Minnesota Department of Health

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

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Toxicological Summary for: Isobutanol

CAS: **78-83-1**

Synonyms: 2-Methyl-propan-1-ol (IUPAC); isobutyl alcohol; 2-methyl-1-propanol; 2-methylpropyl alcohol; IBA; 1-hydroxymethylpropane; isopropylcarbinol; 2-methylpropanol; 2-methylpropan-1-ol

Acute Non-Cancer Health Based Value (nHBVAcute) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Based Value (nHBVShort-term) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Based Value ($nHBV_{Subchronic}$) = 700 µg/L

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

$$= \frac{\text{(0.24 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 686 rounded to **700 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.24 mg/kg-d (Wistar rats)
Source of toxicity value:	determined by MDH in 2014
Point of Departure (POD):	300 mg/kg-d (administered dose NOAEL, BASF 1992 and Schilling et al. 1997)
Dose Adjustment Factor (DAF):	Body weight scaling, default (US EPA 2011)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 300 mg/kg-d x 0.24 = 72 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty (due to lack of oral reproductive/developmental toxicity studies including evaluation of hormones)
Critical effect(s):	Testicular atrophy with histopathological effects
Co-critical effect(s):	None
Additivity endpoint(s):	Male reproductive system

Chronic Non-Cancer Health Based Value ($nHBV_{Chronic}$) = 300 µg/L

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

$$= \frac{(0.072 \text{ mg/kg-d}) \times (0.2)^{*} \times (1000 \text{ µg/mg})}{(0.044 \text{ L/kg-d})^{**}}$$

= 327 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 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.072 mg/kg-d (Wistar rats)
Source of toxicity value:	determined by MDH in 2014
Point of Departure (POD):	300 mg/kg-d (administered dose NOAEL, BASF 1992 and Schilling et al. 1997
Dose Adjustment Factor (DAF):	Body weight scaling, default (US EPA 2011)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 300 mg/kg-d x 0.24 = 72 mg/kg-d
Total uncertainty factor (UF):	1000
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 10 for database uncertainty (due to lack of oral reproductive/developmental toxicity studies including evaluation of hormones), and 3 for use of subchronic study
Critical effect(s):	Testicular atrophy with histopathological effects
Co-critical effect(s):	None
Additivity endpoint(s):	Male reproductive system

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Group D, not classifiable as human carcinogen (EPA 1986a)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (moderate)

Summary of Guidance Value History:
In 2014 MDH derived subchronic and chronic non-cancer HBVs of 600 and 300 µg/L, respectively. In 2016 MDH updated the intake rate values used to derive guidance values. Due to rounding to one significant digit the updated intake rates resulted in a revised Subchronic nHBV of 700 µg/L but did not result in any change to the Chronic nHBV value derived in 2014. MDH intends to re-evaluate guidance values on a five year cycle in order to keep guidance values current with scientific knowledge. Under this process isobutanol would undergo re-evaluation in 2021.

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[2]	Yes	Yes	Yes
Effects observed?	Yes[1]	-	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[1]Isobutanol decreased estrogen and increased progesterone in rats when given a single oral dose about 2,800 times higher than the subchronic RfD and over 9,000 times higher than the chronic RfD. Lower doses were not tested. *In vitro* endocrine assays were negative for estrogen binding activity.

[2]Immunotoxicity of isobutanol has not been studied in humans or animals. *In vitro* cell culture studies reported no effects on splenic B or T cell mitogenic responses. Isobutanol was considered negative for sensitization potential based on Quantitative Structure-Activity Relationship modeling (QSAR) and Read-Across approaches to evaluate weight-of-evidence based on structurally similar chemicals.

[3]Developmental toxicity has not been studied for oral administration of isobutanol. Effects reported during gestational inhalation studies in rats and rabbits and in a two-generation inhalation study in rats included effects on pup survival, body weight and possible cardiac defects. The relevance of the inhalation findings for oral ingestion is unknown; however, the RfD is considered to be protective for the developmental effects noted in the inhalation studies.

[4]Reproductive toxicity of isobutanol has not been directly studied for oral administration. Testicular effects were identified as the critical effect to derive the RfDs. The RfDs were based on testicular atrophy and histological effects from a subchronic drinking water study in rats. Other effects included effects on estrous cyclicity at an acute dose about 2,800 times higher than the subchronic RfD and possible effects on mating indices noted in a two-generation inhalation study. The relevance of the inhalation findings for oral ingestion is unknown; however, the RfD is considered to be protective for the effects noted in the inhalation study.

[5]Isobutanol causes central nervous system depression in humans and animals at high acute oral doses. In animals given a solution containing 100,000 ppm isobutanol, transient reversible nervous system effects were reported within a few minutes of dosing and lasted up to 10 minutes. No nervous system effects were reported when animals were given a lower bolus dose of a 31,600 ppm solution. No nervous system effects were reported in a subchronic drinking water study at the highest dose tested, about 1,500 times higher than the subchronic RfD.

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