2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1,3-BUTADIENE IN THE UNITED STATES

1,3-Butadiene is a highly volatile gas that is used in the production of synthetic rubber; the major end use of the synthetic rubber is automobile tires. 1,3-Butadiene is also used for the production of high impact polystyrene and acrylonitrile-butadiene-styrene (ABS) resin plastics The predominant source of 1,3-butadiene in the atmosphere is industrial releases, which can occur during manufacturing, use, transport, and storage of the chemical. Automobile exhaust is a constant source of low levels of 1,3-butadiene release to the atmosphere. Minor sources of 1,3-butadiene in the atmosphere include cigarette smoke, wood burning (including forest fires), and the burning of rubber and plastics. In the atmosphere, 1,3-butadiene is expected to undergo photo-initiated destruction with a half-life of approximately 6 hours. Relatively low levels of 1,3-butadiene are released to water and soil. 1,3-Butadiene in water or soil is expected to rapidly evaporate to the atmosphere.

Inhalation is the predominant route of exposure for the general population. Mean concentrations of 1,3-butadiene in the air in cities and suburban areas ranges from 0.1 to 2 $\mu g/m^3$ (0.04–1 ppb); the average background concentration of 0.13 $\mu g/m^3$ (0.59 ppb) has been estimated. Higher atmospheric concentrations have been measured in areas near oil refineries, chemical manufacturing plants, and plastic and rubber factories where 1,3-butadiene is manufactured or used; concentrations as high as 40 $\mu g/m^3$ (18 ppb) have been measured near industrial sites. Within the general population, smokers (and individuals exposed to secondhand smoke) and individuals inhaling smoke from wood fires are likely to be exposed to higher levels of 1,3-butadiene. Workers involved in the production of rubber, plastics, and resins are most likely to receive the largest exposures. No data are available to quantify general population exposure to 1,3-butadiene by other routes of exposure, but it is expected to be very low compared to breathing contaminated air. Low levels of 1,3-butadiene have been detected in U.S. drinking water supplies; however, specific quantitative data were not located. 1,3-Butadiene has also been measured at very low levels in the plastic or rubber of food containers and has been found in a few food samples.

Several biomarkers of exposure have been identified for 1,3-butadiene; these include 1,3-butadiene urinary metabolites, M1 and M2, and three hemoglobin adducts, *N*-(2-hydroxy-3-butenyl)valine (MHB-Val), *N*-(2,3,4-trihydroxybutyl)valine (THB-Val), and *N*,*N*-(2,3-dihyroxy-1,4-butadyl)valine (*pyr*-Val), which are surrogate biomarkers for the 1,3-butadiene metabolites 1,2 epoxy-3-butene (EB),

1,2-dihydroxy-3,4-epoxybutane (EBD), and 1,2:3,4-diepoxybutane (DEB), respectively. In workers, the levels of urinary metabolites and hemoglobin adducts have been shown to correlate with 1,3-butadiene exposure levels. However, background levels for the general population have not been established for these biomarkers of exposure.

2.2 SUMMARY OF HEALTH EFFECTS

The available data for 1,3-butadiene exposure and toxicity in humans and animals are limited to inhalation exposures; the effects from significant oral or dermal exposures are not known. Information on the toxicity of 1,3-butadiene in humans comes from case reports and epidemiology studies that primarily focused on the potential carcinogenicity of 1,3-butadiene. Slight eye irritation and difficulty in focusing on instrument scales were reported by two men exposed to 2,000 or 4,000 ppm 1,3-butadiene for 6–7 hours; however, this was not reported when the two men were exposed to 8,000 ppm for 8 hours. Psychomotor tests conducted in these subjects did not find alterations at 2,000–8,000 ppm. Numerous epidemiological studies of multiple occupational cohorts, including one encompassing 15,000 workers, have associated a higher incidence of hemato-lymphopoietic cancer mortality among exposed workers. Although most of these workers were co-exposed to other organic compounds, including styrene, benzene, and dithiocarbamates, multivariate analysis suggested that the estimates of 1,3-butadiene exposure provided the best correlation with the rates of lympho-hematopoietic cancers.

