Minnesota Department of Health

Adopted as Rule: November 2015

Toxicological Summary for: Di-(2-ethylhexyl) phthalate

CAS: **117-81-7**
Synonyms: DEHP; Bis(2-ethylhexyl)phthalate

Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = 20 µg/L

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

$$= \frac{\text{(0.029 mg/kg/d) x (0.2)* x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 20.1 rounded to **20 µg/L**

* MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate Relative Source Contributions (RSCs) (MDH 2008, Appendix K). Typically an RSC of 0.5 is utilized for nonvolatile contaminants for the acute and short-term durations and an RSC of 0.2 is used for subchronic and chronic durations. However, there is evidence that there are significant known or potential sources other than ingestion of drinking water. Therefore, an RSC of 0.2 was selected rather than applying the default RSC value.

Reference Dose/Concentration:	0.029 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	3.8 mg/kg-d (BMDL, Blystone et al. 2010)
Human Equivalent Dose (HED):	3.8 x 0.23 = 0.874 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are addressed by the HED adjustment), 10 for intraspecies variability
Critical effect(s	Male reproductive tract malformations (small testes, small epididymis, small cauda epididymis, small seminal vesicles)
Co-critical effect(s):	Increased fetal testicular testosterone, male reproductive tract lesions, retained nipples in pre-weanling males
Additivity endpoint(s):	Developmental (E), Male reproductive system (E)

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 20 µg/L

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

$$= \frac{\text{(0.029 mg/kg/d) x (0.2)* x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 20.1 rounded to **20 µg/L**

* Rationale for selecting an RSC of 0.2 - same explanation as that provided for the acute duration (see above).

Reference Dose/Concentration	0.029 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value:	MDH, 2013
Point of Departure (POD):	3.8 mg/kg-d (BMDL, Blystone et al. 2010)
Human Equivalent Dose (HED):	3.8 x 0.23 = 0.874 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	30
Uncertainty factor allocation:	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are addressed by the HED adjustment), 10 for intraspecies variability
Critical effect(s):	Male reproductive tract malformations (small testes, small epididymis, small cauda epididymis, small seminal vesicles)
Co-critical effect(s):	Increased fetal testicular testosterone, male reproductive tract lesions, retained nipples in pre-weanling males, hormonal effects in pubertal males (changes in serum testosterone, increased luteinizing hormone, increased serum estradiol, increased testicular interstitial fluid testosterone, and decreased androgen synthesis)
Additivity endpoint(s):	Developmental (E), Male reproductive system (E)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 20 µg/L

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

$$= \frac{\text{(0.029 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 75.3 rounded to 80 µg/L

Reference Dose/Concentration:	0.029 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value	MDH, 2013
Point of Departure (POD):	3.8 mg/kg-d (BMDL, Blystone et al. 2010
Human Equivalent Dose (HED):	3.8 x 0.23 = 0.874 mg/kg-d (Minnesota Department of Health (MDH) 2011)
Total uncertainty factor:	30
Uncertainty factor allocation	3 for interspecies extrapolation to address potential differences in toxicodynamics (toxicokinetic differences are addressed by the HED adjustment), 10 for intraspecies variability
Critical effect(s):	Male reproductive tract malformations (small testes, small epididymis, small cauda epididymis, small seminal vesicles)
Co-critical effect(s):	Increased fetal testicular testosterone, male reproductive tract lesions, retained nipples in pre-weanling and adult males, hormonal effects in pubertal and young adult males

(changes in serum testosterone, increased luteinizing hormone), increased serum estradiol and testicular interstitial fluid testosterone in pubertal males, decreased androgen synthesis in pubertal males

Additivity endpoint(s): Developmental (E), Male reproductive system (E)

The Subchronic nHRL must be protective of exposures that occur within the acute and short-term periods and therefore, the Subchronic nHRLis set equal to the Short-term nHRL of 20 µg/L. Additivity endpoints: Developmental (E), Male reproductive system (E).

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 20 µg/L

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

$$= \frac{\text{(0.029 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043L/kg-d)}}$$

= 135 rounded to 100 µg/L

Reference Dose/Concentration: Same as subchronic RfD, see information above for details about the reference dose. Chronic exposure to adult animals resulted in decreased spermatogenesis and testes tubular atrophy.

