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Toxicological Summaries

HEALTH EFFECTS SUMMARIES

This appendix contains health effects summaries for chemicals of potential concern. These summaries provide information on the occurrence and behavior of the COPCS in the environment, potential exposure mechanisms, and adverse health effects that could result from exposure, and the basis and reliability of the quantitative toxicity values used in the risk assessment. Information in each summary is drawn largely from the Public Health statement in the Toxicological Profile or Fact Sheet for the chemical, prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) and the United States Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) profiles, unless otherwise noted.

Arsenic

Arsenic, a naturally occurring element, is present at low levels in soil, water, and air. It is usually found in combination with one or more elements such as oxygen, chlorine, or sulfur; these compounds are called inorganic arsenic. Arsenic is also found in plants, animals, fish, and shellfish, usually in combination with carbon and hydrogen; these compounds, called organic arsenic, are generally less toxic than inorganic arsenic. Arsenic is widely distributed in the environment from natural sources, but higher concentrations have been found to occur in association with chemical waste, smelting of copper and other metals, fossil fuel combustion, and pesticide use. The primary use of arsenic is as a wood preservative, but it is also used to make insect and weed killers and pharmaceuticals.

Arsenic does not break down in the environment, but it can change from one form to another. Most arsenic compounds are soluble in water but do not evaporate. Arsenic can be released into the air when minerals containing arsenic are processed or smelted, or when materials containing arsenic are burned. Airborne particles containing arsenic can settle on the ground, surface water, and plants. Fish and shellfish accumulate arsenic in their tissues, but most of the arsenic in fish is the less-toxic organic arsenic.

Most people are routinely exposed to low levels of arsenic because it is naturally occurring and low levels are present in food, water, soil, and air. Workers in several industries (nonferrous smelting, wood preservation, arsenical pharmaceutical production, and production and application of arsenical pesticides) may be exposed to significantly higher levels. Higher exposures also can result from breathing sawdust or smoke from wood treated with arsenic.

Ingestion of food or water with high levels of inorganic arsenic (60 mg/kg in food or 60 mg/L in water) can be fatal. Chronic arsenic overexposure may cause many health effects, including body weight changes, changes in the blood, and liver and kidney damage. Arsenic damages many tissues, including nerves, stomach, intestines, liver, kidneys, and skin. Breathing high levels can irritate the throat and lungs. Lower levels of exposure to inorganic arsenic may cause nausea, vomiting, and diarrhea; decreased production of red and white blood cells; abnormal heart rhythm; blood vessel damage; and a "pins and needles" sensation in the hands and feet. Long-term exposure to

inorganic arsenic may lead to a darkening of the skin (hyperpigmentation), and the appearance of small "corns" or "warts" (keratosis) on the palms, soles, and torso. Direct skin contact may cause redness and swelling.

The critical or most sensitive effects of arsenic exposure, based on chronic oral exposure to humans, are hyperpigmentation of the skin, keratosis, and possible vascular complications. The oral RfD for arsenic, 3×10^{-4} mg/kg-day, is based on chronic human exposure to elevated levels of inorganic arsenic in drinking water. The principal study upon which the reference dose is based included more than 40,000 individuals, and there are a number of supporting studies. Confidence in the principal study is considered medium. An extremely large number of people were included in the study, but the doses were not well-characterized and other contaminants were present. The supporting human toxicity database is extensive but somewhat flawed. Problems exist with all of the epidemiological studies; however, the database does support the choice of a NOAEL. Confidence in the database as a whole and in the RfD is considered medium.

Arsenic is classified as a Group A human carcinogen by U.S. EPA. Epidemiologic studies and case reports have shown that ingesting inorganic arsenic increases the risk of cancer of the skin, lungs, bladder, and kidneys. Breathing inorganic arsenic increases the risk of lung cancer.