Numerous target organs for 1,3-butadiene toxicity have been identified in well-conducted laboratory studies ranging from single episode to lifetime exposures. Observed effects include death, neurological dysfunction, reproductive and developmental effects, hematological and lymphoreticular effects, and cancer. Evaluation of the relevance of adverse health effects observed in laboratory animals to human health is encumbered by large species differences in the metabolism of 1,3-butadiene. The metabolism of 1,3-butadiene in humans and laboratory animals involves the same enzymatic pathways; however, there are notable quantitative differences in the production and detoxification of several reactive metabolites, particularly, EB, DEB, and EBD; see Sections 3.4.2 and 3.5.3 for more information on species differences. Mice, the most sensitive species, are more efficient at converting 1,3-butadiene to EB and converting EB to DEB. Using *pyr*-Val hemoglobin adduct levels as a biomarker for blood DEB levels, an exposure to approximately 1 ppm 1,3-butadiene resulted in mouse DEB levels that were 50 times higher than rats and 1,000 times higher than humans. Although the mode of action has not been elucidated for all toxic end points, there are strong data to support the reactive metabolites as the causative agents for the ovarian atrophy, cancer, and genotoxic effects observed in laboratory animals. Without information on

the mode of action, particularly the causative agent, the reader should use caution in evaluating the relevance of the animal data presented in this section to human health.

Lesions of the respiratory tract (olfactory tissues and lungs), liver, kidney, stomach, and eyes have been seen in mice exposed to ≥200 ppm for intermediate durations, but these lesions are typically epithelial or endothelial hyperplasias and are precancerous in nature. Non-neoplastic lesions of the liver (necrosis) in rats and kidney (renal nephrosis) in mice occurred following intermediate-duration exposure to 625 or 8,000 ppm, respectively.

Although no biologically relevant alterations in hematological parameters have been observed in 1,3-butadiene workers, changes in the blood and lymphoid tissues are common observations in rodents exposed for intermediate and chronic durations. Decreases in red blood cell counts and hemoglobin concentration occurred at 65 ppm in mice, progressing to macrocytic megaloblastic anemia from exposures of 200 ppm. These effects are likely associated with observed changes in normal bone marrow function, as indicated by reduced circulation of erythrocytes and leukocytes, and increased proliferative activity with no associated change in bone marrow cellularity. Lymphoreticular toxicity in mice was indicated by significant changes in thymus weight and lesions in lymphoid organs following intermediate-duration exposures to 625–1,250 ppm in mice. A reversible suppression of cytotoxic T-lymphocyte generation to mastocytoma cells and a depression of spleen cellularity were observed at these exposures. The changes in spleen and thymus weights, lymphocytic differentiation, and appearance of lymphoid lesions comport with the onset of lymphoma in mice after chronic exposure to 1,3-butadiene.

Reproductive and developmental effects are the most sensitive non-cancer effects observed in rodents. Wavy ribs and skeletal abnormalities occurred in offspring of rats exposed to 1,000–8,000 ppm during gestation days (GDs) 6–15. In mice, exposure of pregnant dams to 40 ppm on GDs 6–15 resulted in a 5% decrease in fetal body weight among male mice. Exposure of mice to ≥200 ppm resulted in ≥19% reductions in fetal weight. A possible dominant lethal effect was observed in mice in which increased fetal deaths occurred from exposure to 200 ppm. The lowest lowest-observed-adverse-effect level (LOAEL) identified for intermediate-duration exposures was 12.5 ppm in male mice mated with unexposed females, resulting in increased late fetal death, exencephaly, and skull abnormalities of fetuses. Serious lesions of reproductive tissues in male and female mice have arisen from intermediate- and chronic-duration exposures. Ovarian atrophy, including complete loss of oocytes, follicles, and corpora lutea, occurred in mice exposed to 200 ppm for 9 months and as low as 6.25 ppm for 2 years. Male mice

were somewhat less sensitive, with testicular atrophy observed after 15-month exposures to 625 ppm 1,3-butadiene.

