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

Adopted as Rule: November 2023

Toxicological Summary for: Benzophenone

CAS: **119-61-9**

Synonyms: Diphenylmethanone; Methanone, diphenyl-, diphenyl ketone, benzoyl benzene, alpha-oxo-diphenyl methane, alpha oxoditane, phenyl ketone

Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 900 µg/L

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

$$= \frac{\text{(0.52 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.290 L/kg-d)}^{**}}$$

= 896 rounded to **900 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 = 15.5/30 = 0.52 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	67.4 mg/kg-d (administered dose NOAEL, Hoshino et al. 2005)
Dose Adjustment Factor (DAF):	0.23, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 67.4 mg/kg-d x 0.23 = 15.5 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Decreased pup body weight
Co-critical effect(s):	Decreased pup body weight
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = 100 µg/L

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

$$= \frac{(0.053 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.074 \text{ L/kg-d})^{**}}$$

= 143 rounded to **100 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 = 1.6/30 = 0.053 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	6.4 mg/kg-d (administered dose NOAEL, Hoshino et al., 2005)
Dose Adjustment Factor (DAF):	0.25, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 6.4 mg/kg-d x 0.25 = 1.6 mg/kg-d
Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased relative liver weight, relative kidney weight, proximal tubule regeneration, proximal tubule dilatation
Co-critical effect(s):	Increased serum bile salts, relative liver weight, hepatocyte vacuolization, relative kidney weight, renal tubule protein casts
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Subchronic}$ = 100 µg/L

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

$$= \frac{(0.053 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.045 \text{ L/kg-d})^{**}}$$

= 235 rounded to 200 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 = 1.58/30 = 0.053 mg/kg-d (Fischer 344 rats)
Source of toxicity value:	Determined by MDH in 2019
Point of Departure (POD):	5.86 mg/kg-d (administered dose BMDL calculated by MDH from (National Toxicology Program, 2006))
Dose Adjustment Factor (DAF):	0.27, Body weight scaling, default (MDH 2017 and US EPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 5.86 mg/kg-d x 0.27 = 1.58 mg/kg-d

Total uncertainty factor (UF):	30
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability
Critical effect(s):	Increased renal tubule hyperplasia
Co-critical effect(s):	Increased renal pelvis transitional hyperplasia, severity of nephropathy, and bile duct hyperplasia
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system

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 100 µg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification:	2B – Possibly carcinogenic to humans (IARC 2013)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	In male mice: hepatocellular adenoma, combined hepatocellular adenoma, carcinoma and hepatoblastoma. In female mice: histiocytic sarcoma. In male rats: renal tubule adenoma.

Statement for non-linear carcinogens:
Benzophenone was reported to be neither mutagenic nor genotoxic in various *in vivo* and *in vitro* experiments, and is likely to be a nonlinear carcinogen. The chronic RfD is considered to be protective against cancer.

Volatile: Yes (low)

Summary of Guidance Value History:

In 2020 MDH incorporated updated intake rates (US EPA 2019). Use of the updated intake rates resulted in changes to the subchronic and chronic duration water guidance values from 200 µg/L to 100 µg/L. In November 2023, the guidance values were adopted into Minnesota Rules, 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?	Yes	No	Yes	Yes	No

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Effects observed?	Yes[1]	-[2]	Yes[3]	No [4]	-[5]

Comments on extent of testing or effects:

[1] One study identified estrogenic activity of orally-administered benzophenone based on increased uterine weight in ovariectomized rats at doses 200-fold higher than the Short-Term RfD. *In vivo* studies based on other routes of exposure did not show estrogenic effects. Based on *in vitro* studies, it appears that benzophenone and its main metabolite benzhydrol do not possess estrogenic activity, whereas a minor metabolite 4-hydroxybenzophenone is weakly estrogenic.

[2] There were no specific immunotoxicity studies available. Subchronic and chronic studies in rodents did not note any abnormalities in immune cell blood parameters or immune organ histopathology after oral benzophenone exposure at levels up to 300-fold higher than the Short-Term RfD.

[3] A two-generation reproductive/developmental study in rats noted a decrease in pup body weight close to weaning; this effect served as the basis of the Short-Term RfD. Other studies in rats and rabbits found that developmental toxicity only occurred at doses higher than those causing maternal toxicity.

[4] A two-generation reproductive/developmental study in rats did not note any reproductive abnormalities in the following tested parameters: reproductive serum hormones (testosterone, FSH, LH), estrous cycles, sperm morphology and motility and spermatid head count, mating behavior, conception, gestation, parturition, lactation, and weaning at doses up to 100-fold higher than the Short-Term RfD. Additionally, organ weights and histopathology of the testes, epididymes, prostate, seminal vesical, ovary, and uterus were unchanged.

[5] No neurotoxicity studies were found. A two-generation reproductive/developmental study in rats found no changes in reflex or pain response in pups at doses up to 100-fold higher than the Short-Term RfD.

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