Toxicological Summary for: Dibutyl Phthalate

CAS: 84-74-2
Synonyms: DBP; Di-n-butyl phthalate; 1,2-Benzenedicarboxylic acid, dibutyl ester; Dibutyl 1,2-benzenedicarboxylate

Acute Non-Cancer Health Risk Limit (nHRL\textsubscript{Acute}) = 20 µg/L

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)(Acute intake rate, L/kg/d)

\[
= (0.023 \text{ mg/kg/d}) \times (0.2) \times (1000 \text{ µg/mg}) \\
(0.289 \text{ L/kg-d})
\]

= 15.9 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. However, there is evidence that there are significant known or potential sources other than ingestion of water. Therefore, a 0.2 RSC was selected rather than the default value of 0.5 for nonvolatile contaminants.

Human Equivalent Dose (MDH, 2011): 10 x 0.23 = 2.3 mg/kg-d (MDH 2011)

Total uncertainty factor: 100
Uncertainty factor allocation: 3 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database uncertainties (additional study is warranted for potential thyroid and immunological effects)

Critical effect(s): Decreased fetal testosterone, decreased testicular cell number and testes size
Co-critical effect(s): Decreased fetal testosterone, Sertoli cell atrophy, decreased total cell number and number of seminiferous tubules
Additivity endpoint(s): Development (E) (male reproductive system)

Short-term Non-Cancer Health Risk Limit (nHRL\textsubscript{Short-term}) = 20 µg/L

= (Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)
(Short-term intake rate, L/kg/d)
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\[
= (0.023 \text{ mg/kg/d}) \times (0.2) \times (1000 \mu g/mg) \\
(0.289 \text{ L/kg-d})
\]

\[
= 15.9 \text{ rounded to } 20 \mu g/L
\]

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

**Reference Dose/Concentration 0.023 mg/kg-d (Sprague-Dawley rats)
Source of toxicity value MDH 2012
Point of Departure (POD) 10 mg/kg-d (NOAEL from Lehmann et al 2004 and Boekelheide et al., 2009)
Human Equivalent Dose (MDH, 2011): 10 x 0.23 = 2.3 mg/kg-d (MDH 2011)
Total uncertainty factor: 100
Uncertainty factor allocation: 3 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database uncertainties (additional study is warranted for potential thyroid and immunological effects)
Critical effect(s): Decreased fetal testosterone, decreased testicular cell number and testes size
Co-critical effect(s): Decreased fetal testosterone, Sertoli cell atrophy, decreased total cell number and number of seminiferous tubules
Additivity endpoint(s): Development (E) (male reproductive system)

**Subchronic Non-Cancer Health Risk Limit (nHRLSubchronic) = Short-term nHRL = 20 µg/L

\[
= (\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor}) \\
(\text{Subchronic intake rate, L/kg/d})
\]

\[
= (0.023 \text{ mg/kg/d}) \times (0.2) \times (1000 \mu g/mg) \\
(0.077 \text{ L/kg-d})
\]

\[
= 59.7 \text{ rounded to } 60 \mu g/L
\]

**Reference Dose/Concentration: Use the Short-term RfD**

**The calculated Subchronic RfD (0.13 mg/kg-d) is higher than the Short-term RfD (0.023 mg/kg-d), which is based on male reproductive developmental effects. The Subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Subchronic RfD is set to the Short-term RfD.**

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

**Chronic Non-Cancer Health Risk Limit (nHRLChronic) = Short-term nHRL = 20 µg/L**

\[
= (\text{Reference Dose, mg/kg/d}) \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor}) \\
(\text{Chronic intake rate, L/kg/d})
\]
= (0.023 mg/kg/d) x (0.2) x (1000 µg/mg)  

= 107 rounded to **100 µg/L**

Reference Dose/Concentration: Use the Short-term RfD**

**The calculated Chronic RfD (0.043 mg/kg-d) is higher than the Short-term RfD (0.023 mg/kg-d), which is based on male reproductive developmental effects. The Chronic RfD must be protective of all types of adverse effects that could occur as a result of chronic exposure, including short-term effects (MDH 2008, page 34). Therefore, the Chronic RfD is set to the Short-term RfD.**

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

Cancer Health Risk Limit (cHRL) = “Not Applicable”

Cancer Classification: Group D (not classifiable)  
Source: US EPA IRIS 1993

Volatile: Yes (Low)

Summary of Guidance Value History:
The 2012 HBVs (20 µg/L) are 35-fold lower than the 1993 HRL value (700 µg/L) as the result of: 1) utilization of more recent toxicity information resulting in a 4-fold lower RfD; 2) utilization of more recent intake rates which incorporate higher intake rates during early life; and 3) rounding to one significant digit. Health-Based Values (HBVs) developed in 2014 were adopted into rule as HRLs in November 2015.