The consistent carcinogenic responses in rodent bioassays support the associations derived in epidemiological studies between hemato-lymphopoietic cancer and 1,3-butadiene exposure. In rats, 2-year exposure to 1,000 or 8,000 ppm resulted in increased incidences of tumors of the testes, pancreas, uterus, mammary gland, Zymbal gland, and thyroid. In mice, exposure to 200 ppm for 40 weeks resulted in increased tumor incidences of lymphopoietic system, heart, lung, stomach, liver, and eye. These same tumors developed in mice in as little as 13 weeks after exposure to 625 ppm. Chronic exposure of mice to concentrations of 20 ppm (males) and 6.25 ppm (females) of 1,3-butadiene resulted in increased tumor development in the lymphopoietic system, heart, lung, stomach, liver, eye, mammary glands, and ovaries.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

The toxicity of 1,3-butadiene following inhalation exposure has been examined in epidemiology studies, intermediate- and chronic-duration studies in rats and mice, reproductive toxicity studies in mice, and developmental toxicity studies in rats and mice. The epidemiological studies have primarily focused on carcinogenicity and have found increases in lympho-hematopoitic cancers. Observed effects found in animal studies include neurological dysfunction, reproductive and developmental effects, hematological and lymphoreticular effects, and cancer. Acute exposures have resulted in fetal effects (decreased growth and skeletal defects) (DOE/NTP 1987b; Irvine 1981) and reproductive effects (increased intrauterine death following male-only exposure) (DOE 1988b). Intermediate-duration exposures in mice resulted in precancerous lesions of the respiratory tract (olfactory tissues and lungs), liver, kidney, stomach, and eyes (NTP 1984, 1993). Non-neoplastic lesions of the liver (necrosis) in rats and kidney (renal nephrosis) in mice occurred following intermediate-duration inhalation exposure. In mice, intermediate-duration inhalation exposure also resulted in decreases in red blood cell counts and hemoglobin concentration, progressing to macrocytic megaloblastic anemia (NTP 1993), decreases in spleen and thymus weight (NTP 1993), and depressed splenic cellularity (Thurmond et al. 1986). Chronic-duration inhalation exposure studies identified a number of targets of toxicity in mice including, bone marrow, lungs, heart, forestomach, Harderian gland, testes, ovaries, and uterus (NTP 1984, 1993); neoplastic lesions were also observed in a number of tissues. In rats, chronic exposure resulted in histological alterations in the lungs and increased severity of nephropathy (Owen et al. 1987).

Comparison of rat and mouse data identifies large differences in sensitivity to 1,3-butadiene, which are due to metabolic differences between species. As discussed in Sections 3.4.2 and 3.5.3, quantitative differences between humans, rats, and mice in the rate of formation of reactive metabolites, particularly EB and DEB have been found. These differences result in higher tissue levels of reactive metabolites in rodents than in humans (Bond et al. 1993; Csanády et al. 1992; Dahl et al. 1991; Filser et al. 2001, 2007, 2010; Henderson et al. 1996, 2001; Himmelstein et al. 1997; Kirman et al. 2010a; Krause and Elfarra 1997; Schmidt and Loeser 1985; Thornton-Manning et al. 1995b). Following inhalation exposure to 1,3-butadiene, blood EB levels were 2–8 times higher in mice as compared to rats (Filser et al. 2007) and the maximum butadiene-diol levels were 4 times higher in mice than rats (Filser et al. 2007). The DEB levels were >100-fold higher in mice as compared to rats (Filser et al. 2007). At a similar exposure level (1 ppm), mice produce approximately 1,000 times as much DEB as humans, as measured using *pyr*-Val hemoglogin adduct as a biomarker and 50 times as much DEB as rats (Swenberg et al. 2011).

The Agency usually considers humans more sensitive than animals and makes an adjustment to the point of departure to account for species differences when deriving an MRL from an animal study. If possible, chemical-specific data, such as physiologically based pharmacokinetic (PBPK) modeling, is used to account for toxicokinetic differences between species. Although PBPK models for 1,3-butadiene have been developed in rodents (Johanson and Filser 1993; Kohn and Melnick 1993, 1996, 2000) and a preliminary model has been developed in humans (Brochot et al. 2007), the models are limited in their ability to predict internal doses for key metabolites (Kirman and Grant 2012). An alternative to using PBPK models would be to use a biomarker of exposure to reactive metabolites. Several biomarkers of exposure have been identified for reactive 1,3-butadiene metabolites including MHB-Val hemoglobin adducts, THB-Val hemoglobin adducts, and *pyr*-Val hemoglobin adducts, which have been shown to be good surrogate biomarkers for EB, EBD, and DEB, respectively (Georgieva et al. 2010; Slikker et al. 2004). However, there are limited mechanistic data that would allow identification of the 1,3-butadiene metabolite(s) (or parent compound) that is responsible for the non-neoplastic effects, with the exception of ovarian atrophy observed in mice, which is likely due to DEB.

