Adopted as Rule: September 30, 2013

Toxicological Summary for 1,4-Dioxane:
CAS: 123-91-1

Synonyms: diethylene ether; 1,4-diethylene dioxide; diethylene oxide; dioxyethylene ether; and dioxane

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = 300 µg/L

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

$$= \frac{\text{(0.12 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 312 rounded to **300 µg/L**

Reference Dose / Concentration:	0.12 mg/kg-d (F344/DuCrj rats)
Source of toxicity value:	MDH 2011
Point of Departure:	52 mg/kg-d (NOAEL from 13 week drinking water study in rats by Kano et al 2008)
Human Equivalent Dose Adjustment:	52 mg/kg-d x DAF = 52 x 0.23 = 12 mg/kg-d (MDH 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are address by the HED adjustment); 10 for intraspecies variability; and 3 for database insufficiencies (lack of a multigeneration reproductive/developmental study)
Critical effect(s):	Increased relative liver and kidney weight (with histological and clinical chemistry changes at higher dose level); hepatocyte swelling; and nuclear enlargement of the nasal respiratory epithelium
Co-critical effect(s):	Increased nuclear enlargement of the bronchial epithelium
Additivity endpoint(s):	Hepatic (liver) system, Renal (kidney) system, Respiratory system

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

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

$$= \frac{\text{(0.025 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 116 rounded to **100 µg/L**

Reference Dose / Concentration:	0.025 mg/kg-d (Sherman rats)
Source of toxicity value:	MDH 2011 (Note: same basis as EPA IRIS 2010 value that was rounded to 0.03 mg/kg-d)
Point of Departure:	9.6 mg/kg-d (NOAEL from 2 year drinking water study in rats by Kociba et al 1974)
Human Equivalent Dose Adjustment:	9.6 mg/kg-d x DAF = 9.6 x 0.26 = 2.5 mg/kg-d (EPA IRIS 2010, Table 5-7)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are address by the HED adjustment); 10 for intraspecies variability; and 3 for database insufficiencies (lack of a multigeneration reproductive/developmental study)
Critical effect(s):	Histopathological lesions in the liver and kidney (hepatic and renal degeneration and necrosis as well as regenerative hyperplasia in hepatocytes and renal tubule epithelial cells)
Co-critical effect(s):	Increased relative liver weight; nonneoplastic lesions in the nasal cavity, liver and kidney; nuclear enlargement of nasal, tracheal and bronchial epithelium; decreased body weight and growth; and neoplastic lesions in the liver**
Additivity endpoint(s):	Hepatic (liver) system; Renal (kidney) system; Respiratory system

**neoplastic lesions (liver adenomas) are addressed by the Cancer HRL

Cancer Health Risk Limit (cHRL) = 1 µg/L

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

$$= \frac{\text{(1E-5) x (1000 µg/mg)}}{[(0.10 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.10 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.10 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 1.03 rounded to **1 µg/L**

Cancer classification:	"Likely to be carcinogenic to humans"
Slope factor:	0.10 per mg/kg-d (laboratory animal) (hepatocellular adenomas and carcinomas in female mice, Kano et al 2009)
Source of slope factor:	US EPA, IRIS 2010 (United States Environmental Protection Agency 2010)
Tumor site(s):	Slope factor based on liver adenomas and carcinomas. Additional

tumor sites included: nasal squamous cell carcinomas; peritoneal mesotheliomas; and mammary gland adenomas

Volatile: Yes (low volatile)

Summary of Guidance Value History:
In 2002, MDH derived a cancer Health-Based Value (HBV) of 30 µg/L. In 2011, the cancer HBV was updated to 1 µg/L. The 2011 cancer HBV was 30-fold lower as the result of: 1) use of a more recent cancer risk assessment; 2) application of age-dependent early-life cancer sensitivity adjustment factors; 3) utilizing more recent intake rates which incorporate higher intake rates during early life, and 4) rounding to one significant figure. The noncancer subchronic and chronic HBVs were new in 2011. The 2011 HBVs were adopted as HRLs in 2013.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	No[1]	No[2]	Yes	No[4]	Yes
Effects?	-	-	Yes[3]	-	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)] Relevant oral toxicity studies have not been conducted. However, based on available indirect information there is no evidence that 1,4-dioxane exhibits endocrine activity.

[2)] No oral immunotoxicity studies. Based on available indirect information there is no evidence that 1,4-dioxane alters immune function.

[3)] Only one oral study, a teratogenicity study in rats (Giavini et al 1985) is available. In this study, pregnant females and their fetuses exposed to a human equivalent dose of 230 mg/kg-d ($\geq$ 2000-fold higher than the subchronic and chronic RfDs) weighed less than unexposed animals. A slightly but significantly higher incidence of reduced sternum ossification was also noticed in these exposed fetuses. No other significant differences between treated and control groups were observed, including number of implantations and of live fetuses, post-implantation loss, and incidence of malformations.

[4)] No oral reproductive studies have been conducted and therefore only ancillary information is available.

[5)] In laboratory animals, the neurological effects of acute high-dose exposure included staggered gait, narcosis, paralysis, coma, and death. A single oral dose at a human equivalent dose level of 252 mg/kg-d ($\geq$2000-fold higher than the subchronic and chronic RfDs) resulted in reduced the dopamine and serotonin content of the hypothalamus, the neurochemical profile of all other brain regions were not affected.

No repeat oral dosing studies evaluating neurotoxicity per se have been conducted and therefore only ancillary information is available. No histopathologic alterations were observed in the brain, spinal cord,

and sciatic nerve from rats receiving up to 2 year exposure via the drinking water at dose levels up to ~1600 mg/kg-d [HED ~ 416] (~3500-fold higher than the subchronic and chronic RfDs).

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