

APPENDIX G
TOXICOLOGICAL PROFILES

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G.1 TOXICOLOGICAL PROFILES

The purpose of the toxicity assessment is to weigh the available and relevant evidence regarding the potential for chemicals to cause adverse health effects to exposed individuals, and to provide a quantitative estimate of the relationship between the magnitude of exposure and the likelihood of adverse effects (USEPA, 1989). This section summarizes the potential toxic effects of each chemical of potential concern (COPC) as well as the relevant toxicity criteria that are used to assess the risks associated with the dose of the COPCs. Only those chemicals that contributed significantly to estimates of cancer risk or noncancer hazard are presented. A fundamental principle of toxicology is that the dose determines the severity of the effect. Accordingly, the toxicity criteria describe the quantitative relationship between the dose of a chemical and the type and incidence of the toxic effect. This relationship is referred to as the dose-response. The types of toxicity criteria are described below followed by brief discussions of specific criteria and associated health effects for each COPC.

G.1.1 TOXICITY CRITERIA

A dose-response evaluation is the process of quantitatively evaluating toxicity information and characterizing the relationship between the dose of the chemical and the incidence of adverse health effects in the exposed population. From this quantitative dose-response relationship, toxicity criteria are derived that can be used to estimate the potential for adverse health effects as a function of exposure to the chemical. Toxicity values are combined with the summary intake factors calculated in the Exposure Assessment and are used to calculate human risks for various exposure scenarios. For purposes of calculating exposure criteria to be used in risk assessments, adverse health effects are classified into two broad categories: noncarcinogens and carcinogens. Toxicity criteria are generally developed based on the threshold approach for noncarcinogenic effects and the nonthreshold approach for carcinogenic effects. The toxicity criteria are called cancer slope factors (SFs) for cancer effects and reference doses (RfDs) for noncancer effects.

In this assessment, chronic toxicity criteria were selected (in order of preference) from the following sources: (1) Office of Environmental Health Hazard Assessment (OEHHA) Cancer Potency Factors (CalEPA, 2004), (2) USEPA's Integrated Risk Information System (2004); (3) USEPA Health Effects Assessment Summary Tables (HEAST; 1997); and/or (4) USEPA-NCEA Superfund Health Risk Technical Support Center.

G.1.1.1 Cancer Effects

The cancer SF (in units of $(\text{mg}/\text{kg}\cdot\text{day})^{-1}$) expresses excess cancer risk as a function of dose. The dose-response model is based on high- to low-dose extrapolation, and assumes that there is no lower threshold for the initiation of toxic effects. Specifically, cancer effects observed

at high doses in laboratory animals or from occupational or epidemiological studies are extrapolated, using mathematical models, to low doses common to environmental exposures. These models are essentially linear at low doses, such that no dose is without some risk of cancer. USEPA has developed SFs for both the oral (ingestion) and inhalation routes of exposure.

Furthermore, USEPA uses an evaluation process in which chemicals are assigned a “weight-of-evidence” classification. This describes the likelihood, based on scientific evidence, that the substance could cause cancer in humans. USEPA has established the following classification system for weight of evidence (1989):

- **Group A** chemicals (known human carcinogens) are agents for which there is sufficient evidence to support the causal association between exposure to the agents in humans and cancer.
- **Group B1** chemicals (probable human carcinogens) are agents for which there is limited evidence of carcinogenicity in humans.
- **Group B2** chemicals (probable human carcinogens) are agents for which there is sufficient evidence of carcinogenicity in animals, but inadequate evidence or lack of evidence of carcinogenicity in humans.
- **Group C** chemicals (possible human carcinogens) are agents for which there is limited evidence of carcinogenicity in animals and inadequate or lack of human data.
- **Group D** chemicals (not classifiable as to human carcinogenicity) are agents with inadequate human and animal evidence of carcinogenicity or for which no data are available.
- **Group E** chemicals (evidence of noncarcinogenicity in humans) are agents for which there is no evidence of carcinogenicity from human or animal studies, or both.

G.1.1.2 Noncancer Effects

Chronic RfDs are defined as an estimate of a daily exposure level for the human population, including sensitive populations, that is likely to be without appreciable risk of noncancer effects during a lifetime of exposure (USEPA, 1989). Chronic RfDs are specifically developed to be protective for long-term exposure to a chemical and are generally used to evaluate the potential noncancer effects associated with exposure periods of 7 years to a lifetime. RfDs are expressed as mg/kg-day and are calculated using lifetime average body weight and intake assumptions.

