous and intramedullary injection. Oral exposure to beryllium in animals has not resulted in a statistically significant increased incidence of tumors (U.S. EPA, 1998).

EPA has classified beryllium in Group B1 - Probable Human Carcinogen. This classification was based on limited evidence of lung cancer in humans exposed to airborne beryllium and sufficient evidence of carcinogenicity in animals (lung cancer in rats and monkeys inhaling beryllium, lung tumors in rats exposed via intratracheal instillation, and osteosarcomas in rabbits and possibly mice receiving intravenous injection) (U.S. EPA, 1998).

Inhalation Cancer Risk. EPA used the relative risk extrapolation model, based on an epidemiologic study (Wagoner et al., 1980, as cited in U.S. EPA, 1998) to estimate the inhalation unit cancer risk for beryllium. EPA calculated an inhalation unit risk estimate of 2.4 E-03 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1998).

This cancer risk estimate was based on an epidemiologic study having several confounding factors, including the lack of individual exposure monitoring or job history data. Newer studies are currently under peer review and may be used in the future by EPA to derive a revised unit risk estimate (U.S. EPA, 1998).

Oral Cancer Risk. EPA has not calculated an oral unit risk estimate for beryllium because the oral database is considered inadequate for the assessment of carcinogenicity (U.S. EPA, 1998).

7.3.4.3 Noncancer Effects. The major effect from chronic inhalation exposure to beryllium in humans is chronic beryllium disease (berylliosis), in which granulomatous lesions (noncancerous) develop in the lung. The onset of these effects may be delayed by 3 months to more than 20 years. Symptoms of chronic beryllium disease include irritation of the mucous membranes, reduced lung capacity, shortness of breath, fatigue, anorexia, dyspnea, malaise, and weight loss. Chronic beryllium disease may cause death in severe cases. No information is available on the effects of beryllium in humans from chronic oral exposure; a skin allergy may result from chronic dermal exposure to beryllium (ATSDR, 1993b).

Animal studies have also reported effects on the lung, such as chronic pneumonitis, from chronic inhalation exposure to beryllium. Effects on the adrenal gland and immune system have been noted in animals chronically exposed by inhalation. No effects were observed in the lung, heart, blood, liver, or kidney from chronic oral exposure to beryllium in animals. Chronic dermal exposure to beryllium in animals has resulted in effects on the immune system (ATSDR, 1993b).

Reference Dose. EPA has established an RfD for beryllium of 2.0E-03 mg/kg-d, based on a benchmark dose of 0.46 mg/kg-d, an uncertainty factor of 300, and a modifying factor of 1 (U.S. EPA, 1998). This was based on a study (Morgareidge et al., 1976, as cited in U.S. EPA, 1998) in which groups of five male and five female beagle dogs were fed diets containing 0, 5, 50, or 500 ppm beryllium for 172 weeks. Lesions in the small intestine and hypoplasia of the bone marrow were observed. Dose-response modeling of the data for small intestinal lesions in dogs was used to determine a benchmark dose.

An uncertainty factor of 300 was applied based on a tenfold factor for extrapolation for interspecies differences, a tenfold factor for intraspecies variation, and a threefold factor for database deficiencies (U.S. EPA, 1998).

EPA has medium confidence in the study on which the RfD was based, because the study was administered by a relevant route (oral), at multiple dose levels, and for a chronic duration. However, there were a small number of animals, early mortality at the high-dose level, and no measure of immune response or function. EPA has low to medium confidence in the database because there is only one chronic study in dogs showing adverse effect levels; other chronic studies in rodents demonstrated NOAELs at the highest doses tested; consequently, EPA has low-to-medium confidence in the RfD (U.S. EPA, 1998).

EPA also stated that the major areas of scientific uncertainty in the RfD assessment are the lack of chronic oral studies establishing LOAELs, the lack of a chronic oral study examining immunologic endpoints, the lack of critical effects in humans by inhalation as identified in dogs and the lack of sensitive indicators for rickets, the lack of reproductive and developmental studies, and the lack of human toxicity information (U.S. EPA, 1998).

Reference Concentration. EPA has established an RfC for beryllium of 2.0E-05 mg/m^3 based upon two human studies that examined beryllium sensitization and progression to chronic beryllium disease (Kreiss et al., 1996; Eisenbud et al., 1949, as cited in U.S. EPA, 1998). A LOAEL (human equivalent concentration) of 0.20 $\mu g/m^3$ was identified from the Kreiss et al. (1996) study and a NOAEL (human equivalent concentration) of 0.01 to 0.1 $\mu g/m^3$ was identified from the Eisenbud et al. (1949) study. An uncertainty factor of 10 and a modifying factor of 1 were applied (U.S. EPA, 1998).

Kreiss et al. (1996) examined beryllium workers in a plant that made beryllia ceramics from beryllium oxide powder. The study found an increased beryllium sensitization rate among machinists exposed to an average concentration of beryllium of 0.55 $\mu g/m^3$. Eisenbud et al. (1949) evaluated beryllium exposure for 11 cases of chronic beryllium disease in a community located near a beryllium production plant.

An uncertainty factor of 10 was applied based on a threefold uncertainty factor to account for the poor quality of exposure monitoring in the co-principal studies and other epidemiology studies that assessed the incidence of beryllium sensitization and chronic beryllium disease among exposed workers and community residents, and an additional threefold uncertainty factor was applied to account for the sensitive nature of the endpoint (beryllium sensitization) (U.S. EPA, 1998).

EPA has medium confidence in the study on which the RfC was based because it is an occupational study performed on a moderate-to-large-sized group in which sensitive measures were used to identify the affected population. However, there was poor quality monitoring in the co-principal studies. EPA also has medium confidence in the database due to a lack of adequate exposure monitoring in the epidemiology studies, and some uncertainty regarding the mechanisms associated with the progression to chronic beryllium disease in beryllium-sensitized individuals. Confidence in the RfD was also medium, reflecting the other classifications (U.S. EPA, 1998).

7.3.5 Cadmium

7.3.5.1 Introduction. Cadmium is a soft, silver-white metal that occurs naturally in the earth's crust and is usually found in combination with other elements such as oxygen, chlorine, or sulfur. The major uses of cadmium are in the manufacture of pigments and batteries and in the metal-plating and plastics industries. Most of the cadmium used in this country is obtained as a byproduct from the smelting of zinc, lead, or copper ores (ATSDR, 1997a).

7.3.5.2 Cancer Effects. Several occupational studies have reported an excess risk of lung cancer from exposure to inhaled cadmium. However, the evidence is limited rather than conclusive due to confounding factors such as the presence of other carcinogens and smoking. Studies of human ingestion to cadmium are inadequate to assess its carcinogenicity (U.S. EPA, 1998).

Animal studies have reported lung cancer resulting from inhalation exposure to several forms of cadmium, while animal ingestion studies have not reported cancer from exposure to cadmium compounds (U.S. EPA, 1998).

EPA has classified cadmium in Group B1 - Probable Human Carcinogen based on human studies showing a possible association between cadmium exposure and lung cancer, and animal studies showing an increased incidence of lung cancer (U.S. EPA, 1998).

Inhalation Cancer Risk. EPA used the two-stage extrapolation model based on data from an occupational study of workers exposed to cadmium (Thun et al., 1985, as cited in U.S. EPA, 1998) to estimate the inhalation unit risk estimate for cadmium. EPA calculated an inhalation unit risk estimate of 1.8E-03 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1998).

EPA used human data to develop the risk estimate for cadmium because the data were derived from a relatively large cohort, and the effects of arsenic and smoking were accounted for in the quantitative analysis of cadmium's effects. EPA also calculated an inhalation unit risk of 9.2×10^{-2} $(\mu g/m^3)^{-1}$ for cadmium based on animal data (Takenda et al., 1983, as cited in U.S. EPA, 1998). This estimate was higher than that derived from human data and thus more conservative. However, EPA felt that the use of the available human data was more reliable because of species variations in response and the type of exposure (U.S. EPA, 1998).

Oral Cancer Risk. EPA has not calculated an oral unit risk estimate for cadmium (U.S. EPA, 1998).

7.3.5.3 Noncancer Effects. The kidney appears to be the main target organ in humans following chronic inhalation exposure to cadmium. Abnormal kidney function, indicated by proteinuria and a decrease in glomerular filtration rate, and an increased frequency of kidney stone formation are some of the effects noted. Respiratory effects, such as bronchitis and emphysema, have also been noted in humans chronically exposed to cadmium through inhalation. Oral exposure to cadmium in humans also results in effects on the kidney, with effects similar to those seen following inhalation exposure. In humans, dermal exposure to cadmium does not appear to cause allergic reactions (ATSDR, 1997a).

Animal studies have reported effects on the kidney, liver, lung, and blood from chronic inhalation exposure to cadmium. Chronic oral exposure to cadmium in animals results in effects on the kidney, bone, immune system, blood, and nervous system. No information is available on chronic dermal exposure to cadmium in animals (ATSDR, 1997a).

Reference Dose. EPA has established two RfDs for cadmium: one for cadmium ingested in drinking water and one for cadmium ingested in food. The RfD for cadmium in drinking water is 5.0E-04 mg/kg-d and the RfD for dietary exposure to cadmium is 1.0E-03 mg/kg-d. These RfDs were based on a number of human studies that showed kidney effects (significant proteinuria) from chronic exposure to cadmium. Both RfDs were calculated based on the highest level of cadmium in the human renal cortex (200 µg/g) that was not associated with the critical effect, i.e., significant proteinuria (U.S. EPA, 1985, as cited in U.S. EPA, 1998). A toxicokinetic model was then used to determine the NOAEL. This model took into account the difference in absorption between drinking water and food. The NOAELs for water and food were calculated to be 0.005 mg/kg-d and 0.01 mg/kg-d, respectively. The RfDs were calculated by applying an uncertainty factor of 10 and a modifying factor of 1 to each NOAEL (U.S. EPA, 1998).

An uncertainty factor of 10 was applied to account for intrahuman variability to the toxicity of cadmium in the absence of data on sensitive individuals (U.S. EPA, 1998).

EPA has high confidence in the studies and the database on which the RfDs were based. The RfDs were not based on a single study, but rather on data obtained from many studies on the toxicity of cadmium in humans and animals. These data permit calculation of pharmacokinetic parameters of cadmium absorption, distribution, metabolism, and elimination (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for cadmium.

7.3.6 Chlorine

7.3.6.1 Introduction. Chlorine is a greenish-yellow gas that has a suffocating odor. In water, chlorine reacts to form hypochlorous acid and hypochlorite ion. Chlorine is added to drinking water for disinfection purposes and is also used as an intermediate in the manufacture and preparation of a number of products, such as antifreeze, cleaning agents, and pharmaceuticals (U.S. EPA, 1994a).

7.3.6.2 Cancer Effects. No information is available on the carcinogenic effects of chlorine in humans from inhalation exposure. Several human studies have investigated the relationship between exposure to chlorinated drinking water and cancer. These studies were not designed to assess whether chlorine itself causes cancer, but whether trihalomethanes or other organic compounds occurring in drinking water are associated with an increased risk of cancer. These studies show an association between bladder and rectal cancer and chlorinated byproducts in drinking water (U.S. EPA, 1994a).

Chlorine has not been found to be carcinogenic in animals. No tumors were found in rats exposed to chlorine in their drinking water over their lifetime (U.S. EPA, 1994a).