In the absence of chemical-specific data, the Agency generally applies an uncertainty factor of 10 to account for interspecies differences in toxicokinetic and toxicodynamic properties. However, the toxicokinetic data for 1,3-butadiene indicate that mice are many-fold more sensitive than humans. Thus, the Agency can only use an uncertainty factor of 1 (or not apply an uncertainty factor [UF]), which in the case of 1,3-butadiene, may cause the MRL to overestimate the risk to humans. Therefore, in this instance,

the Agency has elected to not derive inhalation MRLs for 1,3-butadiene. Brief discussions of the available literature for each duration period are presented below.

Acute-Duration Inhalation MRL. Death and neurological effects have been observed in rats, mice, and rabbits exposed to 8,000–250,000 ppm from <1 to 4 hours (Carpenter et al. 1944; Shugaev 1969). Studies examining nonlethal effects were limited to three developmental toxicity studies and a reproductive toxicity study. Significant increases in the occurrence of major skeletal defects, predominantly wavy ribs, were observed in the offspring of Sprague-Dawley rats exposed to 1,000 or 8,000 ppm 1,3-butadiene 6 hours/day on GDs 6–15 (Irvine 1981). Other non-concentration-related effects included an increase in minor skeletal defects at 200 ppm, but not at higher concentrations, and increases in the occurrence of minor external/visceral defects at 1,000 ppm, but not at 8,000 ppm. The study also found decreases in fetal growth (body weight and crown-rump length) at 8,000 ppm and decreases in maternal weight gain at ≥200 ppm; at 8,000 ppm, maternal body weight gain was 45% lower than controls. The investigators noted that the increase in the occurrence of wavy ribs was likely secondary to the decrease in maternal weight gain. In a second rat developmental toxicity study, no developmental effects (including alterations in occurrence of skeletal defects, fetal body weight, or maternal body weight) were observed in Sprague-Dawley rats exposed to 40–1,000 ppm 6 hours/day on GDs 6–15 (DOE/NTP 1987a). In a mouse developmental toxicity study, decreases in fetal body weight were observed in the offspring of CD-1 mice exposed to ≥40 ppm 6 hours/day on GDs 6–15 (DOE/NTP 1987b). The male fetal body weights were 5, 18, and 23% lower than controls and no significant alterations in female body weight were observed; interpretation of these results is limited by the lack of statistical adjustment for litter size. In the reproductive toxicity study, the mating of male CD-1 mice exposed to ≥200 ppm 6 hours/day for 5 days with unexposed females resulted in significant increases in dams with two or more intrauterine deaths (DOE/NTP 1988b). This effect was only observed when the mating occurred 1 week post-exposure, suggesting that the mature spermatozoa and/or spermatids were the targets.

The limited available data on the toxicity of 1,3-butadiene following acute-duration inhalation exposure suggest that mice are more sensitive than rats for developmental effects. Exposures to 1,3-butadiene has resulted in decreases in fetal body weights in mice at ≥40 ppm (DOE/NTP 1987b) and rats at ≥200 ppm (Irvine 1981), dominant lethal effects in mice at ≥200 ppm (DOE/NTP 1988b), and increases in skeletal malformations in rat fetuses at ≥1,000 ppm (Irvine 1981). The no-observed-adverse-effect levels (NOAELs) were 40 ppm for dominant lethal effects in mice and 200 ppm for skeletal defects in rats. As noted previously, the Agency has elected to not derive an acute-duration inhalation MRL for 1,3-butadiene due to the large species differences in the metabolism of 1,3-butadiene and the lack of

chemical-specific data to adjust for these differences, which may result in the MRL overestimating the risk to humans.

