

2. RELEVANCE TO PUBLIC HEALTH

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

1,3-Butadiene is a gas used to make synthetic rubber, which is then used mostly for car and truck tires. Some plastics, such as acrylics, use 1,3-butadiene in their formulations. Large amounts of 1,3-butadiene are released into the air by industrial sources, while releases to water and soil are relatively low. Smaller amounts of 1,3-butadiene are constantly released into the air from vehicle exhaust, cigarette smoke, wood burning, and the burning of rubber and plastics. Naturally-occurring 1,3-butadiene in the air comes from forest fires. Half of the 1,3-butadiene that enters into air is expected to be broken down in about 6 hours. Evaporation is expected to remove most 1,3-butadiene spilled into water or soil.

The general public can be exposed to 1,3-butadiene by breathing urban and suburban air. The average amount of 1,3-butadiene in the air is between 0.4 and 1 ppb in cities and suburban areas. Workers involved in the production of rubber, plastics, and resins are most likely to receive the largest exposures. People may be exposed to 1,3-butadiene by breathing air mixed with vehicle engine exhaust, smoke from fires, and cigarettes or cigarette smoke (including second-hand smoke). They may also be exposed to small amounts of 1,3-butadiene by touching gasoline or by breathing air that contains gasoline fumes. Higher amounts of 1,3-butadiene may be in the air near polluted cities or oil refineries, chemical manufacturing plants, and plastic and rubber factories where this chemical is made or used. Leaks or intentional releases from manufacturing plants account for large amounts of 1,3-butadiene in the air. 1,3-Butadiene has been measured at very low levels in the plastic or rubber of food containers, but it has not been found often in food samples. 1,3-Butadiene has been found in drinking water, but no concentrations or sources were identified. Contact with 1,3-butadiene through food and drinking water is expected to be very low compared to breathing contaminated air.

2.2 SUMMARY OF HEALTH EFFECTS

Numerous target organs for 1,3-butadiene toxicity have been suggested in humans, as reported in case reports and epidemiological studies, and in animals, as shown 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. The available data for 1,3-butadiene exposure and toxicity in humans and animals are limited to

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inhalation exposures; the effects from significant oral or dermal exposures are not known. In animals, mice are more sensitive than rats to almost all toxic effects observed for 1,3-butadiene.

Very high exposures to 1,3-butadiene vapors in humans (>10,000 ppm) may result in narcosis and death from respiratory paralysis, although the required concentrations for these frank neurological effects are not known. Nausea, dryness of the mouth and nose, headache, and decreased blood pressure and pulse rate are the first signs observed in humans (Sandmeyer 1981). In rodents, anesthesia and acute death occurred following half-hour to 4-hour exposures to $\geq 120,000$ ppm 1,3-butadiene.

Lesions of the respiratory tract (olfactory tissues and lungs), liver, kidney, stomach, and eyes have been seen in rodents 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.

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. This is similar to humans, in which slightly lower levels of red blood cells, hemoglobin, platelets, and neutrophils were seen in tank car fillers, compared to other styrene-butadiene rubber workers, ostensibly because these workers experienced exposure to 1,3-butadiene that was at least one order of magnitude higher than workers in other areas of the plant. 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%

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decrease in fetal body weight among male mice. This was the lowest LOAEL identified in any of the acute-duration animal studies. Exposure of mice to ≥ 200 ppm resulted in $\geq 19\%$ 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 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.

Numerous epidemiological studies of multiple occupational cohorts, including one encompassing 15,000 workers, have associated a higher incidence of hemato-lymphopoietic, stomach, and respiratory 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. The consistent carcinogenic responses in rodents 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 tumor incidences 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

- An MRL of 0.1 ppm has been derived for acute-duration inhalation exposure (14 days or less) to 1,3-butadiene.

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). In rats, wavy ribs were seen in

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offspring from females inhaling 1,000 ppm 6 hours/day for 10 days, while skeletal abnormalities occurred at 8,000 ppm for the same duration (Irvine 1981). In mice, increased fetal death (a dominant lethal effect) occurred in offspring of males exposed to 200 ppm 6 hours/day for 5 days (DOE/NTP 1988b). However, the most sensitive effect observed during acute-duration exposures was a 5% reduction in male fetal weight following exposure of pregnant dams to 40 ppm (DOE/NTP 1987b). In this study, groups of 18–20 pregnant CD-1 mice were subjected to inhalation exposures of 0, 40, 200, or 1,000 ppm 1,3-butadiene for 6 hours/day on GDs 6–15. On GD 16, decreased maternal weights of 5, 14, and 24% were observed in the 40, 200, and 1,000 ppm groups, respectively. No significant differences in body weights were seen at GDs 6–18. In the 200 and 1,000 ppm groups, GD 18 body weight and gravid uterine weights were 4–7% and 7–13% less than controls, respectively. Male fetal body weights at 40 ppm were significantly less than controls (5%), while female fetal body weights were reduced (4% lower than controls), but not significantly. Mean whole-litter fetal body weights at 40 ppm were reduced (4% lower than controls), but also not statistically significantly. Mean whole-litter fetal weights at ≥ 200 ppm were reduced $>15\%$ lower than controls. There was no observed treatment-related effect on number of implants, total resorptions, or live/dead fetuses/litter. At ≥ 200 ppm, significantly increased incidences of extra rudimentary ribs and reduced sternebral ossification were observed. Male fetal weights on GD 18 were 5, 18, and 23% lower than controls (all significant to $p \leq 0.05$) in the 40, 200, and 1,000 ppm groups, respectively, while female fetal weights were 4, 15, and 22% lower than controls (significant to $p \leq 0.05$ for ≥ 200 ppm). Since the reduced fetal weight in the low-dose males was 5% and was not associated with other fetal effects, it is considered a minimally adverse LOAEL.

An acute-duration inhalation MRL of 0.1 ppm was derived using the LOAEL of 40 ppm for reduced male fetal body weight gain from exposed pregnant mice. The LOAEL of 40 ppm was adjusted for intermittent exposure (6 hours/day) resulting in a duration-adjusted LOAEL of 10 ppm. A $LOAEL_{HEC}$ (human equivalent concentration) of 10 ppm was derived (see Appendix A), which was divided by an uncertainty factor of 90 (3 for use of a minimally adverse effect, 3 for extrapolation from animals to humans, and 10 for human variability).

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

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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 mice exposed to 12.5 ppm for 10 weeks (Anderson et al. 1996). Because the lowest LOAEL identified for intermediate-duration inhalation exposure (12.5 ppm) is a serious effect, no MRL was derived for this duration.

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). Exposures of 1,250 ppm, 6 hours/day for 65 weeks resulted in nasal olfactory epithelial atrophy in mice (NTP 1984). Hepatic necrosis and hyperplasia of gastrointestinal and cardiovascular tissue hyperplasia, as well as megaloblastic anemia, were seen in mice exposed to 625 ppm, 6 hours/day for 65 weeks to 2 years (NTP 1993). 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 exposed to 625 ppm, 6 hours/day for 61 weeks (NTP 1984). Lung cancer in mice occurred following exposure to 6.25 ppm, 6 hours/day for 2 years (NTP 1993). The most sensitive chronic-duration effect observed was ovarian atrophy occurring in mice exposed to 6.25 ppm, 6 hours/day for 2 years (NTP 1993), which included complete destruction of oocytes, follicles, and corpora lutea. No chronic-duration inhalation MRL was derived because the lowest LOAEL (6.25 ppm) identified for this duration was a serious reproductive effect.

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 oral-duration MRLs could be derived.