Health-Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
651-201-4899

Adopted as Rule: November 2023

Toxicological Summary for: Biphenyl

CAS: **92-52-4; DTXSID4020161**
Synonyms: 1,1'-Biphenyl; Phenylbenzene; Diphenyl

Acute Non-Cancer Health-Based Value ($nHRL_{Acute}$) = 400 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Acute Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.58 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

$$= \mathbf{400\ \mu g/L}$$

*Relative Source Contribution: Because inhalation is the predominant route of exposure, and infant exposure does not appear to be significantly less than exposures to older children or adults, an RSC value of 0.2 was used for all exposure durations. MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1 and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 57.5/100 = 0.58 mg/kg-d (F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	250 mg/kg-d (administered dose NOAEL, Kluwe et al 1982)
Dose Adjustment Factor (DAF):	0.23 subchronic male F344 rats, body weight scaling default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 250 mg/kg-d x 0.23 = 57.5 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Increased urine volume (polyuria) accompanied by increased excretion of urinary protein, glucose, and several renal enzymes
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Short-term Non-Cancer Health-Based Value ($nHRL_{Short\text{-}term}$) = 100 µg/L

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

$$= \frac{\text{(0.18 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 124 rounded to **100 µg/L**

*Relative Source Contribution: Because inhalation is the predominant route of exposure, and infant exposure does not appear to be significantly less than exposures to older children or adults, an RSC value of 0.2 was used for all exposure durations. MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.6/100 = 0.18 mg/kg-d (female F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	83.7 mg/kg-d (administered dose NOAEL, Booth et al 1961. LOAEL based on Booth et al 1961 and Kluwe et al 1982.)
Dose Adjustment Factor (DAF):	0.21 female subchronic F344 rat based on body weight scaling, default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 83.7 mg/kg-d x 0.21 = 17.6 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Increased urine volume (polyuria), precipitable urinary sediment, and increased urinary glucose, protein, alkaline phosphatase (AP) and glutamic oxaloacetic transaminase (GOT) excretion
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

Subchronic Non-Cancer Health-Based Value ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.18 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.074 L/kg-d)}^{**}}$$

= 486 rounded to 500 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.

**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 17.6/100 = 0.18 mg/kg-d (female F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	83.7 mg/kg-d (administered dose NOAEL, Booth et al 1961)
Dose Adjustment Factor (DAF):	0.21 female subchronic F344 rats body weight scaling, default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 83.7 mg/kg-d x 0.21 = 17.6 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database limitations, including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Increased urine volume and precipitable sediment accompanied by limited renal histological changes
Co-critical effect(s):	None
Additivity endpoint(s):	Renal (kidney) system

The Subchronic nHRL must be protective of shorter duration exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 100 µg/L. Additivity endpoints: Renal (kidney) system.

Chronic Non-Cancer Health-Based Value ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 100 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.073 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.045 L/kg-d)}^{**}}$$

= 324 rounded to 300 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Reference Dose/Concentration:	HED/Total UF = 7.31/100 = 0.073 mg/kg-d (female F344 rats)
Source of toxicity value:	Determined by MDH in 2020
Point of Departure (POD):	30.45 mg/kg-d (administered dose $BMDL_{10\%}$, Umeda et al 2002)
Dose Adjustment Factor (DAF):	0.24 female chronic F344 rats body weight scaling, default (U.S. EPA 2011a and MDH 2017)
Human Equivalent Dose (HED):	POD x DAF = 30.45 mg/kg-d x 0.24 = 7.31 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database limitations,

	including lack of neurotoxicity testing and inadequate developmental/reproductive testing
Critical effect(s):	Renal transitional cell simple hyperplasia
Co-critical effect(s):	Increased hemosiderin deposits in the kidney and mineralization of outer renal medulla and pelvis
Additivity endpoint(s):	Renal (kidney) system

The Chronic nHRL must be protective of shorter duration exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 100 µg/L. Additivity endpoints: Renal (kidney) system.

Cancer Health-Based Value (cHRL) = 10 µg/L

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

$$= \frac{(1E\text{-}5) \times (1000\ \mu g/mg)}{[(0.008 \times 10^{*} \times 0.155\ L/kg\text{-}d^{**} \times 2) + (0.008 \times 3^{*} \times 0.040\ L/kg\text{-}d^{**} \times 14) + (0.008 \times 1^{*} \times 0.042\ L/kg\text{-}d^{**} \times 54)] / 70}$$

= 12.4 rounded to **10 µg/L**

*ADAF (Age-dependent adjustment factor) and Lifetime Adjustment Factor: MDH 2008, Section IV.E.2.
**Intake Rate: MDH 2008, Section IV.E.2. and US EPA 2019, Exposure Factors Handbook, Tables 3-1, 3-3 and 3-5.

Cancer classification:	Suggestive evidence of carcinogenic potential
Slope factor (SF):	0.008 per mg/kg-d (female BDF1 mice, Umeda et al 2005)
Source of cancer slope factor (SF):	U.S. EPA 2013
Tumor site(s):	Liver adenomas and carcinomas

Volatile: No (moderate)

Summary of Guidance Value History:
MDH promulgated a chronic nHRL of 300 µg/L in 1993. In 2020 MDH conducted a full review and derived nHBVs of 400 µg/L for acute duration and 100 µg/L for short-term, subchronic and chronic durations as well as a cHBV of 10 µg/L for cancer. The 2020 chronic and cancer HBVs are lower than the 1993 HRL value due to the use of MDH's multiduration methodology, more recent toxicological data, and updated water intake rates (U.S. EPA 2019). In November 2023, the guidance values were adopted into Minnesota Rule, 4717.7860 as Health Risk Limits (HRLs).

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	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	No	Yes	Yes	No
Effects observed?	-[1]	-	Yes[2]	Yes[3]	-[4]

Comments on extent of testing or effects:

[1] Endocrine effects have not been specifically tested in animals. *In vitro* estrogenic assays indicate that biphenyl does not exhibit estrogenic activity, however, hydroxylated metabolites of biphenyl do exhibit estrogenic activity. This activity was mainly observed when cultures contained cells from induced rat livers as little effect was observed when cells from untreated rats were used.

[2] Decreased fetal or pup body weights, delayed ossification, and increased dead or resorbed fetuses have been reported at HED doses ~600-fold higher than the short-term and subchronic RfDs. The developmental studies are old and do not include the more extensive evaluation of current study protocols. A database uncertainty factor of 3 was incorporated into the RfD derivation, in part, to address the need for more comprehensive developmental and reproductive toxicity testing.

[3] Decreased fertility in laboratory animals has been reported at HED doses ~1000-fold higher than the short-term and subchronic RfDs. The reproductive studies are old and do not include the more extensive evaluation of current study protocols. A database uncertainty factor of 3 was incorporated into the RfD derivation, in part, to address the need for more comprehensive developmental and reproductive toxicity testing.

[4] Occupational studies in humans have reported neurological effects when exposed to air levels in excess of occupational exposure limits. No animal neurotoxicity testing has been conducted. A database uncertainty factor of 3 was incorporated into the RfD derivation, in part, to address this data gap.

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