Health Based Guidance for Air
Environmental Impacts Analysis Unit, Environmental Health Division
651-201-4899

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Air Toxicological Summary for: BENZENE

CAS: 71-43-2
Synonyms: benzol, benzole, cyclohexatriene, pyrobenzole, benzine

Air Exposure Durations:
Acute - dosing duration of 24-hours or less;
Short-term - repeated dosing for more than 24-hours, up to approximately 30 days;
Subchronic - repeated dosing for more than 30 days, up to approximately 8 years (10 percent of a lifespan in humans; more than 30 days up to approximately 90 days in typical laboratory rodent species); and
Chronic - repeated dosing for more than approximately 8 years (10 percent of a life span in humans; more than approximately 90 days in typical laboratory rodent species).

Acute Non-Cancer Health Based Value ($nHBV_{Acute}$) = 30 µg/m^3

$$= \frac{\text{(Point of Departure (POD) mg/m}^3\text{)}}{\text{(Uncertainty Factors (UF))}}$$

$$= \frac{\text{(8 mg/m}^3\text{)}}{\text{(300)}}$$

$$= 0.026 \text{ mg/m}^3 \text{ (rounded to 30 µg/m}^3\text{)}$$

Reference Concentration:	8 mg/m^3/300 = 0.026 mg/m^3
Source of toxicity value:	Determined by MDH 2020; Dempster and Snyder 1990 (animal study)
POD and Critical Effect:	LOAEL = 10 ppm; dose-dependent depression in bone marrow (hematotoxicity) early erythroid progenitor cells BFU-E (significant for BFU-E) and CFU-E; Splenic CFU-E and BFU-E were significantly increased
Human Equivalent Concentration (HEC):	$LOAEL_{HEC}$ = 2.5 ppm (8 mg/m^3); The regional gas dose ratio (RGDR) for a toxicant with a systemic effect (i.e. hematotoxicity), the default dose adjustment factor is 1 (EPA 1994, 2011). The single 6-hour exposure value was adjusted to a 24-hour exposure from the LOAEL of 10 ppm. (10 ppm x (6h/24h) = 2.5 ppm.

Total uncertainty factor (UF):	300
Uncertainty factor allocation:	An interspecies extrapolation factor of 3 was used to account for dosimetric differences from animal (mice) to human exposure. An intraspecies variability factor of 10 was used to account sensitive subpopulation among humans. A factor of 10 was used for use of a LOAEL (a NOAEL was not identified).

Short-term Non-Cancer Health Based Value ($nHBV_{ShortTerm}$) = 10 µg/m^3

$$= \frac{\text{(POD) mg/m}^3}{\text{(UF)}}$$

$$= \frac{\text{(4 mg/m}^3\text{)}}{\text{(300)}}$$

= 0.013 mg/m^3 = 13 µg/m^3 (rounded to 10 µg/m^3)

Reference Concentration:	4 mg/m^3/300 = 0.013 mg/m^3
Source of toxicity value:	Determined by MDH 2020; Keller and Snyder 1988 (animal study)
POD and Critical Effect:	LOAEL = 5 ppm; significantly decreased number of early nucleated red cells (hematotoxicity) in 2-day old neonates via the inhalation exposure to pregnant female during gestational days 6-15
Human Equivalent Concentration:	$LOAEL_{HEC}$ = 1.25 ppm (4 mg/m^3); The RGDR for a toxicant with a systemic effect (i.e. hematotoxicity), the default DAF is 1 (EPA 1994, 2011). The 6-hour per day for 10 consecutive days exposure value was adjusted to a continuous 24-hour exposure from the LOAEL of 5 ppm. (5 ppm x (6h/24h) = 1.25 ppm.
Total uncertainty factor:	300
Uncertainty factor allocation:	An interspecies extrapolation factor of 3 was used to account for dosimetric differences from animal (mice) to human exposure. An intraspecies variability factor of 10 was used to account sensitive subpopulation among humans. A factor of 10 was used for use of a LOAEL (a NOAEL was not identified).