An oral slope factor and inhalation unit risk has been derived for inorganic arsenic. The oral slope factor of $1.5 \text{ (mg/kg-day)}^{-1}$, which is based on increased incidence of skin cancer in humans who consumed drinking water with high arsenic concentrations, was derived from the same principal study as the oral RfD. Although the study included a large number of people, uncertainties about the dosages of arsenic led the U.S. EPA administrator to conclude that the slope factor estimates based on that study could be modified downward by as much as an order of magnitude relative to estimates for most other carcinogens.

The inhalation unit risk, $0.0043 \text{ (}\mu\text{g/m}^3\text{)}^{-1}$, is derived from observations of increased lung cancer mortality in occupationally exposed males. Data from several studies were combined to obtain the final unit risk estimates. Overall, a large study population was observed. Exposure assessments included both work place air and urinary arsenic measurements. The unit risk estimated from the individual studies that were combined to obtain the final estimate all fell within a factor of 6 of one another. All of these factors lead to medium confidence in the final inhalation unit risk estimate.

Source: ATSDR 2005; U.S. EPA 1995.

Cadmium

Cadmium is a naturally occurring element present in trace amounts in the earth's crust. It is usually found as a mineral combined with other elements such as oxygen (cadmium oxide), chlorine (cadmium chloride), or sulfur (cadmium sulfate, cadmium sulfide). Because cadmium does not corrode easily, it has several industrial applications, including metal plating and the manufacture of pigments, batteries, and plastics.

Cadmium enters the air from mining and industrial processes, and from the burning of coal and household wastes, eventually depositing on land and water surfaces. It also can be released to water and soil by waste disposal processes and spills or leaks at hazardous waste sites. Cadmium can bind to soil particles; however, some cadmium dissolves in water. Cadmium does not break down in the environment, but can change from one form to another. Plants and animals take up cadmium from the environment, and cadmium accumulates in body tissues even as a result of prolonged exposure to low levels. Humans are exposed to small quantities of cadmium because it is widely distributed in air, water, soil, and food. Cadmium can enter the body by absorption from the stomach or intestines after ingestion of food or water containing cadmium, or by absorption from the lungs after inhalation of cadmium-containing dust, mists, or fumes. Food and cigarette smoke are probably the largest sources of cadmium exposure for the general public. Very little cadmium enters the body through the skin.

Cadmium can cause a number of adverse health effects. Ingestion of very high levels of cadmium causes severe irritation to the stomach, leading to vomiting and diarrhea. Breathing high levels of cadmium severely damages the lungs and can cause death. There is very strong evidence that long-term exposure to lower levels of cadmium in air, food, or water leads to a build up of cadmium in the kidneys and possible kidney disease. Long-term human exposure by the inhalation route may cause kidney damage and lung disease such as emphysema.

Studies of animals given cadmium in food or water indicate that high blood pressure, iron-poor blood, liver disease, and nerve or brain damage may result. It is not known if humans get any of these diseases from eating or drinking cadmium. Skin contact with cadmium is not known to cause health effects in humans or animals.

The most sensitive or critical effect of cadmium exposure is abnormal kidney function as indicated by significant proteinuria. Oral RfDs (5×10^{-4} mg/kg-day [water] and 1×10^{-3} mg/kg-day [food]) have been derived for cadmium based on a toxicokinetic model that predicts NOAELs for chronic cadmium exposure in water (5×10^{-3} mg/kg-day) and food (0.01 mg/kg-day). An UF of 10 was applied to each NOAEL to obtain the RfDs. The toxicokinetic model was used to identify the level of chronic human oral exposure that results in a concentration of 200 μ g cadmium/gm human renal cortex (wet), the highest renal level not associated with significant proteinuria. Confidence in the RfDs is high because the NOAEL reflects data obtained from many studies on cadmium toxicity in both humans and animals. These data also permit calculation of pharmacokinetic parameters of cadmium absorption, distribution, metabolism, and elimination. Taken together, this information gives a high level of confidence in the database and, as a result, a high level of confidence in each of the RfDs.