<table>
<thead>
<tr>
<th>Tested?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects?</td>
<td>Yes¹</td>
<td>-</td>
<td>Yes³</td>
<td>Yes⁴</td>
<td>No⁵</td>
</tr>
</tbody>
</table>

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 Some epidemiology studies have identified associations between phthalate exposure and changes in thyroid and reproductive hormones. However, these effects were not consistently observed and studies were generally accompanied by multiple confounding factors such that it is not possible to draw conclusions.

In vitro studies evaluating pituitary cell proliferation and thyroid receptor interactions suggest that DBP may impact thyroid function. The relevance of the in vitro effects to in vivo is unclear. Potential DBP thyroid effects following in vivo exposure have not been evaluated. Changes in thyroid
hormone serum levels were identified as sensitive effects following butyl benzyl phthalate exposure in laboratory animals. The lack of thyroid studies on DBP is part of the rationale for incorporating a database uncertainty factor into the derivation of the RfD.

In studies conducted in laboratory animals changes in FSH, LH and PRL have also been reported but effects were not consistent across doses or time points of evaluation. Disruption of fetal testes steroidogenesis was been identified as a sensitive effect and forms the basis for the RfD.

Several mechanistic toxicological studies and epidemiological studies have been conducted, mainly on other phthalates (e.g., DEHP). The mechanistic studies typically utilized topical or subcutaneous injection as the route of exposure. Epidemiological studies have suggested an association with PVC-related exposure and asthma.

Laboratory animal studies on DEHP suggest immunological effects at doses of similar magnitude to those causing male reproductive developmental effects. The need for immunological study of DBP is part of the rationale for incorporating a database uncertainty factor into the derivation of the RfD.

Some epidemiology studies have identified an association between phthalate exposure and male reproductive and neurobehavioral development. However, effects were not consistently observed and results from these studies are generally accompanied by multiple confounding factors such that it is not possible to draw definite conclusions.

Studies in laboratory animals have identified a variety of developmental effects following exposure to DBP. Disruption of fetal testicular development has been identified as a sensitive effect. Increased malformations and decreased offspring viability were observed at higher doses, doses ~10 to 20-fold higher than those associated with fetal testicular development. The sensitive effects of fetal testicular development and steroidogenesis form the basis of the RfD.

Some epidemiology studies have identified an association between phthalate exposure and male reproductive effects. However, effects were not consistently observed and these studies are generally accompanied by multiple confounding factors such that it is not possible to draw conclusions.

Studies in laboratory animals have identified a variety of male reproductive effects, including testicular effects and decreased fertility. The fetal male reproductive system is more sensitive than the mature male reproductive system following exposure to DBP. Fetal male reproductive effects form the basis of the RfD.

Some epidemiological studies have identified an association between phthalate exposure and changes in neurobehavioral development. However, these studies are generally accompanied by multiple confounding factors such that it is not possible to draw definitive conclusions.

Neurodevelopmental studies have been conducted in laboratory animals. Neurobehavioral impairment was not observed.

References:


California Environmental Protection Agency - OEHHA Proposition 65. "Most Current Proposition 65 No Significant Risk Levels (NSRLs) Maximum Allowable Dose Levels (MADLs)." from [http://www.oehha.ca.gov/prop65/getNSRLs.html](http://www.oehha.ca.gov/prop65/getNSRLs.html).


Stahlhut RW, E van Wijngaarden, TD Dye, S Cook and SH Swan (2007). Concentrations of Urinary Phthalate Metabolites Are Associated with Increased Waist Circumference and Insulin


Zhang Y, X Jiang and B Chen (2004). Reproductive and developmental toxicity in F1 Sprague-Dawley male rats exposed to di-n-butyl phthalate in utero and during lactation and determination of its NOAEL. *Reproductive Toxicology* 18: 669-676.