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 8 µg/m^3

$$= \frac{\text{(POD) mg/m}^3}{\text{(UF)}}$$

$$= \frac{\text{(0.78 mg/m}^3\text{)}}{\text{(100)}}$$

$= 0.008\ mg/m^3 = 8\ \mu g/m^3$

Reference Concentration:	$0.78\ mg/m^3/100 = 0.008\ mg/m^3$
Source of toxicity value:	Determined by MDH 2019; Lan et al. 2004 (occupational human study)
POD and Critical Effect:	LOAEL = 0.57 ppm; Significant decrease in B cell counts (hematotoxicity)
Human Equivalent Concentration:	$LOAEL_{adj}$ = 0.244 ppm ($0.78\ mg/m^3$); The LOAEL was adjusted to a continuous exposure by (0.57 ppm x ($10m^3/20m^3$) x (6d/7d))
Total uncertainty factor:	100
Uncertainty factor allocation:	An intraspecies variability factor of 10 was used to account for sensitive subpopulations among humans. A factor of 10 was applied for use of a LOAEL (no NOAEL was identified in the study).

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = $3\ \mu g/m^3$

$$= \frac{(POD),\ mg/m^3}{(UF)}$$

$$= \frac{(0.78\ mg/m^3)}{(300)}$$

$= 0.003\ mg/m^3 = 3\ \mu g/m^3$

Reference Concentration:	$0.78\ mg/m^3/\ 300 = 0.003\ mg/m^3$
Source of toxicity value:	Determined by MDH 2019; Lan et al. 2004 (occupational human study)
POD and Critical Effect:	LOAEL = 0.57 ppm; Significant decrease in B cells (hematotoxicity)
Human Equivalent Concentration:	$LOAEL_{adj}$ = 0.244 ppm ($0.78\ mg/m^3$); The LOAEL was adjusted to a continuous exposure by (0.57 ppm x ($10m^3/20m^3$) x (6d/7d))
Total uncertainty factor:	300
Uncertainty factor allocation:	An intraspecies variability factor of 10 was used to account for sensitive subpopulations among humans. An factor of 10 was applied for use of a LOAEL (no NOAEL identified in the study). An factor of 3 was used for a subchronic to chronic extrapolation.

Cancer Health Based Value = $0.8\ \mu g/m^3$

Cancer classification:	EPA 2002 - Benzene is classified as a known human carcinogen (Category A); 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 IARC 2012 - Group 1 carcinogen; sufficient evidence of carcinogenicity in humans
Inhalation Unit Risk (IUR):	7.8×10^{-6} $(\mu g/m^3)^{-1}$
Source of IUR:	EPA IRIS 2000
Tumor site(s):	Hematologic
Basis for Cancer HBV:	MDH has utilized the high end of EPA 2000 IRIS's IUR range for purposes of deriving an inhalation cancer value. This IUR was based on the best exposure estimates for the study cohort. Per MDH policy (MDH 2020), ADAF are applied to the IUR (IUR_{adj}) to protect against early-life sensitivity to benzene exposure.

Cancer ADAF and HBV Calculations:

$IUR_{adj} = IUR \times [(2 \text{ yrs} \times 10) + (14 \text{ yrs} \times 3) + (54 \text{ yrs} \times 1)] / 70 \text{ yrs}$

$IUR_{adj} = 7.8 \times 10^{-6} (\mu g/m^3)^{-1} \times 1.657$

$IUR_{adj} = 1.3 \times 10^{-5} (\mu g/m^3)^{-1}$

Cancer HBV = additional lifetime cancer risk / IUR_{adj}

Cancer HBV = $0.00001 / 1.3 \times 10^{-5} (\mu g/m^3)^{-1} = 0.77 \mu g/m^3 = 0.8 \mu g/m^3$

Volatile: Yes; predicted Henry's Law = $5.52e^{-3}$ atm-m^3/mol; EPA CompTox Chemicals Dashboard (accessed October 2020)

Summary of Guidance Value History:

The 2002 acute HRV was 1,000 $\mu g/m^3$, approximately 33x higher that the 2020 acute noncancer HBV. The 2002 acute HRV was based on a now outdated Cal OEHHA value that used a POD of NOAEL = 40 ppm (4x higher than the proposed 2020 acute POD) based on the developmental effect, decreased fetal body weight. Cal OEHHA's most recent benzene reference exposure levels (Cal OEHHA 2014) identified hematotoxicity in fetal and neonatal animal, a developmental effect, to be a more appropriate effect that decreased fetal body weight. The 2020 short-term, subchronic, and chronic HBVs are new.