Intermediate-Duration Inhalation MRL. Intermediate-duration exposures resulted in death in mice exposed to 5,000 ppm, 6 hours/day for 5 weeks (NTP 1984) and 200 ppm, 6 hours/day for 40 weeks (NTP 1993). No systemic effects were seen in rats or mice exposed to 8,000 ppm, 6 hours/day for 13–14 weeks, with the exception of a 13% body weight reduction in mice exposed to 2,500 ppm (NTP 1984). Exposure of mice to 625 ppm, 6 hours/day for 40 weeks resulted in pre-cancerous hyperplasia of the respiratory and gastrointestinal systems (epithelial hyperplasia), as well as a 19% reduction in thymus weight. Multi-site cancer was observed in mice after 13–52 weeks of exposure to 200 ppm for 6 hours/day (NTP 1993). Hematological effects included decreased erythrocyte counts, hemoglobin concentration, and red blood cell volume in mice at 62.5 ppm and macrocytic megaloblastic anemia at 200 ppm, administered 6 hours/day for 40 weeks (NTP 1993). Reproductive effects in mice were the most sensitive effects observed, with ovarian atrophy occurring at exposures of 200 ppm, 6 hours/day for 40 weeks (NTP 1993). The most sensitive developmental effects observed were exencephalies, skull abnormalities, and late fetal death in the offspring of unexposed female mice mated with male mice exposed to 12.5 ppm for 10 weeks (Anderson et al. 1996).

The Agency has elected to not derive an intermediate-duration inhalation MRL for 1,3-butadiene due to the large species differences in the metabolism of 1,3-butadiene and the lack of chemical-specific data to adjust for these differences, which may result in the MRL overestimating the risk to humans.

Chronic-Duration Inhalation MRL. Chronic-duration exposures resulted in increased mortality in rats and mice exposed to 8,000 or 20 ppm, 6 hours/day for 2 years. Rats exposed to 8,000 ppm, 6 hours/day for 2 years exhibited increased lung weight and metaplasia and kidney nephrosis (Owen and Glaister 1990; Owen et al. 1987). In mice, exposure to 1,250 ppm for 65 weeks resulted in nasal olfactory epithelial atrophy in mice (NTP 1984). Hepatic necrosis, forestomach epithelial hyperplasia, megaloblastic anemia, and endothelial hyperplasia of the heart were observed in mice exposed to 625 ppm (6 hours/day, 5 days/week) for 61–65 weeks (NTP 1984, 1993); testicular atrophy and preputial gland hyperplasia were observed in mice exposed to 625 ppm for 2 years (NTP 1993). Ovarian atrophy was observed in mice exposed to 62.5 ppm for 65 weeks or 6.25 ppm for 2 years (NTP 1993); complete destruction of oocytes, follicles, and corpora lutea was also observed. Alveolar epithelial hyperplasia was observed in mice following a 2-year exposure to 6.25 ppm (NTP 1993). In addition to the noncancerous effects, mammary gland tumors developed in rats exposed to 1,000 ppm, 6 hours/day for 2 years (Owen

and Glaister 1990; Owen et al. 1987), while multi-site cancer was observed in mice at 625 ppm, 6 hours/day for 61 weeks (NTP, 1984) and lung cancer occurred in mice following exposure to 6.25 ppm, 6 hours/day for 2 years (NTP 1993).

Considerable species differences were observed in the chronic-duration studies in terms of observed effects and sensitivity. The lowest LOAEL in rats is 8,000 ppm for lung and kidney effects and the lowest LOAEL in mice is 6.25 ppm for ovarian and lung effects. Renal effects have not been observed in mice exposed to up to 625 ppm for 2 years (NTP 1993) and ovarian effects were not observed in rats exposed to concentrations as high as 8,000 ppm for 2 years (Owen et al. 1987). The differences in sensitivity and possibly critical targets are most likely related to species differences in 1,3-butadiene metabolism. As noted previously, mice produce substantially more DEB than rats; one study (Thornton-Manning et al. 1995b) found that peak tissue levels of DEB were 40–160-fold greater in mice than rats. A comparison of blood DEB levels estimated from *pyr*-Val hemoglobin adduct levels found that at similar exposure levels (approximately 1 ppm), mouse DEB levels were 50 times higher than in rats and 1,000 times higher than in humans (Swenberg et al. 2011). In the absence of human data for noncarcinogenic effects following chronic exposure, the species differences in metabolism necessitate estimating human equivalent concentrations for each end point and comparing these values in order to identify the most likely critical target in humans. The available data provide strong evidence that the 1,3-butadiene metabolite, DEB, is the causative agent of the ovarian atrophy observed in mice (Doerr et al. 1996). Mechanistic data that could be used to identify relevant internal dose metrics for other sensitive end points in rats and mice were not identified, which precludes a comparison of human equivalent concentrations for each sensitive target. Thus, the Agency has elected to not derive a chronic-duration inhalation MRL for 1,3-butadiene; the lack of chemical-specific data to adjust for the large species differences in metabolism may result in the MRL overestimating the risk to humans.