Studies of humans or animals have not demonstrated increased cancer rates from ingestion of cadmium. However, there is evidence that long-term inhalation of cadmium by workers may be associated with an increased risk of lung cancer. Laboratory rats that inhaled cadmium also have shown increased cancer rates. U.S. EPA classifies cadmium

as a Group B1, probable human carcinogen, based on the occupational studies. The inhalation unit risk, $0.0018 (\mu\text{g}/\text{m}^3)^{-1}$, is based on increased incidence of cancer from lung, tracheal, and bronchial cancers among occupationally exposed males (for example, a 2-fold excess risk of lung cancer observed in cadmium smelter workers). The cohort consisted of 602 white males who had been employed in production work for a minimum of 6 months during the years 1940-1969. An excess lung cancer risk also was observed in three other occupational studies; however, those studies were compromised by the presence of other carcinogens (e.g., arsenic, smoking) or by a small population. Although the inhalation unit risk for cadmium in one animal study was higher (i.e., more conservative) than that used to derive the unit risk, the use of available human data was considered to be more reliable because of species response variations and differences in the forms of cadmium used in the animal studies.

Source: ATSDR 1999; U.S. EPA 1991.

Cobalt

Cobalt is a naturally occurring element found in rocks, soil, water, plants, and animals. Cobalt is used to produce alloys used in the manufacture of aircraft engines, magnets, grinding and cutting tools, artificial hip and knee joints. Cobalt compounds are also used to color glass, ceramics and paints, and used as a drier for porcelain enamel and paints.

Radioactive cobalt is used for commercial and medical purposes. ^{60}Co (read as cobalt sixty) is used for sterilizing medical equipment and consumer products, radiation therapy for treating cancer patients, manufacturing plastics, and irradiating food. ^{57}Co is used in medical and scientific research. It takes about 5.27 years for half of ^{60}Co to give off its radiation and about 272 days for ^{57}Co ; this is called the half-life.

Cobalt enters the environment from natural sources and the burning of coal or oil or the production of cobalt alloys. Exposure to high levels of cobalt can result in lung and heart effects and dermatitis. Liver and kidney effects have also been observed in animals exposed to high levels of cobalt.

Toxicity values for cobalt are not available from EPA's IRIS system. However, in the absence of IRIS values, EPA suggests use of Provisional Peer Reviewed Toxicity Values (PPRTVs) for assessment. This source includes toxicity values that have been developed by the Office of Research and Development/National Center for Environmental Assessment/Superfund Health Risk Technical Support Center (STSC). The PPRTV Oral RfDs for cobalt is $3 \times 10^{-4} \text{ mg}/\text{kg}\text{-day}$ while the chronic inhalation reference concentration is $6 \times 10^{-6} \text{ mg}/\text{m}^3$

Exposure to large amounts of radiation from radioactive cobalt can damage cells in your body from the radiation. You might also experience acute radiation syndrome that includes nausea, vomiting, diarrhea, bleeding, coma, and even death. This would be a rare event.

Nonradioactive cobalt has not been found to cause cancer in humans or animals following exposure in food or water. Cancer has been shown, however, in animals that breathed cobalt or when cobalt was placed directly into the muscle or under the skin. Based on the laboratory animal data, the International Agency for Research on Cancer (IARC) has determined that cobalt and cobalt compounds are possibly carcinogenic to humans. The PPRTV Inhalation Unit Risk for cobalt is $9 \times 10^{-3}(\mu\text{g}/\text{m}^3)^{-1}$

Iron

Iron is a naturally occurring metallic element. It is commonly used to produce steel, special-purpose alloys with magnetic properties, and heat, corrosion and electrical resistances. In combination with other substances, iron is used to make pigments, polishing compounds, catalysts, feeds, disinfectants, and sewage and industrial wastewater treatment chemicals.

