CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Beryllium is a lightweight metal that occurs naturally in rocks, coal, soil, and volcanic dust. Commercially, bertrandite and beryl ore are mined for the recovery of beryllium. Because beryllium is the lightest non-reactive metal and is very rigid, it has many uses in the electronics, aerospace, and defense industries. Beryllium is released into the atmosphere by windblown dust, volcanic particles, the combustion of coal and fuel oil, and beryllium manufacturing.

As an element, beryllium does not degrade in the environment; it only changes form. Beryllium particulates in the atmosphere will settle out or be removed by precipitation. The annual average concentration of beryllium in ambient air in the United States is typically below 0.2 ng/m^3 (EPA 2022a). Higher concentrations were recorded in industrial land use areas. Beryllium concentration in urban air is usually higher, possibly due to burning of coal and fuel oil. Sax et al. (2006) analyzed indoor and outdoor home air in New York City and Los Angeles. The mean concentrations of beryllium in indoor home air were 0.0015 ng/m^3 for New York City and 0.0018 ng/m^3 in Los Angeles; the mean concentrations in air outside the home were 0.0028 ng/m^3 in New York City and 0.0018 ng/m^3 in Los Angeles.

Beryllium can be released into waterways by the weathering of soil and rocks. Beryllium entering surface water and soil will be retained in the sediment and soil and will be generally immobile. Drinking water samples taken as part of a review of national drinking water regulations contain beryllium in concentrations ranging from 0.002 to 2000 µg/L (0.000002–2 mg/L) (EPA 2016).

Although beryllium occurs naturally in water, soil, and foodstuffs, the most significant route of human exposure to beryllium occurs in the workplace to its commercial forms as beryllium metal, beryllium-containing metal alloys, and beryllium oxide ceramics. People who work in beryllium manufacturing, fabricating, and reclaiming industries have a greater probability of inhalation exposure than nonoccupational groups. Because beryllium is found in all soils, the general population can be exposed to trace amounts of beryllium through inhalation of air, consumption of food, water and incidental soil ingestion, and skin contact with air, water, or soil that contains beryllium. Naturally occurring beryllium has not been associated with beryllium-related health effects. Individuals living near sources of beryllium emissions, such as beryllium manufacturing facilities or municipal waste sites, are potentially at risk of exposure to beryllium levels above background. Dental technicians are exposed to beryllium through

inhalation exposure (Stark et al. 2014). People working in aeronautics and aircraft industries may be exposed to beryllium through repair and maintenance of beryllium-containing parts such as aircraft bushings and bearings (Kreiss et al. 2007). Measurements in water and soil at these sites are generally higher than background levels. Therefore, individuals living near these sites may be at risk of exposure to higher levels of beryllium than background levels of beryllium. Air levels in the vicinity of active beryllium use facilities may also be higher than naturally occurring concentrations.

1.2 SUMMARY OF HEALTH EFFECTS

The general population can be exposed to beryllium via inhalation, oral, and dermal routes of exposure. The inhalation route is of greatest health concern. In inhalation exposures, the lung appears to be the deposition spot from which beryllium may distribute to other parts of the body. Beryllium and its compounds are poorly absorbed after oral exposure. Typically, oral exposures result in the most beryllium accumulation in the bone or liver. Limited available information suggests that beryllium is likely to be poorly absorbed following dermal exposure. Dermal exposure to soluble beryllium compounds can result in beryllium sensitization. The distribution of beryllium in the body is dependent on the form and solubility of beryllium and its particle size.

The primary potential adverse health effects of beryllium are respiratory effects and lung cancer following inhalation exposure, and skin effects following dermal exposure; these effects, along with beryllium sensitization, are discussed in greater detail below. The reader is referred to Chapter 2 for additional information. Human and animal data provide evidence that inhaled beryllium can be a human lung carcinogen; oral data are inadequate for the assessment of carcinogenic potential.

Beryllium exposure may result in acute beryllium disease (ABD), beryllium sensitization, subclinical chronic beryllium disease (CBD), and clinical CBD. Each of these health outcomes have their own diagnostic criteria. A person with any form of CBD will also be diagnosed with beryllium sensitization. These effects have been observed in beryllium process workers, family members exposed to worker's contaminated clothing, or residents living near a beryllium processing facility. A study of miners exposed to naturally occurring beryllium (bertrandite ore) did not find an increased risk of CBD (Deubner et al. 2001b).

