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Chemical Name: Benzene
CAS: 71-43-2

Acute Non-Cancer Health Risk Limit ($nHRL_{acute}$) = 10 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Acute intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.015 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 10.38 rounded to **10 µg/L**

Toxicity value:	0.015 mg/kg/day (laboratory animal)
Source of toxicity value:	MDH 2007
Point of Departure:	4.6 mg/kg/day (NOAEL from Coate et al 1984)
Human Equivalent Dose Adjustment:	Not available
Total uncertainty factor:	300
UF allocation:	10 (intraspecies variability), 10 (interspecies extrapolation) and 3 database insufficiencies (sensitive endpoints, such as hematological, immunological and neurological effects, have not been adequately evaluated in developmental studies)
Critical effect(s):	Reduced fetal body weight, increased skeletal variants, and slight dilation of brain ventricles.
Co-critical effect(s):	[A limited number of developmental inhalation and injection studies suggested increased sensitivity to hematological and neurological effects. These studies were not always consistent and suffered from deficiencies in design. Therefore, these endpoints have not been listed as co-critical effects at this time. However, a database UF has been applied to address these concerns.]
Additivity endpoint(s):	Developmental (BW, skeletal)
Secondary effect(s):	None

Short-term Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = 10 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.014 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 9.68 rounded to **10 µg/L**

Toxicity value:	0.014 mg/kg/day (laboratory animal)
Source of toxicity value:	MDH 2007
Point of Departure:	1.4 mg/kg/day (IRIS BMDL based on Hsieh et al., 1988a)
Human Equivalent Dose Adjustment:	Not available
Total uncertainty factor:	100
UF allocation:	10 (intraspecies variability), 10 (interspecies extrapolation)
Critical effect(s):	Reduced blood cell counts, increased MCV, increased anemia, decreased spleen weight, elevated splenic lymphocytes, H-TdR, Con A, PHA-induced response, CTL responsiveness, PWM or nonmitogen splenocytes, and antibody response to sheep RBCs.
Co-critical effect(s):	Reduced fraction of stem cells in DNA synthesis, lymphopenia, decline in the frequency of T and B lymphocytes, reduced reticulocytes, decreased number of progenitor cells, decreased RBC and WBC, suppressed ability to form antibodies.
Additivity endpoint(s):	Hematologic (blood) system, immune system
Secondary effect(s):	cystic ovaries, testicular atrophy, decreased sperm count and increased abnormal forms, increased motor activity.

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = 3 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.0013 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 3.38 rounded to **3 µg/L**

Toxicity value:	0.0013 mg/kg/day (human)
Source of toxicity value:	MDH 2007
Point of Departure:	0.013 mg/kg/day (ATSDR calculated $BMCL_{0.25sd}$ based on route-to-route extrapolation of Lan et al., 2004 data)
Human Equivalent Dose Adjustment:	Not available
Total uncertainty factor:	10

UF allocation:	10 (intraspecies variability)
Critical effect(s):	Reduction in total WBCs, granulocytes, lymphocytes, platelets, CD4+-T cells, CD4+/CD8+ ratio, and B cells.
Co-critical effect(s):	Leukopenia.
Additivity endpoint(s):	Hematologic (blood) system and immune system.
Secondary effect(s):	anemia, lymphocytosis, thrombocytopenia, leucopenia, and leukocytosis, shorter luteal phase in females.

Chronic Non-Cancer Health Risk Limit ($nHRL_{chronic}$) = $nHRL_{subchronic}$ = 3 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.0013 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 6.05 rounded to 6 µg/L

Toxicity value:	0.0013 mg/kg/day (human)
Source of toxicity value:	MDH 2007
Point of Departure:	0.013 mg/kg/day (ATSDR calculated $BMCL_{0.25sd}$ based on route-to-route extrapolation of Lan et al., 2004 data)
Human Equivalent Dose Adjustment:	Not available
Total uncertainty factor:	10
UF allocation:	10 (intraspecies variability)
Critical effect(s):	Reduction in total WBCs, granulocytes, lymphocytes, platelets, CD4+-T cells, CD4+/CD8+ ratio, and B cells.
Co-critical effect(s):	Leukopenia.
Additivity endpoint(s):	Hematologic (blood) system and immune system.
Secondary effect(s):	anemia, lymphocytosis, thrombocytopenia, leucopenia, and leukocytosis, shorter luteal phase in females.

The Chronic nHRL must be protective of the subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Subchronic nHRL of 3 µg/L. Additivity Endpoints: Hematological (Blood) system, Immune system.