EPA has not classified chlorine for carcinogenicity or calculated a unit risk estimate for chlorine (U.S. EPA, 1998).

7.3.6.3 Noncancer Effects. Chlorine is a potent irritant in humans to the eyes, upper respiratory tract, and the lung. It is also extremely irritating to the skin and can cause severe burns (U.S. EPA, 1994a).

Animal studies have reported decreased body weight gain, eye and nose irritation, and effects on the respiratory tract, liver, and kidney from inhalation exposure to chlorine. No significant effects have been observed in animal studies from oral exposure to chlorine (U.S. EPA, 1994a).

Acute Toxicity Value. EPA proposed an acute toxicity value of 0.5 ppm for chlorine. This value was derived based on data in human volunteers in which no significant sensory irritation or pulmonary effects were associated with 4- or 8-h exposures to 0.5 ppm chlorine (Talmage, 1996; Rotman et al., 1983). The dose-response relationship for irritant gases follows the following equation:

$$C^n \times t = k,$$

where C = concentration, time is time, and k is a constant. For chlorine, n = 2 (ten Berge et al., 1986). Uncertainty factors were not applied since a no-effect-level was identified in humans.

EPA has high confidence in the acute toxicity values for chlorine because the study in human volunteers was well conducted and well documented. In addition, both sensory irritation and pulmonary function parameters were measured in both males and females. Also, the exposure concentrations were measured by several different methods and all of them gave similar results.

Reference Dose. EPA has not established an RfD for chlorine.

Reference Concentration. EPA has not calculated an RfC for chlorine. However, an interim chronic RfC for chlorine of 0.001 mg/m^3 has been calculated based on a lifetime inhalation study in rats and mice (Wolf et al., 1995). In this study, groups of male and female rats and mice were exposed to 0, 0.4, 1.0, or 2.5 ppm chlorine gas for 6 hours per day, 5 days per week (mice and male rats) or 3 days per week (female rats) for 2 years. The study reported several exposure-dependent lesions of the nasal passages in all sex and species groups, including respiratory and olfactory epithelial degeneration, septal fenestration, mucosal inflammation, respiratory epithelial hyperplasia, squamous metaplasia, and other effects. No effects were observed in the larynx or lower respiratory tract (Wolf et al., 1995). Although several statistically significant effects were reported at the lowest exposure concentration, the severity of the lesions were generally judged to be slight to minimal. The changes seen at the lowest exposure concentration are of questionable clinical significance; therefore, 0.4 ppm (1.2 mg/m^3) was considered a NOAEL in mice.

The NOAEL was adjusted for duration of exposure ($NOAEL_{ADJ}$). The $NOAEL_{ADJ}$ was converted to a human equivalent concentration NOAEL ($NOAEL_{HEC}$) based on effects in the extrathoracic region by a category 1 gas in accordance with EPA (1994d) guidelines (equation 4-18 in U.S. EPA, 1994d). A $NOAEL_{HEC}$ of 0.04 mg/m^3 was calculated. An uncertainty factor (UF) of 30 was applied based on a factor of 3 for interspecies extrapolation and a factor of 10 to account for sensitive individuals, resulting in an interim RfC of 0.001 mg/m^3. These calculations were performed as shown below:

$NOAEL_{ADJ}$ = 1.2 mg/m^3 x 6 h/24 h x 5 d/7 d = 0.21 mg/m^3.

$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x RGDR
= $NOAEL_{ADJ}$ x $[V_E/SA_{ET}]_A/[V_E/SA_{ET}]_H$
= 0.21 mg/m^3 x [0.06 /3]/[20/200] = 0.04 mg/m^3

where RGDR = regional gas dose ratio, V_E = minute volume, and SA_{ET} = surface area of extrathoracic region (ET) for the mouse (A) and human (H). $(V_E)_A$ = 0.06 m^3/d, $(V_E)_H$ = 20 m^3/d, $(SA_{ET})_A$ = 3 cm^2, $(SA_{ET})_H$ = 200 cm^2 (U.S. EPA 1994d).

interim RfC = $NOAEL_{HEC}$ ÷ UF = 0.04 mg/m^3 ÷ 30 = 0.001 mg/m^3

EPA has low confidence in the interim chronic RfC for chlorine because tissue dosimetry and susceptibility differences in rodents complicate extrapolation from animal results to humans. There are also some questions regarding the significance of the effects reported and whether or not the low dose should be considered a NOAEL or LOAEL.

7.3.7 Chromium

7.3.7.1 Introduction. Chromium is a metallic element that occurs in the environment in two major valence states: trivalent chromium (chromium III) and hexavalent chromium (chromium VI). Chromium (VI) compounds are much more toxic than chromium (III) compounds; chromium (III) is an essential element in humans, with a daily intake of 50 to

200 µg/d recommended for an adult. Chromium (VI) is quite toxic; however, the human body can detoxify some amount of chromium (VI) to chromium (III) (ATSDR, 1993c).

7.3.7.2 Cancer Effects. Epidemiological studies of workers have clearly established that inhaled chromium is a human carcinogen, resulting in an increased risk of lung cancer. These studies were not able to differentiate between exposure to chromium (III) and chromium (VI) compounds. No information is available on cancer in humans from oral or dermal exposure to chromium (ATSDR, 1993c; U.S. EPA 1998).

Animal studies have shown chromium (VI) to cause lung tumors via inhalation exposure. No studies are available that investigated cancer in animals from oral or dermal exposure to chromium (VI). Chromium (III) has been tested in mice and rats by the oral route, with several studies reporting no increase in tumor incidence. No studies are available on cancer in animals from inhalation or dermal exposure to chromium (III) (ATSDR, 1993c; U.S. EPA, 1998).

EPA has classified chromium (VI) in Group A -Known Human Carcinogen, because results of occupational epidemiologic studies show a dose-response relationship for chromium exposure and lung cancer. Since the human studies could not differentiate between chromium (III) and chromium (VI) exposure and only chromium (VI) was found to be carcinogenic in animal studies, EPA concluded that only chromium (VI) should be classified as a human carcinogen (U.S. EPA, 1998). EPA has not classified chromium (III) for carcinogenicity (U.S. EPA, 1998).

Inhalation Cancer Risk. EPA used the multistage extrapolation model, based on data from an occupational study of chromate production workers (Mancuso, 1975, as cited in U.S. EPA, 1998) to estimate the unit cancer risk for chromium (VI). EPA calculated an inhalation unit risk estimate of 1.2E-02 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1998). EPA has not calculated a risk estimate from inhalation exposure to chromium (III) (U.S. EPA, 1998).

EPA has confidence in the risk estimate for chromium (VI) because results of studies of chromium exposure are consistent across investigators and countries, and a dose-response for lung tumors has been established. However, an overestimation of risk may be due to the implicit assumption that the smoking habits of chromate workers were similar to those of the general white male population, since it is generally accepted that the proportion of smokers is higher for industrial workers than for the general population (U.S. EPA, 1998).

Oral Cancer Risk. EPA has not calculated a risk estimate from oral exposure to chromium (VI) or chromium (III) (U.S. EPA, 1998).

7.3.7.3 Noncancer Effects. Chronic inhalation exposure to chromium (VI) in humans results in effects on the respiratory tract, with perforations and ulcerations of the septum, bronchitis, decreased pulmonary function, pneumonia, asthma, and nasal itching and soreness reported. Chronic exposure to high levels of chromium (VI) by inhalation or oral exposure may also produce effects on the liver, kidney, gastrointestinal and immune systems, and possibly the blood. Dermal exposure to chromium (VI) may cause contact dermatitis, sensitivity, and ulceration of the skin (ATSDR, 1993c).

Limited information is available on the chronic effects of chromium in animals. The available data indicate that, following inhalation exposure, the lung and kidney have the highest tissue levels of chromium. No effects were noted in several oral animal studies with chromium (VI) and chromium (III) (ATSDR, 1993c).

Reference Dose. EPA has established an RfD for chromium (VI) of 5.0E-03 mg/kg-d, based upon a NOAEL (adjusted) of 2.4 mg/kg-d, an uncertainty factor of 500, and a modifying factor of 1 (U.S. EPA, 1998). This was based on a study in rats (MacKenzie et al., 1958, as cited in U.S. EPA, 1998) that reported no adverse effects after exposure to chromium (VI) in the drinking water for 1 year. Other studies support these findings; one study reported no significant effects in female dogs given chromium (VI) in the drinking water for 4 years and a case study in humans reported no adverse health effects in a family of four who drank water for 3 years from a private well containing chromium (VI) at 1 mg/L (U.S. EPA, 1998).

An uncertainty factor of 500 was applied based on two tenfold factors to account for both the expected interhuman and interspecies variability in the toxicity of the chemical in lieu of specific data and an additional fivefold factor to compensate for the less-than-lifetime exposure duration of the principal study (U.S. EPA, 1998).

EPA has low confidence in the study on which the RfD for chromium (VI) was based, in the database, and in the RfD. Confidence in the key study was ranked low due to the small number of animals tested, the small number of parameters measured, and the lack of toxic effects at the highest dose tested. Confidence in the database was also ranked low because the supporting studies are of equally low quality and teratogenic and reproductive endpoints are not well studied, thus a low confidence in the RfD follows (U.S. EPA, 1998).

The RfD for chromium (III) is 1.0E+00 mg/kg-d, based on a NOAEL (adjusted) of 1,468 mg/kg-d, an uncertainty factor of 1,000, and a modifying factor of 1 (U.S. EPA, 1998). This was based on no effects observed in rats fed chromium (III) in the diet for 2 years (Ivankovic and Preussman, 1975, as cited in U.S. EPA, 1998). In this study, groups of 60 male and female rats were fed chromic oxide in the diet for 600 feedings. All major organs were examined histologically, and no effects due to chromium treatment were observed at any dose level. This study also included a 90-day study, where the only effects observed were reductions in the absolute weights of the livers and spleens in animals in the high-dose group.

An uncertainty factor of 1,000 was applied based on two tenfold factors to account for both the expected interhuman and interspecies variability in the toxicity of the chemical in lieu of specific data, and an additional tenfold factor was applied to reflect uncertainty in the NOAEL because the effects observed in the 90-day study were not explicitly addressed in the 2-year study, the absorption of chromium is low, the animals were allowed to die naturally after feeding stopped (2 years), and only then was histology performed (U.S. EPA, 1998).

EPA has low confidence in the study on which the RfD was based, in the database, and in the RfD. The low ranking of the key study was due to the lack of explicit detail on study protocol and results, the low ranking of the database was due to the lack of supporting data, and the low ranking of the RfD was due to the lack of an observed effect level in the key study (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for chromium (III) or chromium (VI) (U.S. EPA, 1998).

7.3.8 Cobalt

7.3.8.1 Introduction. Cobalt occurs naturally in the environment in most rocks, soil, water, plants, and animals. Cobalt is used in superalloys, magnetic alloys, and cutting- and water-resistant alloys, as a drier in paint, a catalyst, for porcelain enameling of steel bathroom fixtures and appliances, in pigment manufacture, and as a feed and nutritional additive. Cobalt is an essential element in humans and animals as a constituent of vitamin B_{12}. Cobalt has also been used as a treatment for anemia, because it stimulates red blood cell production (ATSDR, 1992b; NLM, 1999).