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Occupational exposure to high concentrations of soluble beryllium compounds can result in ABD, while exposure to very low concentrations of soluble or insoluble beryllium compounds can result in CBD. Adherence to worker exposure controls in the workplace have now made the occurrence of ABD rare.

ABD is characterized by inflammation of the respiratory tract tissues, is usually resolved within several months of exposure termination, and has been reduced by control measures implemented in the workplace. In contrast, CBD is an immune response to beryllium observed in individuals who are genetically sensitive to beryllium and become sensitized to beryllium. A Beryllium-Associated Worker Registry of Department of Energy workers and contractors is maintained by Oak Ridge Institute for Science and Education. Descriptions and analysis of this data set can be found at https://oriseapps.orau.gov/BAWR/Default.aspx.

Dermal contact with soluble beryllium compounds may result in an inflammatory skin response, such as dermatitis, skin granulomas, or edema. Skin ulcerations have been reported in workers exposed to soluble beryllium salts with abraded or broken skin.

Unlike inhalation and dermal exposure routes, oral exposures to beryllium have not been shown to have an immune response as the primary effect. There are no reliable human data for oral exposure to beryllium. In animals, the most sensitive effects after oral exposure appear to be ulcerative gastrointestinal lesions and beryllium rickets. Ulcerative lesions were observed in dogs exposed to beryllium sulfate. Beryllium rickets do not appear to be due to a direct effect of beryllium on the bone. Rather, the rickets are due to a phosphorus deficiency, which is hypothesized to result from the precipitation of beryllium with dietary phosphorus in the acidic environment of the digestive tract (Kay and Skill 1934). Additionally, these effects have only been observed following exposure to beryllium carbonate.

Respiratory Effects. Respiratory effects resulting from exposure to beryllium usually manifests as one of two syndromes: ABD or CBD. ABD has a short period of induction and is usually resolved within a couple of months after exposure. ABD is an inflammatory and/or immunological response to beryllium. Most regions of the respiratory tract are affected by ABD; some reported symptoms include nasopharyngitis, shortness of breath, labored breathing, and chemical pneumonitis.

CBD is a granulomatous disorder of the lungs caused by an immune reaction to inhaled beryllium in genetically susceptible persons who are sensitized to beryllium. In general, CBD has been confined to

workers exposed to beryllium metal and insoluble beryllium compounds in the workplace, such as beryllium oxide. However, there have been a few reported cases among residents living near beryllium manufacturing facilities whose first exposures were all in the 1940s and 1950s (Eisenbud et al. 1949; Maier et al. 2008), and in families of workers who wore contaminated clothing at home (Chesner 1950; Dattoli et al. 1964; Eisenbud et al. 1949; Lieben and Metzner 1959; Lieben and Williams 1969; Newman and Kreiss 1992). When genetically predisposed individuals inhale beryllium, it can bind to proteins/peptides and elicit a proliferation of T-lymphocytes, a release of inflammatory mediators, and an accumulation of inflammatory cells in the lungs. This reaction may result in the formation of noncaseating granulomas, accumulation of mononuclear cell infiltrates, and development of fibrosis.

Beryllium sensitization is usually diagnosed as consistent abnormal blood and/or lung beryllium lymphocyte proliferation test (BeLPT) results, and can progress to CBD, but not all sensitized individuals will develop CBD. Individuals with subclinical CBD are sensitized to beryllium and have histological evidence of lung granulomas, but no clinical signs. Individuals with clinical CBD are beryllium sensitized and have histological evidence of lung granulomas, respiratory symptoms, changes on chest radiographs, and/or altered lung function. Beryllium sensitization and/or CBD have been detected at exposure levels as low as 0.2 $\mu g/m^3$. Respiratory disease is not likely to occur from exposure to beryllium levels in the general environment because ambient air levels of beryllium (0.03–0.2 ng beryllium/m^3) are very low. Other than the relatively few historical cases of CBD resulting from beryllium emissions from primary commercial beryllium operations, beryllium disease has not been detected in the general population from either naturally occurring ambient airborne beryllium or anthropogenic ambient airborne emissions from noncommercial beryllium sources such as power plants.