Cancer Health Risk Limit (cHRL) = 2 µg/L

$$= \frac{\text{(Additional Lifetime Cancer Risk) x (Conversion Factor)}}{[(SF \times ADAF_{<2\ yr} \times IR_{<2yr} \times 2) + (SF \times ADAF_{2-<16\ yr} \times IR_{2-<16yr} \times 14) + (SF \times ADAF_{16+\ yr} \times IR_{16+yr} \times 54)] / 70}$$

$$\frac{1 \times 10^{-5} \times 1000\ ug/mg}{[\ (0.055\ (mg/kg\text{-}d)^{-1})(10)(0.137\ L/kg\text{-}d)(2) + (0.055\ (mg/kg\text{-}d)^{-1})(3)(0.047\ L/kg\text{-}d)(14) + (0.055\ (mg/kg\text{-}d)^{-1})(1)(0.039\ L/kg\text{-}d)(54)]/70}$$

= 1.89 rounded to **2 µg/L**

Cancer classification:	A, human carcinogen
Slope factor:	0.015 to 0.055 per (mg/kg)/day (human)
Source of slope factor:	IRIS, 2000
Tumor site(s):	Leukemia

Volatile: Yes (highly volatile)

Summary of changes since 1993/1994 HRL promulgation:
MDH has implemented the method of assessing noncancer toxicity over four durations of exposure (acute, short-term, subchronic, and chronic) and assessing both cancer and noncancer endpoints simultaneously if applicable. The 1993/94 HRL (10 µg/L) is based on cancer; there was not a noncancer HRL derived at that time. Legislation passed in the 2007 regular session (Chapter 147, Article 17, section 2) established new Health Risk Limit (HRL) values, effective July 1, 2007, for chemicals when the federal standard determined by the United States Environmental Protection Agency (US EPA) is more stringent than the 1993/1994 HRL value. Maximum Contaminant Levels (MCLs) are federal standards adopted for regulation of public drinking water in Minnesota. However, MCLs incorporate a consideration of the costs required to reduce contaminant concentrations of a given level and the technological feasibility of reaching that level and therefore are not solely based on consideration of human health.

A comparison of 1993/94 HRL values to the current MCLs from the US EPA identified eleven chemicals, including benzene, that had a lower MCL value than a HRL value. The 1993/94 HRL value of 10 µg/L was revised to the MCL value of 5 µg/L as of July 1, 2007.

The noncancer HRLs (acute 10 µg/L, short-term 10 µg/L, subchronic 3 µg/L, and chronic 3 µg/L) are new. The cancer HRL (2 µg/L) is 2.5-fold lower than the 2007 MCL-based HRl and 5-fold lower than the 1993/94 cancer HRL due to: 1) utilization of more recent lifetime intake rates; 2) use of a more recent cancer risk assessment conducted by EPA; 3) application of age-dependent early-life cancer sensitivity adjustment factors; and 4) rounding to one significant digit.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Secondary Observation	Yes	Yes	Yes	Yes
Effects?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Note: 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. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:

[1]The endocrine system is not a system of particular concern and there was only a single study conducted that examined effects related to the endocrine system. This study demonstrated that women developed a significantly shorter luteal phase following inhalation exposure to benzene at low levels. Also, the urine levels of E1C before ovulation (FSH at early follicular phase and PdG in luteal phase after ovulation) in the exposed group were significantly lower than those in the internal control group. This study failed to define exposure groups and a clear dose-response relationship is unclear. The estimated oral equivalent LOAEL of this study was approximately 3-fold higher than the subchronic and chronic critical study LOAEL. These effects have been identified as secondary effects.

[2]Immunotoxicity effects include reduced immunoglobulin levels and a decline in lymphocyte, leukocyte, erythrocyte, and neutrophil counts as well as other immune responses. These effects have been identified as critical effects.

[3]Low birth weight and increased number of skeletal variants have been identified as critical acute effects. A small number of developmental inhalation studies, all by the same group of investigators, identified potential hematological effects (e.g., bimodal responses in progenitor cell counts and fluctuations in various fetal/neonatal hematological parameters) at concentrations below the acute critical study LOAEL. EPA cautioned that the hematologic effects detected should be interpreted with caution, as there were multiple limitations associated with these studies. These effects have not been identified as co-critical effects, however, a database UF was incorporated into the acute RfD derivation to address these concerns. Other effects such as stillbirth, spontaneous abortion, birth anomolies, and maternal death were effects detected at levels > 10-fold the acute critical study LOAEL.

[4]Females in occupational studies were often examined for adverse reproductive effects as a result of inhalation exposure to benzene and investigators determined that there was an increase in shortened gestation, hypermenhorrhea, hypomenhorrhea, ovarian hypoplasia, sterility, degeneration of the ovary, dysfunction of the ovary, premature interruptions of pregnancy, increased cases where the placental membrane rupture during parturition was impeded, stillbirth, and spontaneous abortions. The results of these studies must be interpreted with caution due to limitations in the study design (e.g., exposure levels) and confounding factors such as multiple chemical exposures. A reproductive inhalation study in rats reported observing testicular and ovarian lesions at estimated oral equivalent doses approximately 3-fold and > 10-fold higher than the short-term and subchronic/chronic critical study LOAELs, respectively. These effects are identified as short-term secondary effects.

[5] Levels of norepinephrine, dopamine, and serotonin were altered within various brain regions at dose levels similar to the short-term critical study LOAEL. EPA noted that although the assay had potential as a biomarker for exposure, the biological significance of these findings is questionable. Behavioral and learning disorders in mice were reported following inhalation exposure to estimated equivalent oral

doses that were > 3-fold higher than the short-term critical study LOAEL. There were, however, several limitations in the experimental procedures used in these experiments. There is a limited body of evidence indicating that benzene is neurotoxic; however, there are no human or animal studies that could be used for quantitative evaluation of potential human health risks.

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