RfD values are derived from experimental data on the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) in animals or humans. The NOAEL is the highest tested chemical dose given to animals or humans that has not been associated with any adverse health effects. The LOAEL is the lowest chemical dose at which health effects have been reported. RfDs are calculated by dividing the NOAEL or LOAEL by a total uncertainty factor, which represents a combination of individual factors for various sources of uncertainty associated with the database for a particular chemical or with the extrapolation of animal data to humans. IRIS also assigns a level of confidence in the RfD. The level of confidence is rated as either high, medium, or low based on confidence in the study and in the database. USEPA has developed RfDs for both the oral (ingestion) and inhalation routes of exposure. If an inhalation RfD is not available, a chronic reference exposure level (REL) was used instead, if available for the specific COPC. The chronic REL is adjusted (using an adult body weight and inhalation rate of 70 kg and 20 m³/day, respectively) to derive an inhalation RfD, which is then used in the risk assessment.

G.1.2 CHEMICAL PROFILES

Toxic effects of the chemicals of concern are summarized in the following subsections along with the toxicity criteria for assessing noncancer and cancer effects. In general, the information has been summarized from the latest available Agency for Toxic Substances and Disease Registry (ATSDR) profile for each chemical.

G.1.2.1 Arsenic

Arsenic (CAS No. 7440-38-2) exists in a number of chemical forms (e.g., elemental arsenic (As), common inorganic compounds arsenic trioxide, arsenic pentoxide, etc.). Arsenic is one of the most abundant elements in the earth's crust and occurs most often as the sulfide in a variety of complex minerals (Budavari et al., 1989). Arsenic trioxide is the most commercially important form of arsenic and is produced primarily from flue dust that is generated at copper and lead smelters. The principal use of arsenic (as arsenic trioxide) is in wood preservatives and a smaller proportion is used in the production of agricultural chemicals such as insecticides, herbicides, algacides, and growth stimulants for plants and animals. The use of many arsenical pesticides has been phased out because of concerns about human health risks during production or use. Arsenic trioxide is no longer produced in the United States. Smaller amounts of arsenic are used in the production of glass and nonferrous alloys and in the semiconductor industry.

An increase of lung cancer mortality was observed in multiple human populations exposed primarily through inhalation. Also, increased mortality from multiple internal organ cancers (liver, kidney, lung, and bladder) and an increased incidence of skin cancer were observed in

populations consuming drinking water high in inorganic arsenic (Chen et al., 1986). There has been no consistent demonstration of carcinogenicity in test animals for various chemical forms of arsenic administered by different routes to several species (IARC, 1980).

The ATSDR has derived a chronic oral minimal risk level (MRL) of 3.0E-04 mg As/kg-day for inorganic arsenic. This MRL is based on a NOAEL of 8.0E-04 mg As/kg-day observed in a large Taiwanese population exposed to arsenic mainly via drinking water (Tseng, 1977; Tseng et al., 1968). An uncertainty factor of three was applied to account for (1) the lack of data to preclude reproductive toxicity as a critical effect, and (2) some uncertainty pertaining to whether the NOAEL of the critical study accounts for all sensitive individuals. USEPA has also derived chronic and subchronic oral Reference Doses (RfDs) of 3.0E-04 mg/kg-day for inorganic arsenic, based on the NOAEL of 8.0E-04 mg/kg-day in humans chronically exposed to arsenic (USEPA, 2004; Tseng, 1977). The oral RfD for arsenic is based on the occurrence of hyperpigmentation and hyperkeratosis and vascular complications observed in the Taiwanese population ingesting elevated levels of arsenic in drinking water. USEPA places medium confidence in the chronic RfD.

An inhalation RfD or reference concentration (RfC) has not been estimated for arsenic (USEPA, 2004). However, a chronic reference exposure level (REL) of 0.03 (ug/m³) was proposed by OEHHA (Cal-EPA, 2004). An adjustment of the REL was made to derive an inhalation RfD of 8.6E-06 mg/kg-day for arsenic (0.03 ug/m³ x 0.001 mg/ug x 20 m³/day x 1/70 kg), which was used in this risk assessment.