7.3.8.2 Cancer Effects. Limited data are available on the carcinogenic effects of cobalt. In one study on workers who refined and processed cobalt and sodium, an increase in deaths due to lung cancer was found for workers exposed only to cobalt. However, when this study was controlled for date of birth, age at death, and smoking habits, the difference in deaths due to lung cancer was found not to be statistically significant. In another study assessing the correlation between cancer deaths and trace metals in water supplies in the United States, no correlation was found between cancer mortality and the level of cobalt in the water (ATSDR, 1992b).

In an animal study, inhalation of cobalt over a lifetime did not increase the incidence of tumors in hamsters. Cobalt, via direct injection (intramuscular and subcutaneous under the muscles or skin) has been reported to cause tumors at the injection site in animals (ATSDR, 1992b; NLM, 1999).

EPA has not classified cobalt for carcinogenicity or calculated a unit risk estimate for cobalt.

7.3.8.3 Noncancer Effects. Acute exposure to cobalt in humans has been reported to result in cough, dyspnea, decreased pulmonary function, weight loss, diffuse nodular fibrosis, and respiratory hypersensitivity. Contact with cobalt in humans has resulted in dermatitis, with eruptions of the erythematous papular type on the ankles, elbows, and neck (NLM, 1998).

Chronic exposure to cobalt by inhalation in humans also results in effects on the respiratory system, such as respiratory irritation, wheezing, asthma, pneumonia, and fibrosis. Other effects noted from inhalation exposure to cobalt in humans include cardiac effects, such as functional effects on the ventricles and enlargement of the heart; congestion of the liver, kidneys, and conjunctiva; and immunological effects that include cobalt sensitization, which can precipitate an asthmatic attack in sensitized individuals (ATSDR, 1992b).

Cardiovascular effects (cardiomyopathy) were observed in people who consumed large amounts of beer over several years containing cobalt sulfate as a foam stabilizer. The effects were characterized by cardiogenic shock, sinus tachycardia, left ventricular failure, and enlarged hearts. Gastrointestinal effects (nausea, vomiting, and diarrhea), effects on the blood, liver injury, and allergic dermatitis have also been reported in humans from oral exposure to cobalt (ATSDR, 1992b).

Animal studies have reported decreased body weight, necrosis of the thymus, and effects on the blood, liver, kidneys, and respiratory, cardiovascular, and central nervous system from inhalation exposure to cobalt (ATSDR, 1992b). Acute oral cobalt toxicity has been demonstrated in some animals; at doses higher than 5 mg/kg of diet/day in chickens and sheep, loss of appetite, loss of weight, and debilitation were observed (NLM, 1999).

Reference Dose. EPA has established a provisional RfD for cobalt of 6.0E-2 mg/kg/d based on the upper range of average intake in children, which is below the levels of cobalt necessary to induce polycythemia in either renally compromised patients or normal patients (U.S. EPA, nd).

Reference Concentration. EPA has not established an RfC for cobalt.

7.3.9 Copper

7.3.9.1 Introduction. Copper occurs naturally in rock, soil, water, sediment, and air and is an essential element for humans. It is extensively mined and processed in the United States and is primarily used as the metal or alloy in the manufacture of wire and sheet metal, in agriculture to treat plant diseases, and as a preservative for wood, leather, and fabrics (ATSDR, 1989).

7.3.9.2 Cancer Effects. An increased incidence of cancer has not been observed in humans or animals exposed to copper via inhalation, oral, or dermal routes (ATSDR, 1989). In laboratory animal studies, two strains of mice administered copper for 53 weeks failed to show any evidence of statistically significant increases in tumor incidence (U.S. EPA, 1998).

EPA has classified copper in Group D - Not Classifiable as to Human Carcinogenicity, based on no human data, inadequate animal data, and equivocal mutagenicity data (U.S. EPA, 1998).

7.3.9.3 Noncancer Effects. The majority of information on copper toxicity in humans involves the consumption of water contaminated with high levels of copper or suicide attempts using copper sulfate. Effects observed in humans include gastrointestinal, hepatic, and immunological (from dermal exposure) and respiratory effects (from inhalation exposure). An example of significant (but rare) copper toxicity in humans is Wilson's Disease, an autosomal recessive disorder that affects normal copper homeostasis. The disease is characterized by excessive retention of hepatic copper, decreased concentration of plasma ceruloplasmin, and impaired biliary excretion (ATSDR, 1989).

Longer-term or chronic human exposure to copper has been associated with a number of effects including metal fume fever and enlarged livers and spleens. Metal fume fever is characterized by chills, fever, aching muscles, dryness in the mouth and throat, and headaches that last for 1 or 2 days. Anorexia, nausea, and occasional diarrhea in factory workers exposed to high concentrations of airborne copper have also been reported (ATSDR, 1989).

The effects observed in animals from exposure to high levels of copper include gastrointestinal, hepatic, hematologic, immunologic, and developmental effects (ATSDR, 1989).

Copper is an essential dietary nutrient for which a recommended daily allowance (RDA) has been developed. Copper is needed for human hemoglobin formation, carbohydrate metabolism, catecholamine biosynthesis, and cross-linking of collagen, elastin, and hair keratin. Copper is also essential for incorporation into copper-dependent enzymes. An RDA of 2 to 3 mg copper/d is recommended by the National Academy of Sciences (ATSDR, 1989).

EPA has not established an RfC or RfD for copper (U.S. EPA, 1998).

7.3.10 Hydrogen Chloride

7.3.10.1 Introduction. Hydrogen chloride (liquid) is an aqueous solution of hydrogen chloride gas and is commercially available in several concentrations and purities. Because of impurities, commercial varieties of hydrogen chloride are generally yellow. Hydrogen chloride is used in the refining of metal ore, as a lab reagent, and in the removal of scale from boilers (Budavari, 1989).

7.3.10.2 Cancer Effects. No information is available on the carcinogenic effects of hydrogen chloride in humans or animals. EPA has not classified hydrogen chloride for carcinogenicity (U.S. EPA, 1998).

7.3.10.3 Noncancer Effects. The acute effects on humans exposed by inhalation to hydrogen chloride include coughing, choking, and inflammation and ulceration of the respiratory tract, chest pain, and pulmonary edema. Oral exposure may result in corrosion of the mucous membranes, esophagus, and stomach, with nausea, vomiting, intense thirst, and diarrhea. Dermal contact with hydrogen chloride can cause burns, ulcerations, and scarring. Cases of gastritis, chronic bronchitis, dermatitis, and photosensitization have been reported among individuals exposed occupationally to hydrogen chloride (NLM, 1998).

In animals, the only study of the effects of long-term inhalation of hydrogen chloride reported epithelial or squamous hyperplasia of the nasal mucosa, larynx, and trachea. In a 90-day inhalation study, decreased body weight gains, minimum-to-mild rhinitis, nasal cavity lesions, and eosinophilic globules in the epithelial lining of the nasal tissues were reported in test animals (U.S. EPA, 1998).

Acute Toxicity Value. EPA proposed an acute toxicity value of 1.4 ppm for hydrogen chloride. This value was derived based on data in human volunteers exposed to 0, 0.8, or 1.8 ppm hydrogen chloride for 45 minutes. The volunteers rated the following symptoms: sore throat, nasal discharge, cough, chest pain, wheezing, fatigue, headache, dizziness, and unusual taste or smell. Respiratory parameters such as total respiratory resistance and forced vital capacity were also measured. No adverse exposure-related effects were observed (Stevens et al., 1992). The dose-response relationship for irritant gases follows the following equation: $C^n \times t = k$, where C = concentration, time is time, and k is a constant. For hydrogen chloride, n =1 (ten Berge et al., 1986). Uncertainty factors were not applied since a no-effect-level was identified in humans.

EPA has low confidence in the acute toxicity value for hydrogen chloride because the study group was limited to 10 subjects with a narrow age distribution. In addition, it is unclear

whether the pulmonary function test used in the study was a sensitive measure of the effects of hydrogen chloride.

Reference Dose. EPA has not established an RfD for hydrogen chloride (U.S. EPA, 1998).

Reference Concentration. EPA has established an RfC for hydrogen chloride of 2.0E-02 mg/m^3 based on a LOAEL (human equivalent concentration) of 6.1 mg/m^3, an uncertainty factor of 300, and a modifying factor of 1 (U.S. EPA, 1998). The RfC was based on a chronic rat inhalation study that reported an increased incidence of hyperplasia of the nasal mucosa as well as the laryngeal-tracheal segments in the group exposed to hydrochloric acid (Sellakumar et al., 1985, as cited in U.S. EPA, 1998).

An uncertainty factor of 300 was applied based on a tenfold factor for intraspecies extrapolation, a tenfold factor to extrapolate from a LOAEL to a NOAEL, and a threefold factor for interspecies differences (U.S. EPA, 1998).

EPA has low confidence in the chronic study on which the RfC was based because it used only one dose and limited toxicological measurements. Confidence in the database is also low because the supporting data consisted of two subchronic bioassays and the database does not provide any additional chronic or reproductive studies. Therefore, EPA's confidence in the RfC is also low (U.S. EPA, 1998).

7.3.11 Lead

7.3.11.1 Introduction. Lead is a naturally occurring, bluish-gray metal that is found in small quantities in the earth's crust. It is present in a variety of compounds such as lead acetate, lead chloride, lead chromate, lead nitrate, and lead oxide (ATSDR, 1997b).

Exposure to lead can occur through the air, drinking water, food, and soil. Most lead exposure occurs through a combination of the inhalation and oral routes, with inhalation generally contributing a greater proportion of the dose for occupationally exposed groups, and the oral route generally contributing a greater proportion for the general population. The effects of lead are the same regardless of the route of exposure (inhalation or oral) and are correlated with internal exposure as blood lead levels. For this reason, the discussion in this summary will not discuss lead exposure in terms of route, but will present it in terms of blood lead levels (ATSDR, 1997b).

Children are at particular risk to lead exposure since they commonly put hands, toys, and other items, that may come in contact with lead-containing dust and dirt in their mouths. In addition, lead-based paints were commonly used for many years and flaking paint, paint chips, and weathered paint powder may be a major source of lead exposure, particularly for children (ATSDR, 1997b).

7.3.11.2 Cancer Effects. Human studies are inconclusive regarding lead and an increased cancer risk. Four major human studies of workers exposed to lead have been carried out; two studies did not find an association between lead exposure and cancer, one study found

an increased incidence of respiratory tract and kidney cancers, and the fourth study found excesses for lung and stomach cancers. However, all of these studies are limited in usefulness because the route(s) of exposure and levels of lead to which the workers were exposed were not reported. In addition, exposure to other chemicals probably occurred (U.S. EPA, 1998).

Animal studies have reported kidney cancer in rats and mice exposed to lead via the oral route. No studies are available on cancer in animals exposed to lead via the inhalation or dermal routes (U.S. EPA, 1998).

EPA has classified lead in Group B2 - Probable Human Carcinogen. This classification was based on animal studies showing an increased risk of kidney tumors and inadequate human evidence (U.S. EPA, 1998).

EPA has not calculated a cancer risk estimate for lead due to the number of uncertainties that are unique to lead. Age, health, nutritional state, body burden, and exposure duration influence the absorption, release, and excretion of lead. In addition, EPA believes that "the current knowledge of lead pharmacokinetics indicates that an estimate derived by standard procedures would not truly describe the potential risk" (U.S. EPA, 1998).