The 2002 cancer HRV was based on EPA IRIS's 2000 inhalation unit risk range ($2.2 \times 10^{-6} – 7.8 \times 10^{-6}$ $(\mu g/m^3)^{-1}$) corresponding to air concentrations of 1.3 – 4.5 $\mu g/m^3$. In 2020 MDH re-evaluated the basis of the exposure assessments used to derive the unit risk values. MDH determined that the exposure assessment used to derive the higher unit risk value was the most appropriate. Application of age dependent adjustment factors (MDH 2020) to reflect the sensitivity of early life to carcinogens resulted in a cancer HBV of 0.8 $\mu g/m^3$.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Developmental/Reproductive	Neurotoxicity	Respiratory
Tested for specific effect?	No	Yes	Yes	Yes	Yes
Effects observed?	No	Yes[1]	Yes[2]	Yes[3]	Yes[4]

Comments on extent of testing or effects:

[1]ATSDR 2007 reports immunological effects have been described in humans with occupational exposure to benzene. Benzene has been shown to alter humoral immunity (i.e., to produce changes in levels of antibodies in the blood). Painters who were exposed to benzene (3–7 ppm[10–22mg/m^3]), toluene, and xylene in the workplace for 1–21 years showed increased serum immunoglobulin values for IgM and decreased values for IgG and IgA. The decreased levels of immunoglobulins may represent suppression of immunoglobulin producing cells by benzene. Benzene also affects cellular immunity by changing circulating leukocytes and lymphocytes. Leukopenia was found in a series of studies of workers exposed to benzene at levels ranging from 15 to 210 ppm (48 to 671 mg/m^3) in various manufacturing processes in Turkey. In one study, routine leukocyte counts conducted every three months on employees of a small-scale industry in China revealed leukopenia in workers exposed to as little as 0.69–140 ppm (2–140 mg/m^3) (mean=6 ppm) for an average period of 5– 6 years. Leukocyte alkaline phosphatase (LAP) activity was increased in benzene workers exposed to about 31 ppm (99 mg/m^3) for a chronic time period. Increased LAP activity is an indicator of myelofibrosis and is associated with both decreased white blood cell counts and with changes in bone marrow activity. ATSDR 2015 reported the effects of benzene exposure on selected immunological end points among 10 workers exposed to benzene while maintaining cargo tanks containing crude oil residues on a crude oil vessel; a group of nine catering workers on the same vessel served as referents. The mean measured benzene air concentration was 0.15 ppm (0.48 mg/m^3) (range 0.01–0.62 ppm) for the tank workers. Mean measured post-shift blood benzene levels were 12.3 nmol/L (range 2–38 nmol/L) for the tank workers and 0.7 nmol/L (0.5–1.0 nmol/L) for the referents. At baseline, mean serum IgM was significantly lower in the tank workers than in the referents. In another human study, hematological parameters in peripheral blood from 49 benzene-exposed workers in shoe-manufacturing factories (measured workplace air level of 15.8±17.9 ppm [mean±SD]; (50 µg/m^3±57 mg/m^3) and 45 unexposed controls from clothing-manufacturing factories in the same vicinity. The benzene-exposed workers exhibited significant decreases in white blood cell count and numbers of granulocytes (18–23% lower than control values) and borderline significantly (p=0.054) decreased lymphocyte count (10% lower than controls). Lymphocyte subset analysis revealed significant decreases in numbers of B cells and CD4+-T cells and CD4+/CD8+ ratio.