Iron is an essential nutrient; required for maintenance of good health. Available data indicate that to protect against the adverse health effects associated with iron deficiency, the RDA (recommended dietary allowance) should be at least 30 mg/day for pregnant women. If ingested in larger quantities iron can be toxic, causing effects such as irritability, seizures, abdominal pain, vomiting, diarrhea, lethargy, and coma. However, apart from accidental or deliberate poisoning, ingestion of sufficient iron to cause these effects is unlikely in most individuals.

Approximately 0.01% of the body burden of iron is excreted daily and the elimination half-time of iron from the body is 10 to 20 years. Humans do not have a mechanism to increase the excretion of absorbed iron in response to elevated body levels. Chronic ingestion of high levels of iron causes an increase in tissue iron levels. During iron overload, excess iron is stored in the liver and other organs. Massive iron overload can lead to liver cirrhosis and damage to other organs including the heart, endocrine glands, and pancreas.

A provisional oral RfD has been developed for iron based on typical dietary intake. The average intakes of iron, which range from 0.15 to 0.27 mg/kg-day do not cause iron overload, yet are sufficient to protect against iron deficiency. Dividing the NOAEL of 0.27 mg/kg-day by an UF of 1 yields a provisional chronic oral RfD of 0.3 mg/kg-day. While confidence in the critical study is high, overall confidence in the overall database is medium because the data are insufficient to determine the chronic dose level that is associated with adverse effects in health individuals. This RfD may not be protective of people with disorders of iron metabolism and could be conservative if applied to forms of iron with low bioavailability.

There is no evidence that iron can cause cancer. Iron has not been assigned a carcinogenicity weight-of-evidence classification by U.S. EPA.

Source: U.S. EPA 1999.

Lead

Lead is a naturally occurring metal that is used in the manufacture of storage batteries and the production of ammunition and miscellaneous metal products (e.g., sheet lead, solder, and pipes). Other uses for lead are in the manufacturing of lead compounds including gasoline additives and pigments. In recent years, the quantity of lead used in paints, gasoline additives, ammunition, and solder has been reduced because of lead's toxic effects.

Lead can enter the body via ingestion and inhalation. Although it may also enter the body through the skin, dermal absorption of inorganic lead compounds is less significant than absorption through other routes. Children appear to be the segment of the population at greatest risk from toxic effects of lead. Children absorb about 50% of ingested lead while adults absorb only 5% to 15%. Initially, lead travels in the blood to the soft tissues (heart, liver, kidney, brain, etc.), then it is gradually sequestered in the bones and teeth. Children retain a larger fraction of the absorbed lead, about 57%, in the blood and soft tissue compartments, whereas in adults roughly 95% of the total body burden of lead is found in bones and teeth.

The most serious effects associated with markedly elevated blood lead levels include neurotoxic effects such as irreversible brain damage. Health effects are the same for inhaled and ingested lead. At blood lead levels of 40 to 100 micrograms per deciliter ($\mu\text{g}/\text{dL}$), children have exhibited nerve damage, permanent mental retardation, colic, anemia, brain damage, and death. Chronic kidney disease is also evident at these levels. For most adults, such damage does not occur until blood lead levels exceed 100 to 120 $\mu\text{g}/\text{dL}$. At these levels, damage to the male reproductive system; miscarriages; anemia; severe digestive system symptoms; decreased reaction time; weakness in fingers, wrists, or ankles; and some increased risk of heart and circulatory system disease may be exhibited.

Developmental effects in children have been identified as the most sensitive or critical effects of lead exposure. IQ, hearing, and growth deficits have been reported in children with blood lead levels of 10 $\mu\text{g}/\text{dL}$. The Center for Disease Control (CDC) regards 10 $\mu\text{g}/\text{dL}$ as a level of concern for blood lead based on the evidence of adverse health effects at that level and above. U.S. EPA has adopted the 10 $\mu\text{g}/\text{dL}$ blood lead level as a target to assist in evaluating progress in reducing lead exposure. This level is not considered to be a threshold for adverse health effects; rather, it is a benchmark that is subject to revision. U.S. EPA recognizes that there may be a small but finite risk of health effects at lower levels.