The oral unit risk factor for estimating excess lifetime cancer risks is based on the incidence of skin cancer observed in the Taiwanese population ingesting elevated levels of arsenic in drinking water. Doses were converted to equivalent doses for males and females in the United States based on differences in body weights and differences in water consumption. It was assumed that skin cancer risk in the US population would be similar to that in the Taiwanese population. The maximum likelihood estimate (MLE) of skin cancer risk for a 70-kg person drinking 2 liters of water per day ranged from 1.0E-03 to 2.0E-03 for an arsenic intake of 1 µg/kg-day. Expressed as a single value, the cancer unit risk for drinking water is 5.0E-05 liters/µg. Details of the assessment are in USEPA (1988a). Using the assumptions of 2 liters/day drinking water consumption and 70-kg body weight, this unit risk factor converts to an oral SF of 1.5E+00 (mg/kg-day)⁻¹. It should be noted that the USEPA's assessment is based on Taiwanese data on the prevalence of skin cancer from the IRIS database. However, arsenic has also been associated with internal organ cancers, particularly lung and bladder cancer (USEPA, 2004). Recent epidemiological data from South America indicate that risks based on fatal internal cancer could be an order of magnitude higher than risks based on skin cancer. Thus, risks calculated from IRIS could be underestimated.

OEHHA (CalEPA, 2004) estimated an inhalation SF of $1.2\text{E}+01$ $(\text{mg}/\text{kg}\text{-day})^{-1}$ and an inhalation unit risk factor of $3.3\text{E}-03$ $(\mu\text{g}/\text{m}^3)^{-1}$, which were the values used in this risk assessment; since occupational exposure to airborne arsenic has been reported to be associated with lung cancer (USEPA, 2004). The data considered in developing the inhalation SF and the unit risk factor was taken from occupational mortality studies of smelter workers in Anaconda, Montana (Welch et al., 1982; Higgins et al., 1985; and Lee-Feldstein, 1986), and in Tacoma, Washington (Enterline et al., 1987).

USEPA (2004) has assigned arsenic to a weight-of-evidence Group A classification, a human carcinogen, based on sufficient evidence of cancer mortality from both ingestion and inhalation exposures in human populations. The International Agency for Research on Cancer (IARC) classifies arsenic as a proven human carcinogen.

G.1.2.2 Benzene

Benzene (CAS No. 71-43-2), also known as benzol, is a colorless liquid with a sweet odor. It is released in the environment by both natural and industrial sources, although anthropogenic emissions are the most significant.

The ATSDR has derived an acute inhalation maximum likelihood estimate (MRL) of 0.05 ppm for benzene based on a LOAEL for immunological effects in mice exposed to 10.2 ppm benzene for 6 hours a day for 6 consecutive days (Rozen et al., 1984). ATSDR has derived an intermediate inhalation MRL of 0.004 ppm for benzene based on a LOAEL for neurological effects in mice exposed to 0.78 ppm benzene for 2 hours a day, 6 days a week for 30 days (Li et al., 1992). The RfC and RfD for benzene are undergoing review by a USEPA workgroup (IRIS, 1996). However, a chronic reference exposure level (REL) of 60 $(\mu\text{g}/\text{m}^3)$ was proposed by OEHHA. An adjustment of the REL was made to derive an inhalation RfD of $1.7\text{E}-02$ $\text{mg}/\text{kg}\text{-day}$ for benzene ($60 \mu\text{g}/\text{m}^3 \times 0.001 \text{ mg}/\mu\text{g} \times 20 \text{ m}^3/\text{day} \times 1/70 \text{ kg}$), which was used in this risk assessment. Furthermore, the oral RfD of $4.0\text{E}-03$ $\text{mg}/\text{kg}\text{-day}$ for benzene, as listed in the (USEPA, 2004), was used in this risk assessment.

USEPA (2004) has assigned benzene to a weight-of-evidence Group A classification, a human carcinogen. Under the Proposed Guidelines for Carcinogen Risk Assessment (USEPA, 1996), benzene is characterized as a known human carcinogen for all routes of exposure based upon convincing human evidence as well as supporting evidence from animal studies. Numerous occupational epidemiological studies have shown that exposure to benzene is causally related to an increase in the risk of cancer, specifically leukemia. Occupational or environmental exposure to benzene or benzene-containing materials usually occurs through the inhalation or dermal route. The main route of exposure is considered to be inhalation. Also, many experimental animal studies support the evidence that exposure to benzene via the inhalation and oral routes increases the risk of cancer in multiple organ

systems including the hematopoietic system, oral and nasal cavities, liver, forestomach, preputial gland, lung, ovary, and mammary gland.