[2]Cal OEHHA 2008 reports a study exposure of 500 ppm (1600 mg/m^3) benzene for 7 hours per day through days 6-15 of gestation was teratogenic in the fetal brain of Sprague-Dawley rats, while 50 ppm and 500

ppm (160 and 1600 mg/m³) resulted in reduced fetal weights on day 20 of gestation. The higher exposure levels also had significantly more fetuses with skeletal variants. A study reported by Cal OEHHA 2008 showed exposure of CFY rats to continuous benzene inhalation (24 h/day) at 150, 450, 1500, or 3000 mg/m^3 from days 7-14 of gestation led to decreased fetal body weights, elevated liver weights, and signs of skeletal retardation at 150 mg/m³ benzene, the lowest concentration tested. ATSDR 2015 states a population-based case-control study in Texas evaluated possible associations between maternal exposure to ambient air levels of selected pollutants (including benzene) and risk of neural tube defects (spina bifida). Ambient air levels for each pollutant were obtained from EPA 1999 National-Scale Air Toxics Assessment. For benzene, estimated air levels ranged from 0.12 to 7.44 µg/m^3 were grouped into ranges. Compared to the referent group (0.12–0.45 µg/m^3), significantly increased risk of spina bifida was associated with the medium-low (>0.45–0.98 µg/m^3) exposure group.

[3]ATSDR 2007 reports following acute inhalation of benzene, humans exhibit symptoms indicative of central nervous system effects. These symptoms, reported to occur at levels ranging from 300 to 3,000 ppm (958 to 9584 mg/m^3), include drowsiness, dizziness, headache, vertigo, tremor, delirium, and loss of consciousness. Acute exposure (5–10 minutes) to higher concentrations of benzene (approximately 20,000 ppm (64000 mg/m^3)) can result in death, which has been associated with vascular congestion in the brain. Chronic exposure to benzene has been reported to produce neurological abnormalities in humans. Of eight patients (six with aplastic anemia and two with preleukemia) with previous occupational exposure to adhesives and solutions containing 9–88% benzene, four of the six patients with aplastic anemia showed neurological abnormalities (global atrophy of lower extremities and distal neuropathy of upper extremities). Air concentrations in the workplace were reported to have reached levels of ≥210 ppm (671mg/m^3). ATSDR 2015 reports a 2007 study investigated a significant trend for increased prevalence of acquired dyschromatopsia (partial color blindness) in the left eye only with increasing benzene exposure (mean exposure levels ranging from 0.27 to 2.43 ppm-years (0.86 to 7.8 mg/m^3) among 736 workers employed in a petrochemical distillation factory compared with 172 non-exposed office workers. Prevalence of dyschromatopsia was significantly correlated with age and duration of work. The results indicate that chronic low-level exposure to benzene may lead to acquired dyschromatopsia, which may be a relatively sensitive indicator of neurological damage.

[4]ATSDR 2007 reports respiratory effects have been reported in humans after acute exposure to benzene vapors. Fifteen male workers employed in removing residual fuel from shipyard tanks were evaluated for benzene exposure. Mucous membrane irritation was noted in 80% and dyspnea was noted in 67% of the workers at occupational exposures of >60 ppm for up to 3 weeks. Male and female workers exposed to 33 and 59 ppm (105 and 188 mg/m3) benzene, respectively, for more than 1 year reported nasal irritation and sore throat. ATSDR 2007 also reported no treatment-related effects on lung tissue in male Sprague-Dawley rats exposed to 0, 100, or 300 ppm (319 or 958 mg/m^3) benzene 5 days/week, 6 hours/day for life. Cal OEHHA 2008 states respiratory tract inflammation, pulmonary hemorrhages, renal congestion, and cerebral edema have been observed at autopsy in persons with acute benzene poisoning by inhalation. In these cases, blood levels of 2 mg percent (2 mg/100 ml) benzene were not associated with hematological changes.

Resources Consulted During Review:

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ATSDR. 2015. Addendum to the Toxicological Profile for Benzene. https://www.atsdr.cdc.gov/toxprofiles/Benzene_Addendum.pdf

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