None of the epidemiology studies conducted to explore the relationship between lead exposure and increased cancer risk found any relationship. However, animal studies have shown increased kidney cancer and central nervous system (CNS) cancer in rats and mice. The U.S. EPA has classified lead as a Group B2 probable human carcinogen.

U.S. EPA currently provides neither a RfD for evaluating noncarcinogenic effects nor a SF for evaluating possible carcinogenic effects of lead exposure. The absence of toxicological values reflects the scientific community's inability to agree on the threshold dose for lead's noncarcinogenic effects or to satisfactorily estimate its carcinogenic potential, despite a rather large body of scientific literature on its toxic effects.

Source: ATSDR 2007, U.S. EPA 1988.

Manganese

Manganese, a naturally occurring element, is usually found combined with other elements such as oxygen, sulfur, and chlorine. Manganese is used in the steel industry; metallurgical processing; the production of dry cell batteries; as a component of some ceramics, pesticides, and fertilizers; and in nutritional supplements. Manganese is an essential element for humans and is a cofactor for a number of enzymatic reactions. The United States National Research Council recommends a provisional daily dietary intake of manganese of 2.0 to 5.0 gram for adults.

Manganese enters the air primarily through the burning of fossil fuels and emissions from factories where metallic manganese is produced from ores. It can be released to water and soil from factories or spills and leaks at hazardous waste sites. Some manganese compounds are soluble in water, and low levels of these compounds are normally present in lakes, streams, and the ocean. Manganese does not break down in the environment, but can change from one form to another.

Because manganese occurs naturally in the environment, humans are exposed to low levels of manganese in water, air, soil, and food. Food is the primary source of manganese for most people. There are few reports of negative health effects in humans exposed to manganese in drinking water or food. Laboratory studies of animals exposed to manganese in water or food have demonstrated adverse health effects, including changes in brain chemical levels, low birth weights in rats when mothers were exposed during pregnancy, slower than usual testes development, decreased body weight gain, and weakness and muscle rigidity in monkeys.

Inhalation of manganese dust at mining or ore processing plants and inhalation of welding fumes may be significant sources of occupational exposure. Following inhalation of manganese dust, absorption into the bloodstream occurs only if particles are sufficiently small to be able to penetrate deeply into the lungs. Long-term inhalation of manganese dust may result in a neurological disorder characterized by irritability, difficulty in walking, and speech disturbances. Impotence and loss of libido also have been reported in men exposed to high levels of manganese in air. Short-term inhalation exposure has been associated with respiratory disease.

Several studies were used to derive the oral RfD for dietary manganese, 1.4E-01 mg/kg-day. While those studies report average levels of manganese in various diets, no

quantitative information is available to indicate toxic levels of manganese in the diet. Because humans maintain homeostatic control of manganese uptake and elimination, there is a wide range of dietary intakes considered to be safe. The determination of a single acceptable intake of manganese in the diet does not reflect the considerable variability in its absorption and elimination by humans, which are influenced by both environmental and biological factors. Confidence in the database and in the dietary RfD for manganese is medium.

For assessments of exposure to manganese in soil or drinking water, U.S. EPA recommends that the oral RfD should be adjusted by subtracting the amount of manganese that would be consumed in a normal diet (assuming 5 mg/day for a 70 kg adult, or 0.071 mg/kg-day) and dividing by an UF of 3. The resulting oral RfD for soil or water is 2.4×10^{-2} mg/kg-day. Region 3 (U.S. EPA 2006) does not conduct this non-standard adjustment to the oral RfD and therefore was not used in this risk assessment.