Benzene has an inhalation unit risk estimate ranging from 2.2E-06 to 7.8E-06 per $\mu\text{g}/\text{m}^3$ and an oral risk factor of 1.4E-01 $\mu\text{g}/\text{kg}\text{-day}$ (USEPA, 1999). However, OEHHA (CalEPA, 2004) estimated an oral SF of 1.0E-01 $(\text{mg}/\text{kg}\text{-day})^{-1}$, an inhalation SF of 1.0E-01 $(\text{mg}/\text{kg}\text{-day})^{-1}$, and an inhalation unit risk factor of 2.9E-05 $(\mu\text{g}/\text{m}^3)^{-1}$, which were the values used in this risk assessment. The data considered in developing the cancer SFs and the unit risk factor was taken from an occupational inhalation exposure study of the leukemogenic effects of benzene exposure in 748 white male workers exposed at least 1 day while employed in the manufacture of rubber products (Rinsky et al., 1981). Seven deaths from leukemia were reported in this cohort study. Epidemiologic studies and case studies provide clear evidence of a causal association between exposure to benzene and acute nonlymphocytic leukemia. These human data are supported by animal studies.

G.1.2.3 Chloroform

Chloroform (CAS No. 67-66-3) is a colorless, volatile liquid that is widely used as a general solvent and as an intermediate in the production of refrigerants, plastics, and pharmaceuticals (Torkelson and Rowe, 1981). Chloroform is rapidly absorbed from the lungs and the gastrointestinal tract, and to some extent through the skin. It is extensively metabolized in the body, with carbon dioxide as the major end product. The primary sites of metabolism are the liver and kidneys.

Target organs for chloroform toxicity are the liver, kidneys, and central nervous system. Liver effects (hepatomegaly, fatty liver, and hepatitis) were observed in individuals occupationally exposed to chloroform (Bomski et al., 1967). Several subchronic and chronic studies by the oral or inhalation routes of exposure documented hepatotoxic effects in rats, mice, and dogs (Heywood et al., 1979). Renal effects were reported in rats and mice following oral and inhalation exposures (Roe et al., 1979; Reuber, 1979), but evidence for chloroform-induced renal toxicity in humans is sparse. Chloroform is a central nervous system depressant, inducing narcosis and anesthesia at high concentrations. Lower concentrations may cause irritability, lassitude, depression, gastrointestinal symptoms, and frequent and burning urination.

A RfD of 1.0E-02 $\text{mg}/\text{kg}\text{-day}$ for subchronic and chronic oral exposure was calculated from a LOAEL of 15 $\text{mg}/\text{kg}\text{-day}$ based on fatty cyst formation in the liver of dogs exposed to chloroform for 7.5 years (Heywood et al., 1979). A chronic reference level (REL) of 300 $(\mu\text{g}/\text{m}^3)$ was established.

USEPA (2004) assigned chloroform to a weight-of-evidence Group B2 classification, a probable human carcinogen, on the basis of an increased incidence of several tumor types in rats and in three strains of mice. OEHHA (CalEPA, 2004) calculated a cancer slope factor (SF) for chloroform of $3.1\text{E-}02$ (mg/kg-day)⁻¹ for oral exposure, a $1.9\text{E-}02$ (mg/kg-day)⁻¹ for inhalation exposure and an inhalation unit risk of $5.3\text{E-}06$ (ug/m³)⁻¹.

G.1.2.4 Carcinogenic Polycyclic Aromatic Hydrocarbon (PAHs)

The IARC has evaluated the carcinogenic potential of many PAHs (IARC, 1983a). IARC groupings correspond to current USEPA IRIS classifications of carcinogenicity except for anthracene, which USEPA considers a Class D carcinogen while IARC finds limited evidence for its carcinogenicity in animals.

Carcinogenic effects have been demonstrated in animal bioassays by oral and dermal exposure routes. However, systemic cancer effects have not been demonstrated via dermal (skin painting) contact. USEPA-verified slope factors are available for both ingestion and inhalation exposures to benzo(a)pyrene. It is believed that benzo(a)pyrene and other carcinogenic PAHs induce tumors both at the site of application and systemically.

Of the PAHs, seven are considered to be potential human carcinogens: benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, chrysene, dibenzo(a,h)anthracene, and indeno(1,2,3-cd)pyrene. Oral and inhalation CSFs are only available for benzo(a)pyrene. Sufficient data are available to support the argument that the carcinogenicity of PAH mixture is due primarily to PAH chemicals with three (or greater) rings and that they share a common mechanism, of cancer induction (USEPA, 1993). Consequently, it is reasonable to assume that the carcinogenicity of the other six PAHs is similar to that of benzo(a)pyrene.