7.3.11.3 Noncancer Effects. The primary effects in humans from chronic exposure to lead are to the nervous system. Neurological symptoms have been reported in workers with blood lead levels of 40 to 60 µg/dL, and slowed nerve conduction in peripheral nerves in adults occurs at blood lead levels of 30 to 40 µg/dL. Children are particularly sensitive to the neurotoxic effects of lead. There is evidence that blood lead levels of 10 to 30 µg/dL, or lower, may affect the hearing threshold and growth in children. Chronic exposure to lead in humans can also affect the blood. Anemia has been reported in adults at blood lead levels of 50 to 80 µg/dL and in children at blood lead levels of 40 to 70 µg/dL. Other effects from chronic lead exposure in humans include effects on blood pressure and kidney function and interference with vitamin D metabolism (ATSDR, 1997b).

Animal studies have reported effects similar to those found in humans, with effects on the blood, kidneys, and nervous, immune, and cardiovascular systems noted (ATSDR, 1997b).

EPA has not established an RfD or RfC for lead. EPA believes that it is inappropriate to develop an RfD for lead because, by comparison to most other environmental toxicants, there is a low degree of uncertainty about the health effects of lead. In addition, "it appears that some of these effects, particularly children's neurobehavioral development, may occur at blood lead levels so low as to be essentially without a threshold" (U.S. EPA, 1998).

The Centers for Disease Control and Prevention (CDC) has set an "intervention level" for childhood lead poisoning of 10 μg/dL. This level was reduced in 1991 from the previous threshold level of 25 μg/dL and was based on scientific evidence that adverse health effects can occur at levels as low as 10 μg/dL (CDC, 1991). However, the CDC does not recommend environmental or medical intervention at 10 μg/dL. They recommend medical evaluation at or above 20 μg/dL or if blood lead levels of 15-19 μg/dL persist. Various counseling, montioring, and communitywide prevention activities were recommended at levels between 10-19 μg/dL (CDC, 1991).

7.3.12 Manganese

7.3.12.1 Introduction. Manganese is a naturally occurring substance found in many types of rock in combination with other chemicals such as oxygen, sulfur, and chlorine. Manganese is an essential element for humans. Manganese metal is produced from rocks containing high levels of manganese and the metal is mixed with iron to make various types of steel. Some manganese compounds are used in the production of batteries, as a component of some ceramics, pesticides, and fertilizers, and in nutritional supplements (ATSDR, 1997c).

7.3.12.2 Cancer Effects. No data are available on the carcinogenic effects in humans following inhalation, oral, or dermal exposure to manganese (ATSDR, 1997c).

No studies were found regarding the carcinogenic effects in animals as a result of inhalation or dermal exposure. Oral animal studies on manganese have produced mixed results, with one study reporting an increased incidence of pancreatic tumors (ATSDR, 1997c).

EPA has classified manganese as a Group D - Not Classifiable as to Carcinogenicity in Humans. EPA has not calculated a unit risk estimate for manganese (U.S. EPA, 1998).

7.3.12.3 Noncancer Effects. Chronic exposure to high levels of manganese by inhalation in humans results in a disease called manganism, characterized by feelings of weakness and lethargy and progressing to other symptoms such as speech disturbances, a mask-like face, tremors, and psychological disturbances. Other chronic effects from inhalation include respiratory effects such as an increased incidence of cough and bronchitis and an increased susceptibility to infectious lung disease (ATSDR, 1997c).

Neurological effects in animals have been detected following inhalation exposure to high manganese levels. No adverse effects have been reported as a result of oral or dermal exposure in animals (ATSDR, 1997c).

Reference Dose. EPA has established an RfD for manganese of 1.4E-01 mg/kg-d based on a NOAEL of 0.14 mg/kg-d, an uncertainty factor of 1, and a modifying factor of l. The RfD is based on data from several sources, including the National Research Council, which has determined that an "estimated safe and adequate daily dietary intake" for manganese is 2 to 5 mg/d for adults (NRC, 1989, as cited in U.S. EPA, 1998).

EPA applied an uncertainty factor of 1 because the information used to determine the RfD was taken from many large populations consuming normal diets over an extended period of time with no adverse health effects (U.S. EPA, 1998).

EPA has medium confidence in the studies on which the RfD was based, in the database, and in the RfD because many studies have reported similar findings with regard to the normal dietary intake of manganese in humans (U.S. EPA, 1998).

Reference Concentration. EPA has established an RfC for manganese of 5.0E-05 mg/m^3 based on a LOAEL (human equivalent concentration) of 0.05 mg/m^3, an uncertainty factor of 1,000, and a modifying factor of 1 (U.S. EPA, 1998). The RfC is based on two studies of

occupational exposure to manganese dioxide that reported increases in the impairment of neurobehavioral function (Roels et al., 1992, 1987, as cited in U.S. EPA, 1998).

EPA applied an uncertainty factor of 1,000, based on a tenfold factor to protect sensitive individuals, a tenfold factor for use of a LOAEL, and a tenfold factor for database limitations reflecting less-than-chronic periods of exposure and lack of developmental data (U.S. EPA, 1998).

EPA has medium confidence in the study on which the RfC is based, because neither of the principal studies identified a NOAEL for neurobehavioral effects, nor did either study provide information on particle size. EPA also has medium confidence in the database and RfC because the duration of exposure was limited in all the studies and insufficient information is available on the developmental and reproductive effects of manganese (U.S. EPA, 1998).

7.3.13 Elemental Mercury

7.3.13.1 Introduction. Elemental mercury is a shiny, silver-white, odorless liquid. Elemental mercury is released to the air by natural and industrial processes. A major route of exposure to elemental mercury is inhalation in occupational settings, such as chlorine-alkaline manufacturing facilities. Exposure may also occur from dental and medical treatments; dental amalgams may contain between 43 and 54 percent elemental liquid mercury (ATSDR, 1997d).

7.3.13.2 Cancer Effects. There are a number of epidemiological studies that have examined cancer mortality and morbidity among workers occupationally exposed to elemental mercury. All of these studies have limitations, including small sample sizes, probable exposure to other lung carcinogens, failure to consider confounding factors such as smoking, and failure to observe correlations between estimated exposure and cancer incidence (U.S. EPA, 1997c).

One available animal study identified cancer incidence in animals exposed to elemental mercury by injection. Tumors were found at the contact sites; however, the study was incompletely reported as to controls and statistics (U.S. EPA, 1997c).

EPA has classified elemental mercury in Group D - Not Classifiable as to Human Carcinogenicity, based on inadequate human and animal data. EPA has not calculated a unit risk estimate for elemental mercury (U.S. EPA, 1998).

7.3.13.3 Noncancer Effects. Nervous system effects are the most sensitive toxicologic endpoint observed following exposure to elemental mercury. Symptoms associated with elemental mercury neurological toxicity include tremors, irritability, excessive shyness, nervousness, insomnia, headaches, polyneuropathy, and memory loss. At higher concentrations, kidney and respiratory effects have been observed (U.S. EPA, 1997c).

Reference Dose. EPA has not calculated an RfD for elemental mercury.

Reference Concentration. EPA has calculated an RfC for elemental mercury of 3.0E-04 mg/m^3, based on a LOAEL (adjusted) of 0.09 mg/m^3, an uncertainty factor of 30, and a modifying factor of 1. A human occupational study was used as the basis for the RfC and the

LOAEL (Fawer et al., 1983, as cited in U.S. EPA, 1998) and several other human occupational studies were used to corroborate this LOAEL. These studies investigated neurological effects in humans exposed to elemental mercury in the workplace; hand tremors, increases in memory disturbances, and evidence of autonomic dysfunction were observed and were the basis for the LOAEL (U.S. EPA, 1998).

An uncertainty factor of 30 was applied based on a tenfold factor for the protection of sensitive human subpopulations and an additional threefold factor for database deficiencies, particularly developmental and reproductive studies (U.S. EPA, 1998).

EPA has medium confidence in the studies on which the RfC was based because there were a sufficient number of human subjects, an appropriate control group, and the exposure levels in a number of studies had to be extrapolated from blood mercury levels. EPA also has medium confidence in the database due to lack of human or multispecies reproductive/ developmental studies and medium confidence in the RfC (U.S. EPA, 1998).

7.3.14 Inorganic Mercury (Mercuric Chloride; Divalent Mercury)

7.3.14.1 Introduction. Inorganic mercury compounds are usually white powders of crystals. Until 30 years ago, inorganic mercury compounds were used extensively as pharmaceuticals, such as components of antiseptics, diuretics, skin lightening creams, and laxatives. Since then, more effective and less harmful alternatives have replaced most pharmaceutical uses of mercury. Today, most exposure to inorganic mercury compounds occurs through dental treatments (ATSDR, 1997d).

7.3.14.2 Cancer Effects. There are no data concerning the carcinogenic effects of mercuric chloride in humans (U.S. EPA, 1997c).

Limited animal data are available on the carcinogenic effects of inorganic mercury. Cancer of the forestomach and thyroid were seen in rats exposed to mercuric chloride by gavage, and evidence of cancer of the forestomach and kidneys was considered equivocal in mice (U.S. EPA, 1997c).

EPA has classified mercuric chloride in Group C - Possible Human Carcinogen, based on the absence of data in humans and limited evidence in rats and mice. EPA has not calculated a unit risk estimate for mercuric chloride (U.S. EPA, 1998).

7.3.14.3 Noncancer Effects. The primary effect from chronic exposure to inorganic mercury is kidney damage, primarily due to mercury-induced autoimmune glomerulonephritis (induction of an immune response to the body's kidney tissue). In addition, several animal studies have reported developmental effects from exposure to inorganic mercury (U.S. EPA, 1997c).

Reference Dose. EPA has established an RfD of 3.0E-04 mg/kg-d for inorganic mercury. This was based on a consensus decision of a panel of mercury experts who used several LOAELs ranging from 0.23 to 0.63 mg/kg-d (Shultz, 1988, as cited in U.S. EPA, 1998), an uncertainty factor of 1,000, and a modifying factor of 1. The LOAELs were derived from several rat feeding

and subcutaneous studies in which autoimmune glomerulonephritis was observed (U.S. EPA, 1998).

An uncertainty factor of 1,000 was applied based a tenfold factor for an animal study with a LOAEL, a tenfold factor for use of a subchronic study, and an additional tenfold factor for sensitive human subpopulations (U.S. EPA, 1998).

The studies on which the RfD was based were not given a confidence ranking; the RfD and database were given a high confidence ranking based on the weight of evidence from several studies using Brown Norway rats (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for inorganic mercury.

7.3.15 Organic Mercury (Methylmercury)

7.3.15.1 Introduction. Organic mercury compounds are white crystalline solids. Most exposure to organic mercury occurs through the diet, with fish and fish products as the dominant source. Sources of past exposure to organic mercury include fungicide-treated grains and meat from animals fed such grain. However, fungicides containing mercury are banned in the United States today and this source of exposure is now negligible (ATSDR, 1997d).

7.3.15.2 Cancer Effects. Three human studies have examined the relationship between methylmercury and cancer incidence. However, these studies were considered extremely limited because of study design or incomplete data reporting (U.S. EPA, 1997c).

Several animal studies have shown an increased incidence of kidney tumors in mice exposed orally to methylmercury. However, these tumors were observed only at a single site (kidney), in a single species (mice), and a single sex (males) (U.S. EPA, 1997c).

EPA has classified methylmercury in Group C - Possible Human Carcinogen, based on the absence of data in humans and limited evidence in animals. EPA has not calculated a unit risk estimate for methylmercury (U.S. EPA, 1998).