The inhalation RfC for manganese, 0.00005 mg/m³, is based on a study in which impairment of neurobehavioral function in occupationally exposed individuals was identified as the critical effect. The principal study included 92 male workers exposed to manganese dioxide dust in a Belgian alkaline battery plant for an average of 5.3 years (range: 0.2 to 17.7 years) and a control group of 101 male workers. Confidence in the study and the database is considered medium. The principal study did not identify a NOAEL for neurobehavioral effects, nor did it measure particle size directly or provide information on particle size distribution. These limitations are mitigated by the fact that the principal study found similar indications of neurobehavioral dysfunction, and these findings were consistent with the results of other human studies. In all of the principal and supporting studies, the exposure duration was relatively limited and the workers were relatively young. These temporal limitations raise concerns that longer exposure durations and/or interactions with aging might result in the detection of effects at lower concentrations. There also is insufficient information on the developmental and reproductive effects of manganese inhalation. Medium confidence in the inhalation RfC follows medium confidence in the principal studies and the database.

There are no human carcinogenicity data for manganese exposure. The data from some animal studies have shown increases in tumors in a small number of animals at high doses of manganese, but the data are inadequate to judge whether manganese can cause cancer. The U.S. EPA has placed manganese in Group D (not classifiable as to human carcinogenicity).

Source: ATSDR 2001; U.S. EPA 1988; U.S. EPA 2006.

Mercury and Methyl Mercury

Mercury is a naturally occurring element that exists in three oxidation states—metallic mercury (Hg⁰), mercurous mercury (Hg¹⁺), and mercuric mercury (Hg²⁺)—and a variety of chemical forms. Mercury is used in a variety of manufactured products, including thermometers, barometers, batteries, mercury lamps, and paint, and as a catalyst in the manufacture of chlorine, caustic soda, and other chemicals. Man-made sources of

mercury in the environment include mercury mining and smelting operations, industrial processes that use mercury, fossil fuel combustion, and waste disposal.

The most important forms of mercury with respect to human exposure are methyl mercury, mercuric mercury, and elemental mercury. Elemental mercury, the principal form in the atmosphere, can be transported long distances, eventually depositing on land and in surface waters. In soils and surface waters, mercury can exist in the mercuric and mercurous states as complex ions with varying water solubilities. Inorganic forms tend to sorb to soil and sediment particles and are relatively immobile; however, chemical and biological processes can convert sorbed mercury to more mobile forms, including elemental mercury and volatile organic forms. The most common organic form, methyl mercury, is relatively mobile, and it quickly enters the aquatic food chain and bioaccumulates in aquatic organisms.

Non-occupational exposure to inorganic mercury and methyl mercury compounds occurs primarily through ingestion, with the major source of human exposure to methyl mercury occurring through the consumption of fish and shellfish. Mercury also can enter the body readily through inhalation of mercury vapor, which is the principal route of occupational exposure.

The form of mercury determines its distribution in the body and its health effects. Metallic mercury and organic mercury distribute primarily to the kidneys; however, they also can readily cross the blood-brain and placental barriers. Long-term exposure to these forms of mercury can permanently damage the brain, kidneys, and developing fetus. Inorganic mercuric compounds also are distributed primarily to the kidneys, similar to metallic mercury; however, the amount that crosses the blood-brain and placental barriers is much lower.

The nervous system appears to be the most sensitive target of low-level exposure to metallic and organic mercury. CNS effects associated with chronic inhalation of mercury vapors or chronic ingestion of methyl mercury include tremors, memory loss, impaired vision, and irritability. Prenatal exposure to methyl mercury via maternal ingestion can cause neurological effects in the children ranging from slowed mental and coordination development at low exposure levels to severe, irreversible brain damage from mercury poisoning. The most sensitive target of exposure to inorganic mercury salts appears to be the kidneys, though brain effects also have been reported.