USEPA and CalEPA have recommended the use of scaling factors for the six PAHs lacking CSFs. These factors relate the carcinogenic potency of each PAH to that of benzo(a)pyrene. These factors are called potency equivalent factors (PEFs) by CalEPA and toxicity equivalent factors for dioxin and furan congeners. The use of PAH relative potency estimates is restricted to evaluation of carcinogenic risks.

-Benzo[a]pyrene

Benzo[a]pyrene (CAS No. 50-32-8) is a polycyclic aromatic hydrocarbon (PAH) that can be derived from coal tar. Benzo[a]pyrene occurs ubiquitously in products of incomplete combustion of fossil fuels and has been identified in ambient air, surface water, drinking water, waste water, and char-broiled foods (IARC, 1983b). Benzo[a]pyrene is primarily released to the air and removed from the atmosphere by photochemical oxidation and dry

deposition to land or water. Biodegradation is the most important transformation process in soil or sediment (ATSDR, 1990a).

Benzo[*a*]pyrene is readily absorbed following inhalation, oral, and dermal routes of administration (ATSDR, 1990a). Following inhalation exposure, benzo[*a*]pyrene is rapidly distributed to several tissues in rats (Sun et al., 1982; Weyand and Bevan, 1986).

No data are available on the systemic (noncarcinogenic) effects of benzo[*a*]pyrene in humans. In mice, genetic differences appear to influence the toxicity of benzo[*a*]pyrene. Subchronic dietary administration of 120 mg/kg benzo[*a*]pyrene for up to 180 days resulted in decreased survival due to hematopoietic effects (bone marrow depression) in a "nonresponsive" strain of mice (i.e., a strain whose cytochrome P-450 mediated enzyme activity is not induced as a consequence of PAH exposure). Neither a RfD nor a RfC has been derived for benzo[*a*]pyrene.

Numerous epidemiologic studies have shown a clear association between exposure to various mixtures of PAHs containing benzo[*a*]pyrene (e.g., coke oven emissions, roofing tar emissions, and cigarette smoke) and increased risk of lung cancer and other tumors. However, each of the mixtures also contained other potentially carcinogenic PAHs; therefore, it is not possible to evaluate the contribution of benzo[*a*]pyrene to the carcinogenicity of these mixtures (IARC, 1983b). An extensive data base is available for the carcinogenicity of benzo[*a*]pyrene in experimental animals. Dietary administration of benzo[*a*]pyrene has produced papillomas and carcinomas of the forestomach in mice (Neal and Rigdon, 1967), and treatment by gavage has produced mammary tumors in rats (McCormick et al., 1981) and pulmonary adenomas in mice (Wattenberg and Leong, 1970).

USEPA (2004) has assigned benzo[*a*]pyrene to a weight-of-evidence Group B2 classification, a probable human carcinogen. USEPA has determined the oral SF for benzo[*a*]pyrene is $7.3\text{E}+00 \text{ (mg/kg-day)}^{-1}$ based on a study by Neal and Rigdon (1967) in which stomach tumors were induced in mice. OEHHA (CalEPA, 2004) calculated an oral and inhalation slope factor for benzo[*a*]pyrene of $1.2\text{E}+01$ and $3.9\text{E}+00 \text{ (mg/kg-day)}^{-1}$, respectively.

G.1.2.5 1,2-Dichloroethane

1,2-dichloroethane (CAS No. 107-06-2) is used primarily in the manufacture of vinyl chloride, as well as in the synthesis of tetrachloroethylene, trichloroethylene, 1,1,1-trichloroethane, vinylidene chloride, aziridines, and ethylenediamines (USAF, 1989 and ATSDR, 1992). It is added to gasoline as a lead-scavenging agent, and, in the past, has been used as a metal degreasing agent; a solvent; and a fumigant for grain, upholstery, and carpets.

It has also been used in paints, coatings, adhesives, varnishes, finish removers, soaps, and scouring agents (USAF, 1989 and ATSDR, 1992).

1,2-dichloroethane is expected to be highly mobile in most soils, and consequently, contamination of groundwater is possible. Adsorption to soil particles is low, particularly for soils with a low organic carbon content. Volatilization from soils and surface waters may be an important transport process. Microbial biodegradation is not expected to be significant.

