

## DIBUTYL PHTHALATE

**CAS number:** 84-74-2

**Synonyms:** n-Butyl phthalate, DBP, phthalic acid dibutyl ester

**Chemical formula:**  $C_{16}H_{22}O_4$

**Structural formula:** —

### Workplace exposure standard (amended)

**TWA:** 0.05 ppm (0.58 mg/m<sup>3</sup>)

**STEL:** —

**Peak limitation:** —

**Notations:** —

**IDLH:** 4,000 mg/m<sup>3</sup>

### Sampling and analysis:

## Recommendation and basis for workplace exposure standard

A TWA of 0.05 ppm (0.58 mg/m<sup>3</sup>) is recommended to protect for irritation of the eyes and respiratory tract in exposed workers.

## Discussion and conclusions

Dibutyl phthalate (DBP) is used as an insect repellent, solvent and plasticiser and in the manufacture of explosives and propellants, nail polish and lubricating agents. Due to its low volatility, vapour saturation occurs at 0.09 ppm (1 mg/m<sup>3</sup>), at which point the substance forms an aerosol (DFG, 2013).

Critical effects of exposure are irritation of the eyes and respiratory tract and potential liver damage; prenatal toxicity is established in animals above the irritation threshold (ACGIH, 2018; DFG, 2013). Developmental effects are reported in rats, with a calculated NOAEL of 1.5 mg/kg and LOAEL of 31.25 mg/kg for abnormal sperm development (DFG, 2013). The critical study for recommending a TWA for DBP reports a LOAEC of 1.18 mg/m<sup>3</sup> for nasal irritation in rats which has a relatively flat dose-response relationship (DFG, 2013). This study is absent from the ACGIH (2018) assessment. Commensurate with the approach presented in DFG (2013), the LOAEC is halved to account for uncertainty in determining a NOAEL, which affords the recommended TWA of 0.05 ppm (0.58 mg/m<sup>3</sup>). At this concentration, the substance is a vapour and provides additional protection for irritant effects.

## Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is not recommended based on the available evidence.

# APPENDIX

## Primary sources with reports

Source	Year set	Standard
<b>SWA</b>	<b>1991</b>	<b>TWA: 5 mg/m<sup>3</sup></b>
<b>ACGIH</b>	<b>2001</b>	<b>TWA: 5 mg/m<sup>3</sup></b>
<p>TLV-TWA intended to minimise potential for irritation to the eyes and respiratory tract and potential testicular injury reported in animal studies.</p> <p>Insufficient data to recommend a STEL or notations for carcinogenicity, sensitisation or skin absorption.</p> <p>Summary of information:</p> <p>Available data indicate low order of toxicity. TLV-TWA derivation not discussed but expected to be sufficiently protective of critical effects.</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>Nausea, dizziness, photophobia, lachrymation and conjunctivitis experienced in worker accidentally exposed to oral dose of 40 mg/kg <ul style="list-style-type: none"> <li>recovery was rapid and uncomplicated</li> </ul> </li> <li>Workplace study (n=150–250) of exposure to 3 mixed alkyl phthalates, including DBP, (average breathing zone concentration of 1–6 ppm or 8–15 mg/m<sup>3</sup>) found no phthalates in blood of workers before or after exposure and no peripheral nervous effects were observed</li> <li>Investigation of artificial leather industry (n=147; 87 female, 60 male) showed ambient air concentrations of 1.7–66 mg/m<sup>3</sup> of various alkyl and aryl phthalates were associated with numbness, pain and spasms of upper extremities; study not used in assessment due to mixed exposures: <ul style="list-style-type: none"> <li>chronic exposure symptoms usually occurred after 6 to 7 yr of work</li> <li>neurological study showed polyneuritis in 32% and vestibular disturbance in 78% of workers</li> </ul> </li> <li>No positive reactions to 48 h occlusive patch with 5% DBP (n=53), 9% in cosmetic formulation caused none to slight irritation; non-sensitising.</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>Aerosol at 250 ppm (mice, 2 h) reported severe irritation to eyes and upper respiratory tract, convulsions, partial paralysis, narcosis and death in some animals</li> <li>Weight loss and changes in haematological parameters at 4 mg/m<sup>3</sup> (rats, no further information provided)</li> <li>No observable irritation when instilled on to rabbit eyes (48 h)</li> <li>Reduced bw gain at 50 mg/m<sup>3</sup> in inhalation study (rats, 6 h/d, 5 d/wk, 3–6 mo)</li> <li>No adverse effects at ≈1 mg/kg (as solution in oil) in sub-chronic and chronic repeat oral dose studies with rats (2 d/wk for 6 wk or for 1.5 yr, latter frequency not specified)</li> <li>No adverse effects in chronic feeding study below 0.25% in diet (rats, 1 yr)</li> <li>No carcinogenic effects were noted in either of the above chronic studies</li> <li>Reduced testes weight in mice and guinea pigs, but not hamsters or rats at 2,000 mg/kg/d (10 d)</li> <li>Reduced number litters and live pups/litter at 1,300 mg/kg/d in combined reproductive/developmental feeding study (rats, 4 mo): <ul style="list-style-type: none"> <li>no effects on reproduction at 390 mg/kg/d (not regarded as NOAEL by agency)</li> <li>oral or intraperitoneal doses near the LD<sub>50</sub> (not specified) caused higher number of resorptions, skeletal abnormalities and increased foetal death (pregnant rats/mice).</li> </ul> </li> </ul>		