Gastrointestinal Effects. No human data were located regarding gastrointestinal effects following exposure to beryllium. Gastrointestinal effects have been observed in a dog study but not in a study in rats; the toxicological significance of these effects to humans is unclear given the conflicting results in the animal studies. Extensive ulcerative and inflammatory lesions of the small intestine, stomach, and large intestine have been observed in dogs exposed to dietary beryllium sulfate tetrahydrate over 26–33 weeks (2.7–3.3 years) (Morgareidge et al. 1976). In a study by the same group, no lesions in small or large intestines were observed in rats exposed to a similar beryllium-containing diet for 2 years (Morgareidge et al. 1975). The difference in observed gastrointestinal outcomes between dogs and rats may be associated with the difference in the frequency of beryllium exposure due to different eating patterns. Dogs that had access to the beryllium-containing diet for 1 hour/day showed higher concentrations of beryllium in gastrointestinal tract tissues than rats that had unlimited access to the diet.

Dermal Effects. Dermal responses to soluble beryllium compound exposure involve immune system reactions. Edematous papulovesicular dermatitis was observed in workers exposed to airborne beryllium sulfate, beryllium fluoride, or beryllium oxyfluoride; this is likely an inflammatory response to beryllium (VanOrdstrand et al. 1945). Biopsied skin granulomas from beryllium workers had the same mononuclear infiltrates as detected in the lungs (McConnochie et al. 1988). Guinea pigs sensitized with beryllium sulfate developed granulomatous lesions and other delayed hypersensitivity reactions following dermal exposure to beryllium sulfate, beryllium fluoride, beryllium oxide, or beryllium chloride (Belman 1969; Marx and Burrell 1973).

Immunological Effects. Beryllium exposure may cause an immune reaction that presents with respiratory, dermal, or other symptoms. Beryllium and the soluble and insoluble compounds can be sensitizing and induce a cell-mediated immune response to beryllium (CDC 1983; Cullen et al. 1987; Rossman et al. 1988; Saltini et al. 1989). This heightened immune response to beryllium is the cause of CBD and certain skin lesions (NRC 2008). Granuloma formation in the lungs is the principal immunological effect caused by exposure to airborne beryllium. Certain genetic variations can cause increased risk of beryllium sensitization.

Cancer Effects. Fifteen epidemiology studies have assessed the carcinogenic potential of beryllium inhalation exposure. Several retrospective cohort mortality studies have observed increased incidence of lung cancer mortality among workers at beryllium extraction, processing, and fabrication facilities. Increased lung cancer mortality was also seen in studies looking at entrants to the Beryllium Case Registry administered by Massachusetts General Hospital (Infante et al. 1980; Steenland and Ward 1991). In addition, a positive association between length of latency (length of time since onset of exposure) and lung cancer mortality was observed, with the highest mortality rate among workers with a latency of 25 years (Wagoner et al. 1980). Increased bronchiole tumor incidence has also been observed in rats exposed to beryllium (Vorwald and Reeves 1959).

The Department of Health and Human Services (HHS) lists beryllium and certain beryllium compounds (beryllium-aluminum alloy, beryllium chloride, beryllium fluoride, beryllium hydroxide, beryllium oxide, beryllium phosphate, beryllium sulfate, beryllium zinc silicate, and beryl ore) as human carcinogens (NTP 2021). The U.S. Environmental Protection Agency (EPA) concluded that the human data provided limited evidence and the animal data provided sufficient evidence of carcinogenicity and therefore classified inhaled beryllium as a probable human carcinogen (IRIS 2002). They determined that

beryllium had inadequate evidence to be able to classify it as carcinogenic by the oral route. Studies in different species of animals demonstrate a similar immunological response as humans as well as other toxicity. However, there are deficiencies in these studies; they do not adequately reproduce features of human CBD. Therefore, these studies cannot reliably predict exposure-response effects of beryllium exposure (NRC 2008). Humans are exposed to lower concentrations of beryllium than levels used in most animal studies; hence, it is pertinent to examine the physiological changes happening at those lower doses. It is potentially likely that prior sensitization in humans is exacerbating the toxic effects. The International Agency for Research on Cancer (IARC) has classified beryllium and beryllium compounds as carcinogenic to humans (IARC 2012).