Acute inhalation exposures to 1,2-dichloroethane (75-125 ppm) can result in irritation of the eyes, nose and throat, dizziness, nausea, vomiting, stupor, partial paralysis, degenerative heart changes, liver and kidney damage, pulmonary edema, and hemorrhages throughout the body (NIOSH, 1976; CEC, 1986; ATSDR, 1992; Nouchi et al., 1984). Short-term exposures to animals have resulted in central nervous system depression; pulmonary congestion; renal tubular degeneration; fatty degeneration of the liver and, less commonly, necrosis and hemorrhage of the adrenal cortex; and immunodeficiency (Spencer et al., 1951; Heppel et al., 1946; Storer et al., 1984; Sherwood et al., 1987). Chronic occupational exposure to 1,2-dichloroethane may result in central nervous systems effects including irritability, sleeplessness, and decreased heart rate; loss of appetite; nausea; vomiting; epigastric pain, as well as irritation of the mucous membranes; and liver and kidney impairment (NIOSH, 1976). Subchronic or chronic inhalation exposures to animals resulted in pathological lesions in the kidney, liver, heart, lungs, and testes (Heppel et al., 1946; Spencer et al., 1951; Cheever et al., 1990). A subchronic or chronic inhalation RfC for 1,2-dichloroethane has not been adopted and verified by USEPA (2004).

USEPA (2004) has assigned 1,2-dichloroethane to a Group B2 classification, a probable human carcinogen by both the oral and inhalation exposure routes, based on evidence for the induction of several types of tumors in rats and mice. Male rats treated by gavage with 1,2-dichloroethane exhibited increased incidences of fibromas of the subcutaneous tissue; hemangiosarcomas of the spleen, liver, pancreas, and adrenal gland; and squamous-cell carcinomas of the forestomach. Female rats treated by gavage developed mammary adenocarcinomas. Increased incidences of hepatocellular carcinomas and pulmonary adenomas were observed in male mice treated by gavage, and increased incidences of mammary adenocarcinomas, pulmonary adenocarcinomas, and endometrial polyps and sarcomas were observed in female mice (NCI, 1978a). Mice treated by topical application of 1,2-dichloroethane exhibited an increased incidence of lung papillomas (Van Duuren et al., 1979). OEHHA (CalEPA, 2004) has calculated an oral SF of $4.7\text{E-}02 \text{ (mg/kg-day)}^{-1}$, an inhalation SF of $7.2\text{E-}02 \text{ (mg/kg-day)}^{-1}$, and an inhalation unit risk factor of $2.1\text{E-}05 \text{ (}\mu\text{g/m}^3\text{)}^{-1}$ for 1,2-dichloroethane.

G.1.2.6 Methylene Chloride

Methylene chloride (CAS No. 75-09-2), also known as dichloromethane, is a colorless volatile liquid with a penetrating ether-like odor. In industry, methylene chloride is widely used as a solvent in paint removers, degreasing agents, and aerosol propellants; as a polyurethane foam-blowing agent; and as a process solvent in the pharmaceutical industry. The compound is also used as an extraction solvent for spice oleoresins, hops, and caffeine (ATSDR, 1989b; IARC, 1986).

Methylene chloride is readily absorbed from the lungs, the gastrointestinal tract, and to some extent through the skin. Metabolism of methylene chloride produces CO₂ and CO, which readily binds with blood hemoglobin to form carboxyhemoglobin (CO-Hb). The primary adverse health effects associated with methylene chloride exposure are central nervous system (CNS) depression and mild liver effects. Neurological symptoms described in individuals occupationally exposed to methylene chloride included headaches, dizziness, nausea, memory loss, paresthesia, tingling hands and feet, and loss of consciousness (Welch, 1987). Major effects following acute inhalation exposure include fatigue, irritability, analgesia, narcosis, and death (ATSDR, 1989b). CNS effects have also been demonstrated in animals following acute exposure to methylene chloride (Weinstein et al., 1972; Berger and Fodor, 1968).

The oral toxicity of methylene chloride was investigated in a chronic drinking water study in rats (NCA, 1982 as cited in USEPA, 2004). The critical effect observed was liver toxicity in male and female rats. An oral RfD of 6.0E-02 mg/kg-day for methylene chloride was calculated from NOAELs, derived from this study, of 5.85 and 6.47 mg/kg-day for males and females, respectively. The RfD value reflects incorporation of an uncertainty factor of 100. Confidence in the RfD and database is rated medium to high. The inhalation toxicity of methylene chloride was investigated in a 2-year inhalation toxicity study in rats (Nitschke et al., 1988, as cited in USEPA, 1997). The critical effect observed was also liver toxicity. The chronic REL of 4.0E-01 was proposed by OEHHA (CalEPA, 2004). Based on the REL value, the inhalation RfD used in this assessment was thus 1.1E-01 mg/kg-day.