A chronic oral RfD of 3×10^{-4} has been established for mercuric chloride and other soluble salts based on rat subchronic feeding and subcutaneous studies that reported autoimmune effects. An UF of 1000 was applied to the LOAEL, 10 to convert to and expected NOAEL, 10 for the use of subchronic studies, and 10 for both animal-to-human extrapolation and protection of sensitive human subpopulations. While no one study was considered adequate, based on the weight of evidence from available studies and the entirety of the data base, confidence in this oral RfD is high.

The oral RfD for methylmercury, 1×10^{-4} mg/kg-day, is based on neurologic abnormalities observed in human infants whose mothers ingested methylmercury in their diet. An UF of 10 was applied to the NOAEL to account for variability in the human population and for the lack of a two-generation reproductive study and lack of data for the effect of exposure duration on longer-term effects. Confidence in the RfD is medium.

The inhalation RfC, 0.0003 mg/m^3 , which is specifically for elemental mercury, is derived from a human inhalation study in which neurotoxicity was identified as the critical effect. A NOAEL of 0.009 mg/m^3 was identified in the critical study and an UF of 30 was applied.

Mercuric chloride and methylmercury have been classified by U.S. EPA as Group C possible human carcinogens; however, SFs have not been derived for these chemicals. Inorganic mercury has not been found to be carcinogenic in animals or humans and has been placed in Group D, not classifiable as to human carcinogenicity, by the U.S. EPA.

Source: ATSDR 1999; U.S. EPA 2005.

Nickel

Nickel is a naturally occurring metal found in small quantities in the earth's crust. Nickel is used industrially in making various steels and alloys and in electroplating. Exposure to nickel and nickel compounds may occur through inhalation of dust and particles, ingestion of food and drinking water containing nickel, and by absorption through the skin. Nickel has been shown to be essential nutrients for some species of animals and may be essential to humans.

Inhalation exposure to high levels of nickel and nickel compounds may have adverse effects on the lungs. Exposure by oral and inhalation routes may also affect the immune system, kidneys, and blood. Inhalation of nickel at concentrations greater than 0.001 mg/m^3 in air may cause immune system depression, lung irritation, and pulmonary disease. Death may result from inhalation of concentrations greater than 0.1 mg/m^3 .

An oral RfD for soluble salts of nickel, 0.02 mg/kg-day , is based on decreased organ and body weights in rats who ingested nickel in their diet. The NOAEL of 5 mg/kg-day was multiplied by an UF of 300 to account for interspecies extrapolation, protection of sensitive populations, and inadequacies in the reproductive studies. Confidence in the oral RfD is medium.

Inhalation of nickel refinery dust has caused cancer of the lung, nasal cavity, and voice box in humans. Nickel refinery dust and nickel subsulfide have been classified as Group A human carcinogens. EPA's inhalation unit risk for nickel subsulfide is $0.00026 (\mu\text{g/m}^3)^{-1}$ and is based on four data sets, all from human exposure, offer a range of incremental unit risk estimates that are consistent with each other. In addition,

increased tumor incidences in animals by several routes of administration in several animal species and strains; and positive results in genotoxicity assays provide additional evidence for carcinogenicity.

Source: ATSDR 2005; U.S. EPA 1987; U.S. EPA 1991.

THALLIUM

Pure thallium is a bluish-white metal that is found in trace amounts in the earth's crust. In the past, thallium was obtained as a by-product from smelting other metals; however, it has not been produced in the United States since 1984. Currently, all the thallium is obtained from imports and from thallium reserves.

In its pure form, thallium is odorless and tasteless. It can also be found combined with other substances such as bromine, chlorine, fluorine, and iodine. When it's combined, it appears colorless-to-white or yellow. Thallium enters the environment primarily from coal-burning and smelting, in which it is a trace contaminant of the raw materials. It stays in the air, water, and soil for a long time and is not broken down. Some thallium compounds are removed from the atmosphere in rain and snow. It's absorbed by plants and enters the food chain. It builds up in fish and shellfish. Exposure may also occur via ingestion of food that contains trace amounts of thallium and smoking cigarettes.