Figure 1-1 summarizes the health effects observed in animals and humans after inhalation exposure and Figure 1-2 summarizes the health effects observed in animals after oral exposure to beryllium.

Figure 1-1. Health Effects Found in Animals and Humans Following Inhalation Exposure to Beryllium

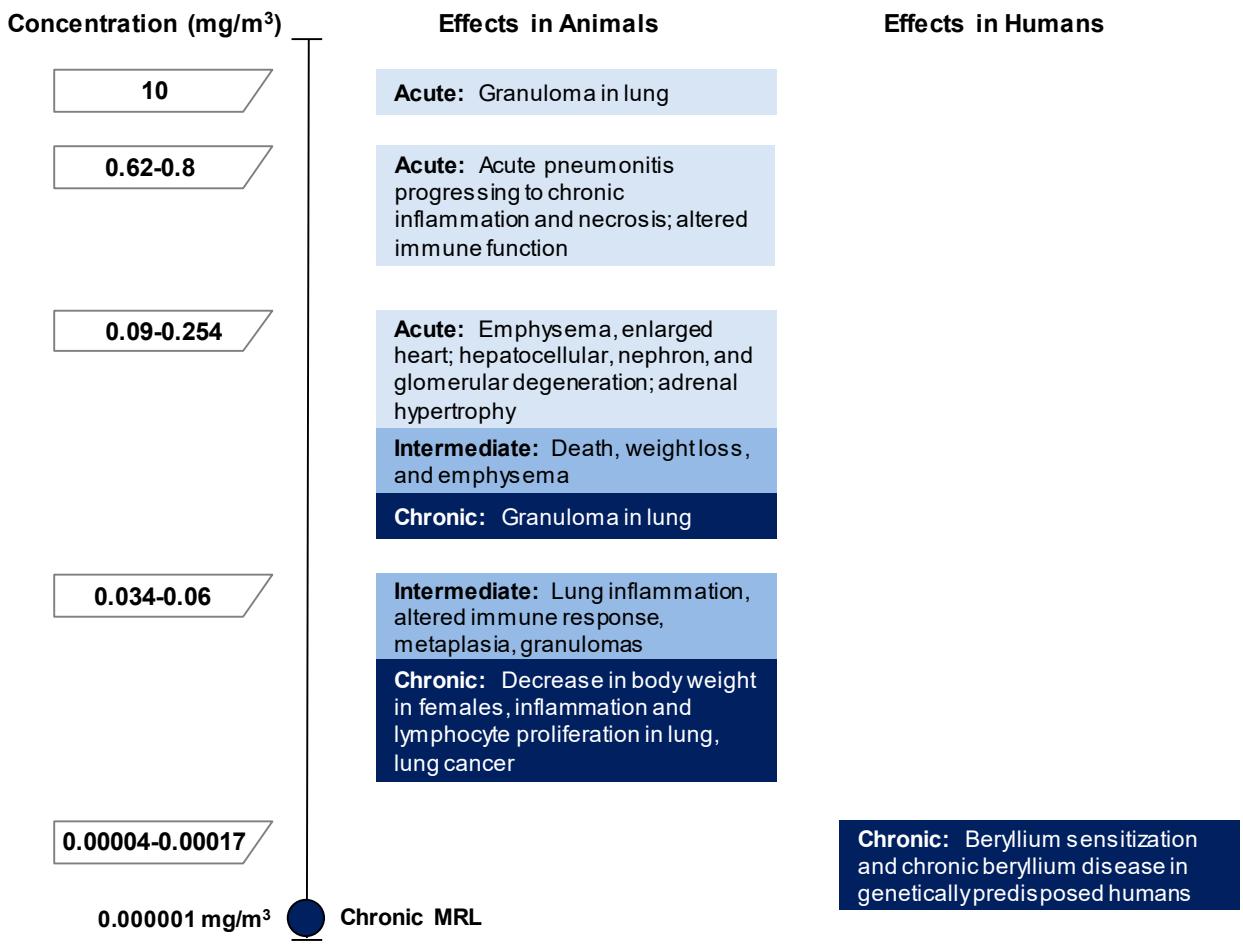
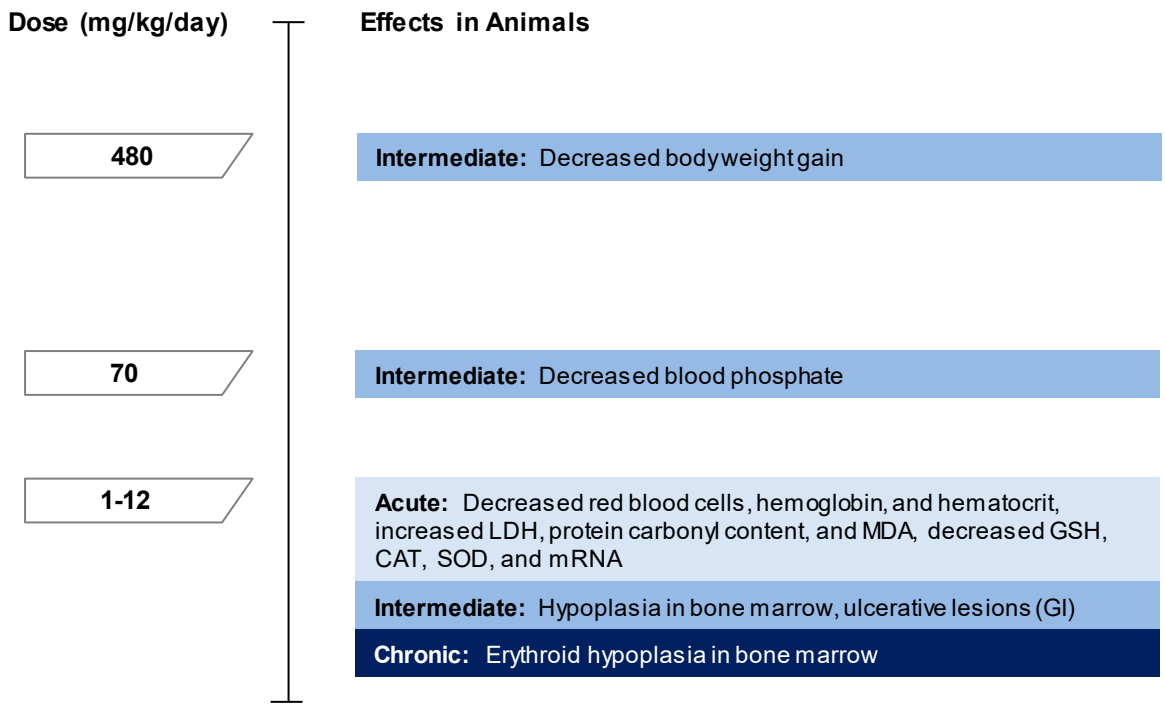