7.3.15.3 Noncancer Effects. A large number of human studies are available on the systemic effects of methylmercury. This database is the result of two large-scale poisoning episodes in Japan and Iraq, as well as several epidemiologic studies investigating populations that consume large quantities of fish. Methylmercury mainly affects the central nervous system. Early symptoms from chronic exposure to low levels of methylmercury are prickling on the skin, blurred vision, and malaise. At higher doses, deafness, speech difficulties, and constriction of the visual field are seen. The fetus is at particular risk from methylmercury exposure. Offspring born to women exposed to methylmercury during pregnancy have exhibited a number of developmental abnormalities including delayed onset of walking and talking, cerebral palsy, altered muscle tone, and reduced neurological test scores (U.S. EPA, 1997c).

Reference Dose. EPA has established an RfD of 1.0E-04 mg/kg-d for methylmercury, based on a benchmark dose of 0.0011 mg/kg-d, an uncertainty factor of 10, and a modifying factor of 1 (U.S. EPA, 1998). This was based on developmental abnormalities in infants born to

mothers exposed to methylmercury in contaminated grain in Iraq (Marsh et al., 1987, and Ahmed, 1991, as cited in U.S. EPA, 1998). EPA used a benchmark dose, the lower 95 percent confidence level for a 10 percent incidence rate of neurologic changes, based on modeling of all effects in children. This lower bound was 11 ppm methylmercury in maternal hair. A dose conversion was used to estimate a daily intake of 1.1 µg methylmercury/kg body weight/d that, when ingested by a 60-kg individual, will maintain a concentration of approximately 44 µg/L of blood or a hair concentration of 11 µg mercury/g hair (11 ppm) (U.S. EPA, 1997c, 1998).

EPA applied an uncertainty factor of 10, based on a threefold factor for variability in the human population and an additional threefold factor for the lack of a two-generation reproductive study and lack of data for the effect of exposure duration on developmental neurotoxicity effects and on adult paresthesia (U.S. EPA, 1998).

EPA has medium confidence in the studies on which the RfD was based, in the database, and in the RfD. These rankings are based on the fact that the benchmark dose approach allowed use of the entire dose-response assessment with a resulting value that is consistent with the traditional NOAEL/LOAEL approach. However, EPA has some concerns related to the applicability of a dose-response estimate based on a grain-consuming population when the actual application is likely to help characterize risk for fish-consuming segments of the population (U.S. EPA, 1998).

It is also important to consider the fact that the RfD represents a "no-effect" level that is presumed to be without appreciable risk. As discussed above, EPA used an uncertainty factor of 10 to derive the RfD for methylmercury. An uncertainty factor of 100 to 1,000 is usually applied when the RfD is based on animal data; however, since this RfD was based on human data, an uncertainty factor of 10 was deemed appropriate. In addition, the RfD was based on a benchmark dose that itself was derived as the lower 95 percent confidence level for the 10 percent incidence rate of neurologic abnormalities in children. Therefore, there is a margin of safety between the RfD and the level corresponding to the threshold for adverse effects, as indicated by the human data.

Considerable new data on the health effects of methylmercury are becoming available. Large studies of fish- and marine-mammal-consuming populations in the Seychelles and Faroe Islands have been carried out. Smaller-scale studies also describe effects in populations around the U.S. Great Lakes. However, EPA has decided "that it is premature to make a change in the methylmercury RfD at this time (U.S. EPA, 1997c). In November 1998, EPA and other federal Agencies participated in an interagency review of available human neurodevelopmental data on methylmercury, including the most recent studies from the Seychelles and Faroe Islands. Preliminary review of the Seychellois and Faroese data supports the current RfD as scientifically valid and protective of human health. The National Academy of Sciences (NAS) is currently independently assessing the EPA's RfD for methylmercury. Pending the completion of the NAS study, EPA will reevaluate the RfD for methylmercury following careful review of the results of the NAS study.

Reference Concentration. EPA has not established an RfC for methylmercury.

7.3.16 Nickel

7.3.16.1 Introduction. Nickel is a silvery-white metal that is usually found in nature as a component of silicate, sulfide, or arsenide ores. The predominant forms of nickel in the atmosphere are nickel sulfate, nickel oxides, and the complex oxides of nickel. Each form of nickel exhibits different physical properties. Most nickel is used to make stainless steel; other uses include the manufacture of batteries, electroplating baths, textile dyes, coins, sparkplugs, and machinery parts (ATSDR, 1997e).

7.3.16.2 Cancer Effects. Human studies have reported an increased risk of lung and nasal cancers among nickel refinery workers exposed to nickel refinery dust. Nickel refinery dust is defined as the "dust from pyro-metallurgical sulfide nickel matte" refineries and is a mixture of many nickel compounds, including nickel subsulfide. It is not certain which compound is carcinogenic in the nickel refinery dust (U.S. EPA, 1998). No information is available on the carcinogenic effects of nickel in humans from oral or dermal exposure (ATSDR, 1997e; U.S. EPA, 1998).

Animal studies have reported lung tumors from inhalation exposure to the following nickel compounds and mixtures: nickel refinery dusts, nickel subsulfide, and nickel carbonyl. Oral animal studies have not reported tumors from exposure to nickel acetate in the drinking water. No information is available on the carcinogenic effects of nickel in animals from dermal exposure (ATSDR, 1997e; U.S. EPA, 1998).

EPA has classified nickel refinery dust in Group A - Known Human Carcinogen. The Group A classification was based on an increased risk of lung and nasal cancer in humans through inhalation exposure and increased lung tumor incidences in animals by inhalation and injection (U.S. EPA, 1998).

Inhalation Cancer Risk. EPA used the additive and multiplicative extrapolation method, based on human data, to estimate the unit cancer risk for nickel refinery dust. EPA calculated an inhalation unit risk estimate of 2.4E-04 $(\mu g/m^3)^{-1}$. EPA used four data sets, all from human exposure, to calculate the unit risk estimates for nickel refinery dusts. A range of incremental unit risk estimates were calculated from these data sets that were consistent with each other (U.S. EPA, 1998).

Oral Cancer Risk. EPA has not calculated an oral cancer risk estimate for any nickel compound.

7.3.16.3 Noncancer Effects. Contact dermatitis is the most common effect in humans from exposure to nickel via inhalation, oral, or dermal exposure. Cases of nickel-contact dermatitis have been reported following occupational and nonoccupational exposure, with symptoms of itching of the fingers, wrists, and forearms. Chronic inhalation exposure to nickel in humans also results in respiratory effects. These effects include direct respiratory effects such as asthma due to primary irritation or an allergic response and an increased risk of chronic respiratory tract infections (ATSDR, 1997e).

Animal studies have reported effect on the lungs, kidneys, and immune system from inhalation exposure to nickel, and effects on the respiratory and gastrointestinal systems, heart, blood, liver, kidney, and decreased body weight from oral exposure to nickel. Dermal animal studies have reported effects on the skin (ATSDR, 1997e).

Reference Dose. EPA has established an RfD for nickel (soluble salts) of 2.0E-02 mg/kg-d, based upon a NOAEL (adjusted) of 5 mg/kg-d, an uncertainty factor of 300, and a modifying factor of 1. This was based on a study in rats (Ambrose et al., 1976, as cited in U.S. EPA, 1998) that showed decreased body and organ weights from chronic (2-year) exposure to nickel in the diet. Several other studies showed similar results, with decreased body and organ weights after exposure to nickel chloride via gavage and through the drinking water (U.S. EPA, 1998).

An uncertainty factor of 300 was applied, based on a tenfold factor of interspecies extrapolation, a tenfold factor to protect sensitive subpopulations, and a threefold factor for inadequacies in the reproductive studies (U.S. EPA, 1998).

EPA has low confidence in the study on which the RfD was based because, although it was properly designed and provided adequate toxicological endpoints, high mortality occurred in the controls. EPA has medium confidence in the database because it provided adequate supporting subchronic studies and consequently medium confidence level in the RfD (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for any nickel compound.

7.3.17 Selenium

7.3.17.1 Introduction. Selenium is a naturally occurring substance in the earth's crust and is commonly found in sedimentary rock combined with other substances, such as sulfide minerals, or with silver, copper, lead, and nickel minerals. Selenium is an essential element for humans and animals and exposure occurs daily through food intake. lt is used in the electronics industry; the glass industry; in pigments used in plastics, paints, enamels, inks, and rubber; in pharmaceuticals manufacturing; and as a constituent of fungicides (ATSDR, 1996).

7.3.17.2 Cancer Effects. Several epidemiological studies have examined the relationship between cancer death rates in humans and selenium levels in forage crops. These studies have reported an increased incidence of colon, breast, and other forms of cancer in areas where selenium is deficient and a lowered cancer incidence with higher selenium concentrations. Other studies have reported that blood serum levels in patients with cancer had significantly lower selenium levels than healthy patients (U.S. EPA, 1998).

Several animal studies have investigated the carcinogenicity of selenium. However, the data are conflicting and difficult to interpret because of apparent anticarcinogenicity and high toxicity of some selenium compounds (U.S. EPA, 1998).

EPA has classified selenium in Group D - Not Classifiable as to Carcinogenicity in Humans because of inadequate human data and inadequate evidence of carcinogenicity in animals (U.S. EPA, 1998).

7.3.17.3 Noncancer Effects. No information is available on the chronic effects of selenium in humans from inhalation exposure. Ingestion of high levels of selenium in food and water has led to "selenosis," characterized by discoloration of the skin, deformation and loss of nails, hair loss, excessive tooth decay and discoloration, lack of mental alertness, and listlessness. Dermal exposure has resulted in skin rashes and contact dermatitis (ATSDR, 1996).

No data are available on the chronic effects in animals from inhalation exposure. Livestock exposed through consumption of high levels of selenium develop "alkali disease." (ATSDR, 1996).

Reference Dose. EPA has established an RfD for selenium of 5.0E-03 mg/kg-d based on an adjusted NOAEL of 0.015 mg/kg-d, an uncertainty factor of 3, and a modifying factor of 1. The RfD is based on an epidemiological study (Yang et al., 1989, as cited in U.S. EPA, 1998), which reported selenosis in a population in China. Clinical signs observed included "garlic odor" of the breath and urine, thickened and brittle nails, hair and nail loss, lowered hemoglobin levels, mottled teeth, skin lesions, and central nervous system abnormalities (U.S. EPA, 1998).

EPA applied an uncertainty factor of 3 to account for sensitive individuals. A full factor of 10 was not deemed necessary since similar NOAELs were identified in two moderate-sized populations exposed to selenium in excess of the recommended daily allowance without apparent signs of selenosis (U.S. EPA, 1998).

EPA has medium confidence in the study on which the RfD was based, because even though this was a study in which a sizable population with sensitive subpopulations was studied, there were still several possible interactions that were not fully accounted for. EPA has high confidence in the database because many animal studies and epidemiologic studies support the principal study and consequently high confidence in the RfD (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for selenium (U.S. EPA, 1998).

7.3.18 Silver

7.3.18.1 Introduction. Silver is a naturally occurring element that is often found deposited as a mineral ore in association with other elements. It is acquired as a by-product during the retrieval of copper, lead, zinc, and gold ores. It is used in photographic materials, electrical products, silver paints, batteries, sterling ware, and jewelry (ATSDR, 1990b).

7.3.18.2 Cancer Effects. No evidence of cancer in humans has been reported despite frequent therapeutic use of silver compounds over the years. Animal studies have shown local sarcomas after the implantation of foils and discs of silver (U.S. EPA, 1998).