Exposure to high levels of thallium can result in harmful health effects. A study on workers exposed on the job over several years reported nervous system effects, such as numbness of fingers and toes, from breathing thallium. Studies in people who ingested large amounts of thallium over a short time have reported vomiting, diarrhea, temporary hair loss, and effects on the nervous system, lungs, heart, liver, and kidneys. It has caused death. It is not known what the effects are from ingesting low levels of thallium over a long time.

RfD values for thallium soluble salts range from 8×10^{-5} to 9×10^{-5} mg/kg-day. These estimates were based on a principal study conducted in by Midwest Research Institute (MRI); 1988). The high-dose group in the principal study (0.25 mg/kg-day thallium sulfate or 0.20 mg/kg-day Tl) was identified as the no-observed-adverse-effect level (NOAEL) and a NOAEL-LOAEL approach was used to identify the point of departure (POD). The RfD was derived by using a composite uncertainty factor (UF) of 3,000 (10 to extrapolate from subchronic to chronic data, 10 for intraspecies extrapolation, 10 to account for interspecies variability, and 3 to account for lack of reproductive and chronic toxicity data).

However, EPA has recently withdrawn the thallium RfD (for soluble salts) based on data quality issues. EPA states that the principal study [MRI (1988)] suffers from certain critical limitations (e.g., high background incidence of alopecia, lack of histopathological examination of skin tissue in low- and mid-dose groups, and inadequate examination of objective measures of neurotoxicity), and there are particular difficulties in the selection of appropriate endpoints. Therefore, even though an RfD would generally be derived with

a combined uncertainty factor of 3000, and RfD for soluble thallium salts is not derived in this specific case.

Source: ATSDR 1992, EPA 2009

Vanadium

Vanadium is a naturally occurring gray metal. In the environment, vanadium is usually combined with elements such as oxygen and sulfur. Vanadium compounds, primarily vanadium pentoxide, are used extensively in industry. The largest industrial use of vanadium oxide is in steel manufacturing, but vanadium compounds also are used in plastic, rubber, ceramic, and other chemical manufacturing.

Burning of fuel oil is the largest source of vanadium releases to the atmosphere, which are generally in the form of vanadium oxides. Deposition of atmospheric vanadium is an important source of vanadium in soil and water; however, natural releases from weathering of rocks and soil erosion are far greater than anthropogenic sources to the atmosphere. Vanadium is not generally very soluble in water, but it can be carried with small particles in surface water and groundwater.

Because vanadium occurs naturally, people are likely to be exposed to low concentrations of vanadium in food and drinking water. People can be exposed to vanadium in air near industries that use vanadium, waste disposal areas of these industries, or downwind of fuel oil or coal burning areas. Most inhaled or ingested vanadium is not absorbed from the respiratory or digestive tract. Only a small amount is absorbed into the bloodstream, and most of that leaves the body quickly in the urine. Vanadium is not believed to be absorbed through skin. Humans exposed to large amounts of vanadium in air have experienced coughs, and eye and throat irritation. However, these effects stop soon after exposure ceases.

Long-term oral exposure of rats to vanadium causes minor cell changes in the kidney and lungs. Female rats exposed to vanadium have offspring of decreased body weights. It is unknown whether humans experience effects similar to vanadium-exposed rats. The oral RfD for vanadium is currently under review by the U.S. EPA. The provisional oral RfD for vanadium, 0.001 mg/kg-day, is based on a study in which rats were administered vanadium in their drinking water.

There have been no specific studies of the carcinogenicity of vanadium. No increased incidence of cancer has been noticed in studies of long-term oral exposure of rats, but these studies are less sensitive than specific cancer studies. Vanadium has not yet received a weight-of-evidence classification from the U.S. EPA.

Source: ATSDR 1995.