The Chronic nHRL must be protective of exposures that occur within the acute, short-term, and subhchronic periods and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 20 µg/L. Additivity endpoints: Developmental (E), Male reproductive system (E).

Cancer Health Risk Limit (cHRL) = 7 µg/L

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

$$= \frac{\text{(1E-5) x (1000 ug/mg)}}{[(0.014 \times 10 \times 0.137\ L/kg\text{-}d \times 2) + (0.014 \times 3 \times 0.047\ L/kg\text{-}d \times 14) + (0.014 \times 1 \times 0.039\ L/kg\text{-}d \times 54)] / 70}$$

= 7.3 rounded to **7 µg/L**

Cancer classification: Group B2, probable human carcinogen
Slope factor: 0.014 $(mg/kg\text{-}d)^{-1}$ (laboratory animal) (NTP, 1982)
Source of slope factor: EPA 1993
Tumor site(s): Liver

Volatile: No

Summary of Guidance Value History:
The noncancer Health-Based Values (HBVs) (20 µg/L) for acute, short-term, and subchronic durations

were developed in 2013 and adopted into rule as Health Risk Limits (HRLs) in 2015. Previously, there was a 2009 HRL_{MCL} of 6 µg/L based on the US EPA Maximum Contaminant Level (MCL). There was a previous 1993/94 cancer HRL of 20 µg/L (based on liver cancer and an oral slope factor of 0.014 from IRIS 1991).

The 2015 cancer HRL (7 µg/L) is slightly higher than the 2009 MCL-based chronic HRL (6 µg/L) due to: 1) utilization of more recent lifetime intake rates which incorporate higher intake rates during early life; 2) application of age-dependent early-life cancer sensitivity adjustment factors; and 3) rounding to one significant digit.

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

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	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]It is well documented in an extensive number of laboratory animal studies that DEHP is anti-androgenic, causing decreases in fetal testosterone at critical windows of male reproductive development *in utero*, leading to postnatal male reproductive organ malformations. The effect of DEHP and/or metabolites on testosterone and thyroid hormone levels in humans have been studied in several epidemiology studies with conflicting results. In animal studies, thyroid hormones have been affected at doses over 3,000 times higher than the RfD. DEHP does not appear to have estrogenic effects in animals or humans. Endocrine effects, based on anti-androgenic responses, are identified as co-critical effects.

[2]In humans, associations between inhalation of phthalate dust, including DEHP, and asthma-like symptoms have been reported in some epidemiology studies; however, there are no reported associations between oral exposure and asthma or allergy in humans. Low doses of phthalates have affected antibodies in animal studies only when given by subcutaneous or intraperitoneal injection, but not by oral ingestion. No developmental immune effects were found in offspring at doses over 2,000 times higher than the RfDs. Spleen and thymus weights were decreased in offspring exposed prenatally to doses over 800 times higher than the RfD.

[3]As an anti-androgen, DEHP inhibits the normal biological effects of androgens (male sex hormones). This interference results in alterations in normal male sexual development. Interference at different stages of life can alter fetal, neonatal, and adolescent (puberty) development, based on laboratory animal studies. In humans, the effects of DEHP and/or metabolites on neurobehavioral development, male reproductive and pubertal development have been reported in several epidemiology studies with conflicting results. Developmental effects on the male reproductive system are identified as critical effects and provide the basis for the RfDs.

[4]Reproductive system effects of DEHP and/or metabolites in humans, including effects on male fertility, have been reported in several epidemiology studies with conflicting results. Male reproductive system effects are identified as critical effects based on laboratory animal studies and provide the basis for

the RfDs.

[5]Neurobehavioral developmental effects in humans, including effects on psychomotor development, IQ, internalizing and socializing behaviors, have been associated with phthalates in some epidemiology studies. In laboratory animals, DEHP caused some neurotoxicity including reduced grip strength, reduced hind-limb splay, and increased brain weight in offspring exposed prenatally at doses over 8,000 times higher than the RfD. No neurobehavioral effects were reported in a 14-day neurotoxicity study at doses over 10,000 times higher than the RfDs. Impaired spatial learning and memory in aged animals exposed prenatally were reported at a dose about 10 times higher than the RfD. No neurobehavioral effects were reported in chronic studies although increased brain weights in rats and mice were reported at doses over 6,500 times higher than the RfD.

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