EPA has classified silver in Group D - Not Classifiable as to Human Carcinogenicity, based on questionable interpretation of the local sarcomas seen in animal studies. Even insoluble solids such as plastics have been shown to result in local sarcomas (U.S. EPA, 1998).

7.3.18.3 Noncancer Effects. The only clinical condition that is known in humans to be associated with long-term exposure to silver is argyria, a gray or blue-gray discoloring of the skin. Argyria was common around the turn of the century when many pharmacological preparations contained silver. It is much less common now. Today, case reports in humans have reported that repeated dermal contact with silver may in some cases lead to contact dermatitis and a generalized allergic reaction to silver (ATSDR, 1990b).

EPA has established an RfD for silver of 5.0E-03 mg/kg-d based on a LOAEL (adjusted) of 0.014 mg/kg-d, an uncertainty factor of 3, and a modifying factor of 1 (U.S. EPA, 1998). The RfD is based on a report summarizing 70 cases of argyria following use of silver medication in humans (Gaul and Staud, 1935, as cited in U.S. EPA, 1998).

An uncertainty factor of 3 was applied to account for minimal effects in a subpopulation that has exhibited an increased propensity for the development of argyria. The critical effect is cosmetic, with no associated adverse health effects (U.S. EPA, 1998).

EPA has medium confidence in the critical study used as the basis for the RfD because it is an old study and only describes patients who developed argyria; no information is presented on patients who received injections of silver and did not develop argyria. EPA has low confidence in the database because the studies used to support the RfD were not controlled studies, and low-to-medium confidence in the RfD because the RfD is based on a study using intravenous administration, which necessitated a dose conversion with inherent uncertainties (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for silver (U.S. EPA 1998).

7.3.19 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin

7.3.19.1 Introduction. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) belongs to the class of compounds, chlorinated dibenzo-*p*-dioxins, that are referred to as dioxins. 2,3,7,8-TCDD is a colorless solid with no known odor. It does not occur naturally nor is it intentionally manufactured by any industry, although it can be produced inadvertently in small amounts as an impurity during the manufacture of certain herbicides and germicides and has been detected in products of incineration of municipal and industrial wastes. The only current use for 2,3,7,8-TCDD is in chemical research (ATSDR, 1998).

EPA issued a draft *Health Assessment Document for 2,3,7,8-TCDD and Related Compounds* in 1994. This document is a three-volume series consisting of a complete reassessment of the toxic effects of 2,3,7,8-TCDD (U.S. EPA, 1994b, c). The document was reviewed by EPA's Science Advisory Board (SAB) but has not yet been issued in final form. Most of the information in this summary is from this draft document and is subject to change, pending the release of the final document.

7.3.19.2 Cancer Effects. An increase in lung cancer risks was observed among Japanese males exposed to 2,3,7,8-TCDD as a result of an oil poisoning accident. Human studies have also found an association between 2,3,7,8-TCDD and soft-tissue sarcomas, lymphomas, and stomach carcinomas, although for malignant lymphomas, the increase in risk is not consistent.

The increase in risk is of borderline significance for highly exposed groups and is less among groups exposed to lower levels of 2,3,7,8-TCDD (U.S. EPA, 1994c).

An increased incidence of soft tissue sarcoma was found to be elevated in several recent studies. EPA stated that (U.S. EPA, 1994c)

> . . . the fact that similar results were obtained in independent studies of differing design and evaluating populations exposed to dioxin-like compounds under varying conditions, along with the rarity of this tumor type, weighs in favor of a consistent and real association. On the other hand, arguments regarding selection bias, differential exposure misclassification, confounding, and chance in each individual study have been presented in the scientific literature which increase uncertainty around this association. In addition excess respiratory cancer was noted in other studies. These results are also supported by significantly increased mortality from lung and liver cancers subsequent to the Japanese rice oil poisoning accident where exposure to PCDFs and PCBs occurred. Again, while smoking as a confounder cannot be totally eliminated as a potential explanation of these results, analyses conducted to date suggest that smoking is not likely to explain the entire increase in lung cancer. The question of confounding exposures, such as asbestos and other chemicals, in addition to smoking, has not been entirely ruled out and must be considered as potentially adding to the observed increases. Although increases of cancer at other sites (e.g., non-Hodgkin's lymphoma, stomach cancer) have been reported, the data for an association with exposure to dioxin-like compounds are less compelling.

Information on the carcinogenicity of 2,3,7,8-TCDD following inhalation exposure of animals is not available. In animal studies of oral exposure to 2,3,7,8-TCDD, multisite tumors in rats and mice, including the tongue, lung, nasal turbinates, liver, and thyroid, have been reported from long-term bioassays. It has also been shown to be carcinogenic in hamsters (U.S. EPA, 1994c).

EPA has classified 2,3,7,8-TCDD as a Group B2 - Probable Human Carcinogen (U.S. EPA, 1984, 1997b).

Toxicity Equivalency Factors. EPA has assigned the dioxin compounds individual toxicity equivalency factors (TEFs). TEFs are estimates of the toxicity of dioxin-like compounds relative to the toxicity of TCDD, which is assigned a TEF of 1.0. Table 7-2 lists the TEFs for dioxin compounds (Van den Berg et al., 1998).

Cancer Risk. EPA examined the available carcinogenicity data for 2,3,7,8-TCDD and stated (U.S. EPA, 1994c):

> Epidemiology studies suggest that the lung in the human male is a much more sensitive target organ for TCDD than is the liver and that the human is a sensitive species for cancer response, probably more sensitive than the rat. Although smoking may be a modifier for the lung cancer response, the studies also show increases for all cancers combined. Estimates derived from the human data

Table 7-2. Toxicity Equivalency Factors (TEFs) for Dioxin Compounds

Compound	TEF
2,3,7,8-TCDD	1
1,2,3,4,5,7,8,9-OCDD	0.0001
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
1,2,3,4,6,7,8,9-OCDF	0.0001
1,2,3,4,7,8-HxCDD,	0.1
1,2,3,7,8-PeCDD,	1
2,3,7,8-TCDF	0.1
1,2,3,4,7,8,9-HpCDF	0.01
2,3,4,7,8-PeCDF	0.5
1,2,3,7,8-PeCDF	0.05
1,2,3,6,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDD	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1

suggest a unit risk for lung cancer of 3 to $5x10^{-4}$ $(pg/kg\text{-}day)^{-1}$, for all cancers combined the unit risk estimate is 2 to $3x10^{-3}$ $(pg/kg\text{-}day)^{-1}$. While unit risk estimates based on rat tumors are somewhat less, they are within the range of uncertainty of those based on human data. Both animal and human responses are consistent with low-dose linearity.

EPA then concluded:

With regard to carcinogenicity, a weight of evidence evaluation suggests that dioxin and related compounds (CDDs, CDFs, and dioxin-like PCBs) are likely to present a cancer hazard to humans. While major uncertainties remain, efforts of this reassessment to bring more data into the evaluation of cancer potency have resulted in a risk specific dose estimate (1×10^{-6} or one additional cancer in one million exposed) of approximately 0.01 pg TEQ/kg body weight/day. This risk

> specific dose estimate represents a plausible upper bound on risk based on the evaluation of animal and human data. "True" risks are not likely to exceed this value, may be less, and may even be zero for some members of the population.

Dose-Response Modeling. EPA recently completed a draft assessment of the scientific foundation for dose-response modeling for 2,3,7,8-TCDD. Different models were reviewed for use in risk assessment. An empirical analysis was done for a broad range of experimental data on 2,3,7,8-TCDD. For each data set with enough data for a dose-response analysis, benchmark doses were calculated at levels of 1, 5, and 10 percent (animal data) and 0.1, 0.5, and 1 percent (epidemiological data). In addition, for the experimental data, the shape of the overall dose-response curve was examined (U.S. EPA, 1997a).

EPA stated that it was not possible to make any firm conclusions about the shape of the dose-response curve for 2,3,7,8-TCDD beyond the experimental range. In addition, EPA felt that there were a sufficient number of dose-response curves consistent with linearity to warrant concern about nonlinear extrapolations, but there is no way to disprove scientifically the existence of nonlinearity in the area below the experimental region (U.S. EPA, 1997a).

In summary, EPA (U.S. EPA, 1997a) stated,

> It is clear from this analysis that dioxin causes a variety of toxicities in test animals following chronic and bolus exposures. The human data is less clear, but qualitatively and quantitatively consistent with the animal findings when expressed on the basis of steady-state body burden rather than a daily dose or area-under-the-curve basis. There are sufficient data suggesting response proportionate to dose to warrant concern that this compound will induce toxic effects in humans in the range of the experimental animal data. Also, based on a lack of data to argue for an immediate and steep change in slope for many of the responses analyzed there is the possibility of response 1 to 2 orders of magnitude below this range.

Inhalation Cancer Risk. EPA has calculated an inhalation cancer slope factor for 2,3,7,8-TCDD of 1.56E+05 $(mg/kg\text{-}d)^{-1}$ and an inhalation unit risk estimate of 3.3E-05 $(pg/m^3)^{-1}$. These values are under review and are subject to change; they are based on an oral study in which rats were exposed to 2,3,7,8-TCDD in the diet for 720 days with resulting tumors of the respiratory system and liver (Kociba et al., 1978, as cited in U.S. EPA, 1984). This cancer slope factor is identical with the oral cancer slope factor; the inhalation unit risk estimate was based on route-to-route extrapolation from the oral cancer slope factor, assuming 75 percent absorption (U.S. EPA, 1984, 1997b).

Oral Cancer Risk. EPA has derived an oral cancer slope factor of 1.56E+05 $(mg/kg\text{-}d)^{-1}$ for 2,3,7,8,-TCDD, based on the Kociba et al. (1978) study as discussed above (U.S. EPA, 1984).

7.3.19.3 Noncancer Effects. The major noncarcinogenic effect from exposure to 2,3,7,8-TCDD is chloracne, a severe acne-like condition that develops within months of first exposure to high levels of 2,3,7,8-TCDD. For many individuals, the condition disappears after

discontinuation of exposure, for others it may remain for years. There are limited human data to suggest the doses at which chloracne is likely to occur. Occupational studies suggest that persistent chloracne is more often associated with high-intensity exposures, for long periods of time, and starting at an early age (U.S. EPA, 1994b, c). Acute exposures or chronic exposures to 2,3,7,8-TCDD at low levels have usually resulted in chloracne lasting for no longer than a few months to a few years (U.S. EPA 1994b, c).

Epidemiological studies have reported conflicting evidence on the immunotoxicity of 2,3,7,8-TCDD in humans. Some studies have suggested evidence of immunotoxicity, such as alterations in lymphocyte populations, cell surface markers, or lymphocyte proliferative response (ATSDR, 1998). However, studies have not reported changes in the immune system directly related to 2,3,7,8-TCDD exposure (U.S. EPA, 1994b, c).

An association has been reported between levels of male reproductive hormones and 2,3,7,8-TCDD exposure. Decreased testosterone levels were detected in several human studies, and animal data are available to support these findings. Other effects noted in human studies include an association between 2,3,7,8-TCDD exposure and

- An increased risk of diabetes and an elevated prevalence of abnormal fasting serum glucose levels
- The induction of cytochrome P-450 1A1, an enzyme involved in biotransformation reactions
- Elevation of gamma glutamyl transferase, a liver enzyme
- A possible increased risk of endometriosis, a disease of the female reproductive system (U.S. EPA, 1994b, c).