Studies of workers exposed to methylene chloride have not recorded a significant increase in cancer cases above the number of cases expected for nonexposed workers (Hearne et al., 1987; Ott et al., 1983; Friedlander et al., 1978). However, long-term inhalation studies with rats and mice demonstrated that methylene chloride causes cancer in laboratory animals. Mice exposed via inhalation to high concentrations of methylene chloride (2000 or 4000 ppm) exhibited a significant increase of malignant liver and lung tumors compared with nonexposed controls (NTP, 1986a). Rats of both sexes exposed to concentrations of methylene chloride ranging from 500 to 4000 ppm showed increases of benign mammary tumors (NTP, 1986a; Burek et al., 1984). An inhalation study with rats and hamsters revealed

sarcomas of the salivary gland in male rats, but not in female rats or hamsters (Burek et al., 1984).

Based on inadequate evidence of carcinogenicity in humans and on sufficient evidence in animals, USEPA (2004) has assigned methylene chloride to a weight-of-evidence Group B2 classification, a probable human carcinogen. OEHHA (CalEPA, 2004) has established an inhalation unit risk of $1.0\text{E-}06$ ($\mu\text{g}/\text{m}^3$)⁻¹, an inhalation SF of $3.5\text{E-}03$ ($\text{mg}/\text{kg}\text{-day}$)⁻¹ and an oral SF of $1.4\text{E-}01$ ($\text{mg}/\text{kg}\text{-day}$)⁻¹.

G.1.2.7 Tetrachloroethene

Tetrachloroethene (CAS No. 127-18-4) is a halogenated aliphatic hydrocarbon with a vapor pressure of 17.8 mm Hg at 25C (USEPA, 1982). The chemical is used primarily as a solvent in industry and, less frequently, in commercial dry-cleaning operations (ATSDR, 1990b). Occupational exposure to tetrachloroethene occurs via inhalation, resulting in systemic effects, and via dermal contact, resulting in local effects. Exposure to the general population can occur through contaminated air, food and water (ATSDR, 1990b).

The respiratory tract is the primary route of entry for tetrachloroethene (NTP, 1986b; USEPA, 1988b). The chemical is rapidly absorbed by this route and reaches an equilibrium in the blood within 3 hours after the initiation of exposure (Hake and Stewart, 1977). Tetrachloroethene is also significantly absorbed by the gastrointestinal (g.i.) tract, but not through the skin (ATSDR, 1990b). The chemical accumulates in tissues with high lipid content, where the half-life is estimated to be 55 hours (Stewart, 1969; ATSDR, 1990b), and has been identified in perirenal fat, brain, liver, placentofetal tissue, and amniotic fluid.

RfDs for subchronic and chronic oral exposure to tetrachloroethene are $1.0\text{E-}01$ $\text{mg}/\text{kg}\text{-day}$ and $1.0\text{E-}02$ $\text{mg}/\text{kg}\text{-day}$, respectively (Buben and O'Flaherty, 1985, USEPA, 1990; 1992). These values are based on liver toxicity observed in mice given 100 mg tetrachloroethene/kg body weight for 6 weeks and a NOAEL of 20 mg/kg . The inhalation RfD used in this risk assessment is $1.0\text{E-}02$ $\text{mg}/\text{kg}\text{-day}$. This value was based on a chronic REL of 0.035 mg/m^3 derived from chronic toxicity of the kidney, liver, and gastrointestinal system.

Epidemiology studies of dry cleaning and laundry workers have demonstrated excesses in mortality due to various types of cancer, including liver cancer, but the data are regarded as inconclusive because of various confounding factors (USEPA, 1988b). The tenuous finding of an excess of liver tumors in humans is strengthened by the results of carcinogenicity bioassays in which tetrachloroethene, administered either orally or by inhalation, induced hepatocellular tumors in mice (NCI, 1977b; NTP, 1986b). The chemical also induced mononuclear cell leukemia and renal tubular cell tumors in rats. Tetrachloroethene was

negative for tumor initiation in a dermal study and for tumor induction in a pulmonary tumor assay (Van Duuren et al., 1979; Theiss et al., 1977).