Although ATSDR considers that the lack of data that can be used to evaluate the most sensitive target of chronic toxicity in humans precludes derivation of a chronic-duration inhalation MRL, the U.S. EPA (IRIS 2012), the Texas Commission on Environmental Quality (TCEQ) (Grant et al. 2010), and Kirman and Grant (2012) have derived chronic risk assessment values based on ovarian atrophy in mice. These three approaches share several commonalities, but also have several differences. All three approaches use a time-to-response benchmark dose (BMD) model; EPA and TCEQ used incidence data from the National Toxicology Program (NTP 1993) chronic mouse study and Kirman and Grant (2012) used incidence data from intermediate- and chronic-duration rat and mouse studies. The EPA approach did not make any adjustments for chemical-specific differences in metabolism. TCEQ derived chemical-specific

uncertainty factors to account for species differences in DEB formation, whereas Kirman and Grant (2012) ran the BMD modeling using an internal dose metric for DEB. A summary of these risk assessment values are presented in Table 2-1 and a more detailed discussion of the three approaches follows.

EPA (IRIS 2012). In 2002, EPA derived a reference concentration (RfC) of 0.0009 ppm based on a $BMCL_{10}$ of 0.88 ppm using the concentration-response data for ovarian atrophy in mice exposed to 1,3-butadiene for 2 years (NTP 1993) and an uncertainty factor of 1,000 (3 for interspecies extrapolation with dosimetric adjustments, 10 for intraspecies variability, 3 for incomplete database, and 10 for extrapolation to a level below the 10% effect level). The BMD modeling used the Weibull time-to-response model and incorporated the incidence data from the interim and final sacrifices; the data were modeled to include extra risk only until age 50 years. Human equivalent concentrations were calculated by adjusting the $BMCL_{10}$ for intermittent exposure (6 hours/day, 5 days/week) and multiplying the adjusted $BMCL_{10}$ by an RGDR (ratio of blood:gas partition coefficients) of 1.

Texas Commission on Environmental Quality (Grant et al. 2010). The TCEQ (Grant et al. 2010) derived a chronic reference value of 0.0154 ppm based on a $BMCL_{05}$ of 0.462 ppm for ovarian atrophy in mice (NTP 1993) and a total uncertainty factor of 30. Similar to EPA, the Weibull time-to-response model was used for BMD analysis of the ovarian atrophy incidence data for mice exposed to 1,3-butadiene for 2 years (9- and 15-month interim sacrifice data were also included in the model). The component uncertainty factors were 1 for animal to human extrapolation, 10 for intraspecies variability, and 3 for database deficiencies (lack of a multigenerational reproductive study). Both the intraspecies and the interspecies uncertainty factors were divided into toxicokinetic and toxicodynamic components. For the intraspecies uncertainty factor, a default value of 3 was used to account for toxicodynamic factors because data are lacking on the key sequence of events and how DEB interacts in different subpopulations to produce ovarian atrophy; a toxicokinetic factor of 3 was used because metabolic genetic polymorphisms may account for differences in susceptibility of 2–3.5-fold in humans. For the interspecies uncertainty factor, 3 was used for toxicodynamic differences because data are not available on possible differences on how DEB would react in different species to produce ovarian atrophy; a toxicokinetic factor of 0.3 was selected to account for species differences in 1,3-butadiene metabolism. The basis of this 0.3 factor was: (1) a comparison of the levels of DEB-specific hemoglobin adduct (*pyr*-Val adduct) formation in mice and humans; (2) a comparison of total 1,3-butadiene metabolite levels in the blood; and (3) comparisons of DEB blood concentrations, DEB tissue levels, and blood area-under-