Animal studies have reported reproductive and developmental effects from exposure to 2,3,7,8-TCDD. These studies have suggested that altered development may be among the most sensitive endpoints of 2,3,7,8-TCDD exposure. Several animal species have reported developmental toxicity occurring at lower levels than male and female reproductive toxicity effects. 2,3,7,8-TCDD appears to affect a large number of critical developmental effects at specific developmental stages. These changes can lead to increases in fetal mortality, disruption of organ system structure, and irreversible impairment of organ function. Developmental toxicity from 2,3,7,8-TCDD has been seen in fish, birds, and mammals. Thus, it is likely to occur at some level in humans. However, it is not possible to state what sort of effects will occur or at what levels (U.S. EPA, 1994b, c).

Animal studies have reported changes in the skin resembling chloracne from 2,3,7,8-TCDD exposure. Distinctive changes in animals include swelling and inflamed eyelids, nail loss, and facial hair loss (ATSDR, 1998).

The immune system also appears to be a target from 2,3,7,8-TCDD exposure in animal studies. Alterations in specific immune effector functions and increased susceptibility to infectious diseases have been observed in animals exposed to 2,3,7,8-TCDD. Both cell-mediated

and humoral immune responses were suppressed following 2,3,7,8-TCDD exposure (U.S. EPA, 1994b, c).

EPA has not calculated an RfD or an RfC for 2,3,7,8-TCDD.

7.3.20 Thallium

7.3.20.1 Introduction. Thallium is a metallic element that exists in the environment combined with other elements, such as oxygen, sulfur, and the halogens. Thallium is quite stable in the environment, since it is neither transformed nor biodegraded. It is released to the environment from coal burning and smelting, and its major use is in the semiconductor industry where it is used in the production of switches and closures (ATSDR, 1990c).

7.3.20.2 Cancer Effects. Limited human studies are available on the carcinogenic effects of thallium. One epidemiologic study did not report an increase in tumors in workers exposed to thallium. No animal studies are available (U.S. EPA, 1998).

EPA has classified thallium in Group D - Not Classifiable as to Human Carcinogenicity, based on the lack of carcinogenicity data in animals and humans (U.S. EPA, 1998).

7.3.20.3 Noncancer Effects. Thallium compounds can affect the respiratory, cardiovascular, and gastrointestinal systems, liver, kidneys, and the male reproductive systems in humans. Temporary hair loss has also been associated with ingestion of thallium in humans. Developmental effects were not noted in children born to mothers who had been exposed to thallium during pregancy (ATSDR, 1990c).

Reference Dose. EPA has established an RfD for thallium (thallium sulfate, thallium chloride, and thallium carbonate) of 8.0E-05 mg/kg-d based on an adjusted NOAEL of 0.25 mg/kg-d, an uncertainty factor of 3,000, and a modifying factor of 1. The RfD is based on a subchronic toxicity study of thallium sulfate in rats in which no adverse effects were reported (U.S. EPA, 1986, as reported in U.S. EPA, 1998).

An uncertainty factor of 3,000 was applied, based on a tenfold factor to extrapolate from subchronic to chronic data, a tenfold factor for intraspecies extrapolation, a tenfold factor for interspecies variability, and a threefold factor to account for lack of reproductive and chronic toxicity data (U.S. EPA, 1998).

EPA has low confidence in the critical study used as the basis for the RfD due to uncertainties in the results and because supporting studies show adverse health effects at doses slightly higher than the NOAEL; low confidence in the database because there is only one subchronic study and some anecdotal human data, and consequently low confidence in the RfD (U.S. EPA, 1998).

Reference Concentration. EPA has not established an RfC for thallium (U.S. EPA, 1998).

7.4 Particulate Matter (PM_{10} and $PM_{2.5}$)

Epidemiological studies that have estimated relationships between ambient PM concentrations and health effects are available for several health effects and several different population groups. The broad categories of health endpoints for which concentration-response functions have been estimated based on measures of PM are

- Mortality
- Hospital admissions
- Respiratory symptoms and restricted activity days (not requiring hospitalization).

The health endpoints included in each of these categories and the possible overlap among health effects and populations studied are described in Table 7-3. Descriptions of the populations investigated in the relevant studies are important because, in most cases, the concentration-response functions from these studies are applied only to the subpopulation (e.g., asthmatic children) investigated in the epidemiologic study. A detailed discussion of modeling analysis conducted to evaluate PM health effects for this risk assessment, including uncertainties in the data and modeling methods, is provided in Appendix E.

7.4.1 Mortality Studies

The studies that associate PM exposures with premature mortality presented in this analysis differ primarily in the type of PM exposure used as input to the concentration response functions (i.e., whether $PM_{2.5}$ or PM_{10} is used and whether short-term or long-term exposure is used). The mortality studies also differ slightly in the populations studied. Brief descriptions of the mortality studies used in this analysis and the issues related to the overlap in the incidence predicted from these studies are discussed here.

One long-term exposure study is presented here. Pope et al. (1995) is a prospective cohort study that investigated the association between long-term exposure to ambient $PM_{2.5}$ concentrations (measured in the study as the median of all daily concentrations measured over a 4-year period) and mortality in a cohort of adults age 30 and older.[1]

Two estimates of the relationship between mortality and short-term exposure to PM are presented. One estimate is from a pooled analysis of 10 individual studies in which PM_{10} concentrations are averaged over a period of 1 to 5 days. The second estimate is taken from Schwartz et al. (1996) and uses a 2-day average $PM_{2.5}$ measure. In both cases, short-term exposure is related to daily mortality for the full population.

Long-term studies may be preferable to "short-term" (daily average) studies for estimating health effects for a couple of reasons. First, by their basic design, daily studies detect acute effects but cannot detect the effects of long-term exposures. A chronic exposure study

[1]Dockery et al., 1993, is another study relating long-term exposures to PM to premature mortality. However, the study by Pope et al. considered a much larger population and included many more locations (52 cities versus 6 in the Dockery study). The Pope study is therefore considered to be preferable.

Table 7-3. Concentration-Response Functions Used To Estimate Health Effects Associated with Exposure to Particulate Matter

Endpoint	Concentration-Response Function		PM Averaging Time		Population[a]	Annual Baseline Incidence (per 100,000 population)[b]	Pollutant Coefficient[c]
	Source	Functional Form	Studied	Applied			
Mortality							
Mortality (long-term exposure), using $PM_{2.5}$ indicator	Pope et al., 1995	Loglinear	Median of 4 years of data	Annual median[d]	Ages 30+	759 (number of nonaccidental deaths in the population ages 30 + divided by 100,000 individuals of all ages)	0.006408
Mortality (short-term exposure), using $PM_{2.5}$ indicator	Schwartz et al., 1996a (Boston, Knoxville, St. Louis, Steubenville, Portage & Topeka)	Loglinear	2-day average	1-day average[e]	All	803 (nonaccidental deaths in general population)	0.001433
Mortality (short-term exposure), using PM_{10} indicator[e]	Ito & Thurston, 1996 (Chicago)	Loglinear	2-day average	1-day average[f]	All	803 (nonaccidental deaths in general population)	0.000782
	Kinney et al., 1995 (Los Angeles)	Loglinear	1-day average		All		
	Pope et al., 1992 (Utah)	Loglinear	5-day average		All		

(continued)

Table 7-3. (continued)

Endpoint	Concentration-Response Function		PM Averaging Time		Population[a]	Annual Baseline Incidence (per 100,000 population)[b]	Pollutant Coefficient[c]
	Source	Functional Form	Studied	Applied			
	Schwartz, 1993a (Birmingham)	Loglinear	3-day average		All		
	Schwartz et al., 1996 (Boston)	Loglinear	2-day average		All		
	Schwartz et al., 1996 (Knoxville)	Loglinear	2-day average		All		
	Schwartz et al., 1996 (St. Louis)	Loglinear	2-day average		All		
	Schwartz et al., 1996 (Steubenville)	Loglinear	2-day average		All		
	Schwartz et al., 1996 (Portage)	Loglinear	2-day average		All		
	Schwartz et al., 1996 (Topeka)	Loglinear	2-day average		All		
Hospital Admissions							
All respiratory illnesses, using $PM_{2.5}$ indicator	Thurston et al., 1994 (Toronto)	Linear	1-day average	1-day average	All	n/a	3.45×10^{-8} [f]
All respiratory illnesses, using PM_{10} indicator	Schwartz, 1995 (Tacoma)	Loglinear	1-day average	1-day average	Age 65+	504 (general population)	0.00170
	Schwartz, 1995 (New Haven)	Loglinear	1-day average		Age 65+		
	Schwartz, 1996 (Spokane)	Loglinear	1-day average		Age 65+		
COPD, using PM_{10} indicator	Schwartz, 1994a (Birmingham)	Loglinear	1-day average	1-day average	Age 65+	103	0.002533

(continued)

Table 7-3. (continued)

Endpoint	Concentration-Response Function		PM Averaging Time		Population[a]	Annual Baseline Incidence (per 100,000 population)[b]	Pollutant Coefficient[c]
	Source	Functional Form	Studied	Applied			
	Schwartz, 1994b (Detroit)	Loglinear	1-day average		Age 65+	(general population)	
	Schwartz, 1996 (Spokane)	Loglinear	1-day average		Age 65+		
Pneumonia, using PM_{10} indicator	Schwartz, 1994a (Birmingham)	Loglinear	1-day average	1-day average	Age 65+	229 (general population)	0.0013345
	Schwartz, 1994b (Detroit)	Loglinear	1-day average		Age 65+		
	Schwartz, 1994c (Minneapolis)	Loglinear	1-day average		Age 65+		
	Schwartz, 1996 (Spokane)	Loglinear	1-day average		Age 65+		
Congestive heart failure, using PM_{10} indicator	Schwartz & Morris, 1995 (Detroit)	Loglinear	2-day average	1-day average	Age 65+	231 (general population)	0.00098
Ischemic heart disease, using PM_{10} indicator	Schwartz & Morris, 1995 (Detroit)	Loglinear	1-day average	1-day average	Age 65+	450 (general population)	0.00056
Respiratory Symptoms/Illnesses Not Requiring Hospitalization							
Chronic bronchitis, using PM_{10} indicator	Schwartz, 1993b		Annual mean	Annual mean	All	N/A	0.012
Acute bronchitis, using $PM_{2.5}$ indicator	Dockery et al., 1989	Logistic	Annual mean	Annual mean[d]	Ages 10-12	N/A	0.0298

(continued)

Table 7-3. (continued)

Endpoint	Concentration-Response Function		PM Averaging Time		Population[a]	Annual Baseline Incidence (per 100,000 population)[b]	Pollutant Coefficient[c]
	Source	Functional Form	Studied	Applied			
Upper respiratory symptoms (URS), using PM_{10} indicator	Pope et al., 1991	Loglinear	1-day average	1-day average	Asthmatics, ages 9-11	38,187 (applied population)	0.0036
Lower respiratory symptoms (LRS), using $PM_{2.5}$ indicator	Schwartz et al., 1994	Logistic	1-day average	1-day average	Ages 8-12	N/A	0.01823
MRADs, using $PM_{2.5}$ indicator	Ostro and Rothschild, 1989	Loglinear	2-week average	1-day average	Ages 18-65	780,000 d/yr (applied population)	0.00741
RADs, using $PM_{2.5}$ indicator	Ostro, 1987	Loglinear	2-week average	1-day average	Ages 18-65	400,531 d/yr (applied population)	0.00475
Acute respiratory symptoms (any of 19), using PM_{10} indicator	Krupnick et al., 1990	Logistic	1-day average COH	1-day average	Ages 18-65 (study examined "Adults")	N/A	0.00046
Shortness of breath (days), using PM_{10} indicator	Ostro et al., 1995	Logistic	1-day average	1-day average[d]	African-American asthmatics, ages 7-12	N/A	0.00841

(continued)

Table 7-3. (continued)

Endpoint	Concentration-Response Function		PM Averaging Time		Population[a]	Annual Baseline Incidence (per 100,000 population)[b]	Pollutant Coefficient[c]
	Source	Functional Form	Studied	Applied			
Work loss days (WLDs), using $PM_{2.5}$ indicator	Ostro, 1987	Loglinear	2-week average	1-day average	Ages 18-65	150,750 d/yr (applied population)	0.0046

NOTES:

[a] The population examined in the study and to which this analysis applies the reported concentration-response relationship. In general, epidemiological studies analyzed the concentration-response relationship for a specific age group (e.g., ages 65+) in a specific geographical area. This analysis applies the reported pollutant coefficient to all individuals in the age group nationwide.