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Beryllium



1.3 MINIMAL RISK LEVELS (MRLs)

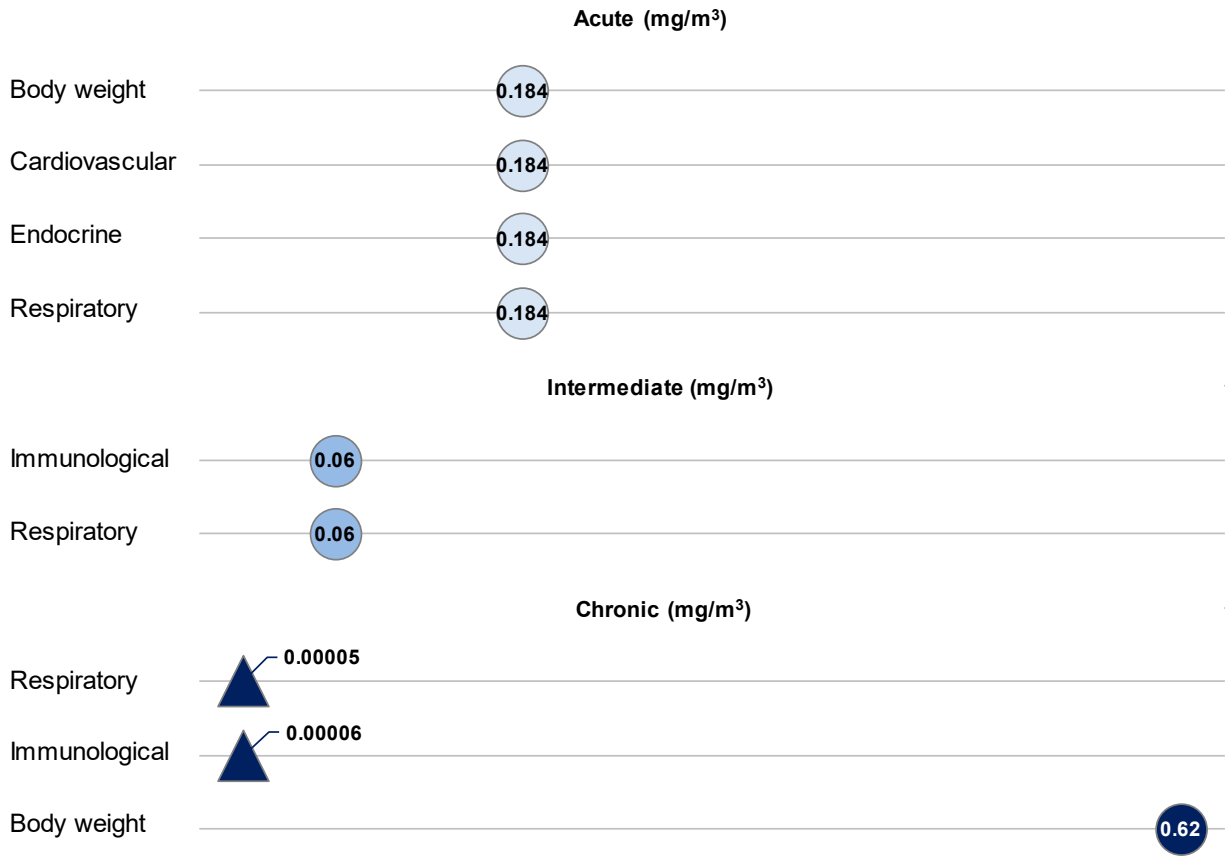
Based on the available human and animal data, the respiratory tract is the critical target of beryllium after inhalation exposures. However, except for the chronic duration, available data were deemed insufficient for deriving inhalation MRLs. The existing animal database is inadequate for developing inhalation MRLs for both acute- and intermediate-duration exposures. In general, animal studies have not identified a reliable no-observed-adverse-effect level (NOAEL) for respiratory effects, and the lowest-observed-adverse-effect levels (LOAELs) are several orders of magnitude higher than the lowest LOAEL identified in occupational exposure studies, suggesting that humans may be the most sensitive species.

As presented in Figure 1-3, following inhalation exposure, the respiratory system is consistently the most sensitive target of beryllium toxicity and immunological health effects manifest as the duration of the exposure increases. The hematological system appears to be the sensitive target of oral beryllium toxicity, as shown in Figure 1-4. The oral database was considered inadequate for derivation of chronic-, intermediate-, and acute-duration oral MRLs. The chronic-duration inhalation MRL is listed in Table 1-1, and the MRL details are discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Beryllium – Inhalation

Respiratory and immunological endpoints are consistently the most sensitive targets of beryllium inhalation exposure across exposure durations.

Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively.*



*For acute inhalation exposure, death, hepatic, and body weight effects were also seen at this dose.

Figure 1-4. Summary of Sensitive Targets of Beryllium – Oral

The hematological endpoint is the most consistently sensitive target of beryllium oral exposure across durations.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

Table 1-1. Minimal Risk Levels (MRLs) for Beryllium[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	None	–	–	–	–	–
	Intermediate	None	–	–	–	–	–
	Chronic	**0.001 µg/m^3**	Beryllium sensitization	LOAEL	0.04 µg/m^3	UF: 30	Schuler et al. 2012
Oral	**No oral MRLs were derived for any duration.**						

[a]See Appendix A for additional information.

LOAEL = lowest observed adverse effect level; POD = point of departure; UF = uncertainty factor