Although USEPA's Science Advisory Board recommended a weight-of-evidence classification of C-B2 continuum (C = possible human carcinogen; B2 = probable human carcinogen), the agency has not adopted a current position on the weight-of-evidence classification (USEPA, 1992). In an earlier evaluation, tetrachloroethene was assigned to a weight-of-evidence Group B2 classification, a probable human carcinogen, based on sufficient evidence from oral and inhalation studies for carcinogenicity in animals and no or inadequate evidence for carcinogenicity to humans (NCI, 1977b; NTP, 1986b; USEPA, 1987a). The unit risk and slope factor values for tetrachloroethene have been withdrawn from IRIS and HEAST. The upper bound risk estimates from the USEPA (1985a) Health Assessment Document as amended by inhalation values from the 1987 addendum (USEPA, 1987a) have not yet been verified by the IRIS-CRAVE Workgroup.

OEHHA (CalEPA, 2004) calculated an oral SF of $5.4E-01$ (mg/kg-day)⁻¹, an inhalation SF of $2.1E-02$ (mg/kg-day)⁻¹, and an inhalation unit risk factor of $5.9E-06$ (ug/m³)⁻¹, which were the values used in this risk assessment. The data considered in developing the cancer SFs and the unit risk factor was taken from a lifetime bioassay on mice and rats exposed to 99% pure PCE by inhalation for 103 weeks (NTP, 1986). The critical effects observed in this study included significant increases in mononuclear cell leukemia and increased incidence of both renal tubular-cell adenomas and adenocarcinomas in rats. In addition, a statistically significant increase of hepatocellular adenomas and hepatocellular carcinomas in treated mice was observed.

G.1.2.8 Trichloroethene

Trichloroethene (CAS No. 79-01-6) has been in commercial production for more than 75 years in the United States. This chemical has been used extensively for degreasing of fabricated metal parts; in dry cleaning; as a solvent for oils, resins, waxes, paints, lacquers, printing inks, fabric dyes, and disinfectants; and as an intermediate in the manufacture of other chemicals. Trichloroethene is present in most underground water sources and many surface waters as a result of the manufacture, widespread use, and disposal of the chemical (ATSDR, 1997). In addition, thousands of workers have been chronically exposed to substantial amounts of trichloroethene.

Acute exposure to high levels of trichloroethene vapors may cause impaired heart function, coma, and death, while chronic exposures may cause headaches, fatigue, vomiting, as well as nerve, lung, kidney, and liver damage. Dermal contact for a short period may cause skin rashes, but severe erythema and blistering may result after longer periods of exposure. The dermal effects usually result from direct skin contact with concentrated solutions of

trichloroethene but can also occur following contact with vapors in occupational situations. No dermal effects were reported from exposure to diluted solutions of trichloroethene (ATSDR, 1993b).

High doses of trichloroethene given by oral administration have resulted in liver and lung tumors in mice, but not in rats, cats, or dogs. Rats, but not mice, do develop kidney tumors following high dose exposures to trichloroethene (NTP, 1990; ACGIH, 1992). The differences in biotransformation mechanisms are believed to be the basis for different trichloroethene effects observed in these species (Steinberg and DeSasso, 1993). No increased incidence of tumors was observed in mice with trichloroethene applied to their backs and no studies were located regarding cancer in humans after dermal exposure to trichloroethene (ATSDR, 1993b).

The RfDs for chronic oral and inhalation exposures to trichloroethene are both 6.0E-03 mg/kg-day, as reported in USEPA Region IX's PRG table (2000). Although, the oral RfD has been withdrawn as indicated in the PRG table, it was used in this risk assessment to evaluate oral exposures to trichloroethene.

Although USEPA's Science Advisory Board recommended a weight-of-evidence classification of C-B2 continuum (C = possible human carcinogen; B2 = probable human carcinogen), the agency has not adopted a current position on the weight-of-evidence classification (USEPA, 1992). In a Health Assessment Document (EPA600/8-82/006F) for trichloroethene (USEPA, 1985b), trichloroethene was assigned to weight-of-evidence Group B2 classification, a probable human carcinogen, based on sufficient evidence from oral and inhalation studies for carcinogenicity in animals and no or inadequate evidence for carcinogenicity to humans. The unit risk and slope factor values for trichloroethene have been withdrawn from IRIS and HEAST. However, OEHHA (CalEPA, 2004) estimated an oral SF of 1.5E-02 (mg/kg-day)⁻¹, an inhalation SF of 1.0E-02 (mg/kg-day)⁻¹, and an inhalation unit risk factor of 2.0E-06 (μg/m³)⁻¹.

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