[b] Annual baseline incidence in the applied population per 100,000 individuals in the indicated population. For hospital admissions and mortality, the national baseline incidence rates are meant to provide the reader with a general perspective of the potential magnitude of the baseline incidence; for other endpoints, the annual baseline incidence estimates were taken directly from the epidemiological literature and were applied to all sectors in the analysis.

[c] A single pollutant coefficient reported for several studies indicates a pooled analysis; see text for discussion of pooling concentration-response relationships across studies.

[d] The following studies report a lowest observed pollution level:

Pope et al., 1995	Mortality (long-term exposure)	9 $\mu g/m^3$ $PM_{2.5}$
Dockery et al., 1995	Acute bronchitis	11.8 $\mu g/m^3$ $PM_{2.5}$ (20.1 $\mu g/m^3$ PM_{10})
Ostro et al., 1995	Shortness of breath, days	19.63 $\mu g/m^3$ PM_{10}

The remaining studies did not report lowest observed concentrations.

[e] Pooling of the ten studies used for this endpoint is described in EPA (1996).

[f] All 1-day averages are 24-hour averages, 2-day averages are 48-hour averages, etc.

design (a prospective cohort study) is best able to identify the long-term exposure effects and will likely detect some of the short-term exposure effects as well.

The second reason that long-term studies may be preferable to short-term studies is that long-term study results may be less likely to be affected by deaths that are premature by only a very short amount of time. Critics of the use of short-term studies for policy analysis purposes correctly point out that an added risk factor that results in terminally ill individuals dying a few days or weeks earlier than they otherwise would have (a phenomenon referred to as "harvesting") is potentially included in the measured PM mortality "signal" detected in such a study. Because the short-term study design does not examine individual people (but instead uses daily mortality rates in large, typically city, populations), it is impossible to know anything about the overall health status of the people who die on any given day. Although some of the excess deaths associated with peak PM exposures may have resulted in a substantial loss of life (measuring loss of life in terms of lost years of remaining life), others may have resulted in a relatively short amount of lifespan lost. Although it is not clear that the results of prospective cohort (long-term) studies are completely unaffected by "harvesting," because they follow individuals, such studies are better able to examine the health status of individuals who die during the course of the study.

Although long-term exposure studies may be preferable, only one is presented in this analysis. Therefore, results of studies that use short-term PM exposures are also presented in this analysis for comparison. However, because a long-term exposure study may detect some of the same short-term exposure effects detected by short-term studies, including both types of study in a benefit analysis would likely result in some degree of double counting of benefits.

7.4.2 Hospital Admissions Studies

Several studies have investigated the association between ambient PM concentrations and increased hospital admissions for a variety of ailments and among different population groups. These studies and the issues of overlap among the endpoints and populations investigated are described below. All of these studies compare PM concentrations averaged over 1 to 2 days with daily hospital admissions.

7.4.2.1 Hospital Admissions for Respiratory Illnesses. Several studies have investigated hospital admissions specifically for respiratory ailments. Two estimates are available for hospital admissions for "all respiratory illnesses." The first study, Thurston et al. (1994), investigated respiratory admissions for individuals of all ages. The pooled analysis using information from Schwartz (1995, 1996) estimates all respiratory hospital admissions for individuals aged 65 years and older. Studies of hospital admissions for chronic obstructive pulmonary disease (COPD) and pneumonia, which are both subsets of hospital admissions for all respiratory diseases, are also presented.

Because Thurston et al. (1994) include hospital admissions for a large group of respiratory illnesses and all age groups, this study is the most comprehensive and is therefore considered to be the most appropriate study for predicting changes in hospital admissions for respiratory illnesses related to PM exposure. Because Schwartz (1994a,b,c, 1996) estimates incidence for a subset of hospital admissions counted by Thurston et al. (1994), the incidence

predicted by the Schwartz studies should not be added to the incidence predicted by Thurston et al. (1994).

7.4.2.2 Hospital Admissions for Cardiac Disease. Hospital admissions for ischemic heart disease and congestive heart failure related to PM exposure have been investigated by Schwartz and Morris (1995). These admissions are not included in the group of respiratory illness hospital admissions. In addition, there is no overlap between hospital admissions for ischemic heart disease and admissions for congestive heart failure. Therefore, they can both be counted as benefits associated with reducing exposure to PM.

7.4.3 Respiratory Symptoms and Restricted Activity Days

Several studies have investigated changes in a variety of respiratory symptoms not requiring admission to the hospital. These studies have investigated illnesses in both the general population and in asthmatic individuals; many of the studies have used children as the study population. The types of symptoms investigated and issues related to potential overlap among the symptoms examined in these studies are described here. Because some of these symptoms may vary only slightly among the studies, there is considerable overlap among the health effects investigated in these studies. Table 7-4 defines the symptoms and the populations investigated for each of the studies presented in this analysis.

7.4.3.1 Respiratory Illnesses Measured in the General Population. There may be some overlap between bronchitis studied by Dockery et al. (1989) and chronic bronchitis defined by Schwartz (1993b). In particular, Dockery et al. (1989) considered the effects of PM exposure on bronchitis that was diagnosed by a doctor within the previous year, which may include some of the same types of cases investigated by Schwartz (1993b). Although the bronchitis measured in Dockery et al. (1989) is likely to include more cases of acute bronchitis than the bronchitis cases measured by Schwartz (1993b), the measure in Dockery et al. (1989) may also include some cases of chronic bronchitis if the cases diagnosed in the year prior to the study continue into future years. For this reason, and because the populations studied overlap each other, the estimates of avoided incidence based on these studies are not necessarily mutually exclusive. However, both studies give valuable information regarding the incidence of bronchitis avoided in two different population groups.

Lower respiratory symptoms (LRS), as described in Schwartz et al. (1994), are distinct from doctor-diagnosed bronchitis and therefore do not overlap with the avoided cases of bronchitis.

There are several aggregation issues related to the set of endpoints that are studied in adults. Acute respiratory symptoms (any of 19 symptoms) studied by Krupnick et al. (1990) may overlap with minor restricted activity days (MRADs) studied by Ostro and Rothschild (1989) because the age ranges of the populations studied are the same, and it is possible that an acute respiratory symptom could result in a minor respiratory restricted activity day. The degree of overlap, however, is not known, and it is possible that some of the benefit associated with each endpoint is not included within the benefit associated with the other endpoint.

Table 7-4. Descriptions of Studies of Respiratory Symptoms Not Requiring Hospitalization

Health Endpoint, PM Indicator	Definition of Health Endpoint	Population Studied	Reference
Chronic bronchitis, using PM_{10} indicator	Chronic bronchitis was defined as positive responses to the following questions: (1) whether a doctor had ever told the subject that he or she had chronic bronchitis and (2) whether he or she still had bronchitis at the time of the study.	All	Schwartz, 1993b
Acute bronchitis, using $PM_{2.5}$ indicator	Bronchitis was defined as a doctor's diagnosis of bronchitis reported within the year prior to the study. Occurrence of bronchitis diagnosed during the year was compared with the annual mean PM concentration reported during the year.	Ages 10-12	Dockery et al., 1989
Upper respiratory symptoms (URS), using PM_{10} indicator	URS includes runny or stuffy nose; wet cough; and burning, aching, or red eyes. Presence of symptoms on a given day were compared with the PM concentration on the same day.	Asthmatics, ages 9-11	Pope et al., 1991
Lower respiratory symptoms (LRS), using $PM_{2.5}$ indicator	LRS is the presence of at least two of the following symptoms: cough, chest pain, phlegm, or wheeze. Presence of symptoms on a given day was compared with PM concentrations measured on the previous day; symptoms were counted only if they were not present on the previous day.	Ages 8-12	Schwartz et al., 1994
Minor Restricted Activity Days (MRADs), using $PM_{2.5}$ indicator	An MRAD is a day in which an individual restricts his or her activity due to either respiratory or nonrespiratory symptoms; an MRAD does not result in either work loss or bed disability Occurrence of MRADs was compared with PM concentrations averaged over a 2-week period.	Ages 18-65	Ostro and Rothschild, 1989
Restricted Activity Days (RADs), using $PM_{2.5}$ indicator	A RAD is a day in which an individual restricts his activity; RADs include both days of work loss or bed disability as well as minor restrictions. Occurrence of RADs was compared with 2-week average PM concentrations.	Ages 18-65	Ostro, 1987

(continued)

Health Endpoint, PM Indicator	Definition of Health Endpoint	Population Studied	Reference
Acute respiratory symptoms (any of 19), using PM_{10} indicator	The study measured daily presence of any of 19 symptoms, including chest discomfort, coughing, wheezing, sore throat, cold, doctor-diagnosed flu, asthma, hay fever (all symptoms considered were not reported in the study)	Adults	Krupnick et al., 1990
Shortness of breath, using PM_{10} indicator	The study measured daily presence of shortness of breath.	African-American asthmatics, ages 7-12	Ostro et al., 1995
Work loss days (WLDs), using $PM_{2.5}$ indicator	Days of work loss were compared with 2-week average PM concentrations.	Ages 18-65	Ostro, 1987

MRADs and Work Loss Days (WLDs) are defined specifically as mutually exclusive endpoints (Ostro and Rothschild, 1989). Both of these estimates (MRADs and WLDs) are subsets of Restricted Activity Days (RADs). However, because the concentration-response functions for RADs and MRADs were estimated by different studies, there is no guarantee that the predicted incidence of MRADs will be less than the predicted incidence of RADs.

7.4.3.2 Respiratory Illnesses Measured in the Asthmatic Population. Three studies in Table 7-4 measured respiratory illnesses exclusively in asthmatic individuals. Pope et al. (1991) studied upper respiratory symptoms (URS) in children ages 9 to 11. Ostro et al. (1995) measured shortness of breath among African-American asthmatics ages 7 to 12[2].

Estimates using Pope et al. (1991) do not appear to overlap with estimates predicted using Ostro et al. (1995).

7.5 References

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[2]Another study, Ostro et al. (1991), measured days of moderate or worse asthma status in adults. Although this study investigated health effects in a population (asthmatics) that is important to consider, the concentration-response function from the study was not used in the current analysis because the incidence estimated using the study is very sensitive to the actual baseline and control scenario air quality data. Because this analysis uses only the air quality contributed by hazardous waste combustors without adding other ambient anthropogenic and natural air concentrations, the actual incidence could not be estimated.

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