Table 2-1. Summary of Available Chronic Risk Assessment Values for 1,3-Butadiene

Source	Source of data for benchmark analysis	POD	UF (UF_L, UF_A, UF_H, UF_{DB})	Issues and considerations
EPA (IRIS 2012)	2-Year mouse study (including interim sacrifices)	$BMCL_{10}$: 0.88 ppm	1,000 (10, 3, 10, 3)	The RfC does not have a chemical-specific adjustment for the increased production of DEB (reactive metabolite) in mice, as compared to humans. Does not take into consideration that ovarian atrophy may not be the most sensitive target in humans and that effects due to exposure to other reactive metabolites may occur at lower doses.
TCEQ (Grant et al. 2010)	2-Year mouse study (including interim sacrifices)	$BMCL_{05}$: 0.462 ppm	30 (NA, 1, 10, 3)	Accounts for species differences by quantifying toxicokinetic differences between mice and humans and selecting the low end of the range as an uncertainty factor to account for interspecies toxicokinetic differences. Does not take into consideration that ovarian atrophy may not be the most sensitive end point in humans and that effects due to exposure to other reactive metabolites may occur at lower doses.
Kirman and Grant 2012	Intermediate and chronic rat and mouse studies	$BMCL_{01}$: 1.5 ppm	10 (NA, 3, 1, 3)	Accounts for species differences by including rat incidence data in BMD model and using *pyr*-Val hemoglobin adduct levels as a biomarker of DEB levels. Does not take into consideration that ovarian atrophy may not be the most sensitive end point in humans and that effects due to exposure to other reactive metabolites may occur at lower doses.

BMCL = 95% lower confidence limit of the benchmark concentration; BMD = benchmark dose;
DEB = 1,2:3,4-diepoxybutane; LOAEL = lowest-observed-adverse-effect level; NA = not applicable;
NOAEL = no-observed-adverse-effect level; POD = point of departure; RfC = reference concentration;
UF = uncertainty factor: UF_L = extrapolation from NOAEL to LOAEL; UF_A = extrapolation from animals to humans;
UF_H = human variability; UF_{DB} = database limitations

the-curve levels in rats and mice; these comparisons resulted in a range of toxicokinetic uncertainty factors of 0.01–0.2 and the value of 0.3 was selected.

Kirman and Grant (2012). Kirman and Grant (2012) based their RfC of 0.2 ppm on a $BMCL_{01}$ of 1.5 ppm for ovarian atrophy and an uncertainty factor of 10 (3 for extrapolation from animals to humans and 3 for database deficiencies [lack of a multigenerational study and lack of dose-response data for follicle depletion]). A multi-stage Weibull time-to-response BMD model was applied to the combined dose-response data for ovarian atrophy in mice exposed for 2 years (including 40- and 65-week interim sacrifices (NTP 1993), mice exposed for 61 weeks (NTP 1984), mice exposed for 13 weeks (Bevan et al. 1996), rats exposed for 2 years (Owen et al. 1987), and rats exposed for 13 weeks (Bevan et al. 1996). To account for species differences in the metabolism of 1,3-butadiene, the BMD model was run using blood DEB levels as the internal dose metric. Blood DEB levels were estimated using a multistep process that used *pyr*-Val adduct burden as a biomarker for DEB levels. *Pyr*-Val adduct burdens were estimated using data on *pyr*-Val adduct efficiency (amount of adducts formed per ppm of 1,3-butadiene in air) in rats and mice as a function of 1,3-butadiene exposure concentration following a 4-week exposure (6 hours/day, 5 days/week). The estimated *pyr*-Val adduct burden were then used to calculate blood DEB concentrations using species-specific rate constants for the reaction of DEB with the terminal valine of hemoglobin and erythrocyte lifespan. For the time-to-response model, the exposure duration of interest was set equal to the window of susceptibility for ovotoxicity. Since the window of susceptibility is dependent on the number of follicles present at birth, the model was run for three scenarios: an average number of follicles at birth, the lower bound of central tendency for number of follicles, and the upper bound of the central tendency for the number of follicles; the range of susceptibility for depletion of follicle reserves for 95% of the population ranges from 8.5 higher and 8.5 lower than the average individual. The BMD model also included a 3-fold shift to account for toxicokinetic variation among humans. Since the model accounts for toxicokinetic and toxicodynamic differences in humans, no additional uncertainty factors were added to account for human variability.

Oral MRLs

There are no data available for effects in humans or animals exposed orally to 1,3-butadiene. For this reason, no acute-, intermediate-, or chronic-duration oral MRLs could be derived.