Source	Year set	Standard
DFG	2009	MAK: 0.05 ppm (0.58 mg/m <sup>3</sup> )
<p>Summary of additional data:</p> <p>MAK derived from LOAEC of 1.18 mg/m<sup>3</sup> for hyperplasia in the nasal cavity of rats. Preliminary value of 0.58 mg/m<sup>3</sup> considered sufficiently protective because it is below the vapour saturation point and thus unlikely to form aerosols as reported at the LOAEC; aerosol exposure is likely to result in higher local concentrations versus the vapour. Observance of the MAK should also protect for abnormal sperm development observed in rats, for which a NOAEL of 1.5 mg/kg/d was calculated. An equivalent inhalational exposure is estimated at 10 mg/m<sup>3</sup> (assuming a 70 kg worker, with a respiratory volume of 10 m<sup>3</sup> during an 8 h shift).</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>An inadequately designed study reported an increased incidence of hypospadias and breast cancer in children of soldiers exposed to DBP impregnated clothing <ul style="list-style-type: none"> <li>study was dismissed due to incorrect interpretation and representation of data</li> </ul> </li> <li>Isolated cases suggest weak skin sensitisation effect in some individuals, but insufficient to warrant classification as a skin sensitiser <ul style="list-style-type: none"> <li>no studies available regarding respiratory sensitisation</li> </ul> </li> <li>Skin absorption rate of 2.4 µg/cm<sup>2</sup>/h=0.28 mg/kg/d (assuming 2,000 cm<sup>2</sup> of skin on arms of 70 kg worker) considered too low for systemic toxicity to occur at a calculated NOAEL of 1.5 mg/kg for systemic reproductive effects.</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>Studies used in the mechanistic evaluation of testes toxicity: <ul style="list-style-type: none"> <li>inhibition of steroid/testosterone production at 50 or 250 mg/kg/d (rats, 90 d)</li> <li>reduced sperm count/motility due to oxidative stress at 250 mg/kg/d (rats, 2 wk)</li> <li>collapse of Sertoli cell vimentin filaments caused apoptosis of spermatogonia at 500 mg/kg in prepubertal rats</li> </ul> </li> <li>Maternal and foetal NOAELs: 500 mg/kg/d for prenatal mortality, foetal weight, external malformations in repeat gavage study (rats, on gestation d 7–15) <ul style="list-style-type: none"> <li>LOAELs: 630 mg/kg/d</li> </ul> </li> <li>Hyperplasia in nasal cavity, increased lung weights and reduced testis weights observed in repeat inhalation study under aerosol conditions, treatment range: <ul style="list-style-type: none"> <li>1.18–509 mg/m<sup>3</sup> (rats, 6 h/d, 5 d/wk, 28 d);</li> <li>LOAEC: 1.18 mg/m<sup>3</sup>; as regarded by EU Risk Assessment Report (2003)</li> <li>relatively flat dose-response curve suggests no increased effect over longer exposure periods and a NOAEC near the experimental LOAEC</li> </ul> </li> <li>Increased liver weight, anaemia and changes in clinical biochemistry in chronic feeding study, treatment range: 30–752 mg/kg/d (rats, 13 wk); histopathology showed reduction of fat deposits in hepatocytes: <ul style="list-style-type: none"> <li>NOAEL: 152 mg/kg/d</li> </ul> </li> <li>Dose-dependent increase in abnormal sperm development in repeat gavage study, treatment range: 31.25–500 mg/kg/d (rats, 4 wk); LOAEL: 31.25 mg/kg/d, no NOAEL determined: <ul style="list-style-type: none"> <li>benchmark calculation (Hill model) yielded benchmark dose of 1.5 mg/kg/d at the lower 95% confidence limit</li> </ul> </li> <li>Peroxisome proliferation demonstrated in some studies suggests potential carcinogenicity <i>via</i> non-mutagenic mechanisms <ul style="list-style-type: none"> <li>humans are less susceptible to peroxisome proliferation than rats</li> </ul> </li> <li>Overall evaluated as non-mutagenic: <ul style="list-style-type: none"> <li>negative results for 2 <i>in vivo</i> micronucleus tests, no other <i>in vivo</i> mutagenicity tests available for assessment</li> </ul> </li> </ul>		

Source	Year set	Standard
<ul style="list-style-type: none"> <li>histological examination of rat foetuses showed effects to germ cells.</li> </ul>		
<b>SCOEL</b>	<b>2016</b>	<b>TWA: 0.05 ppm (0.58 mg/m<sup>3</sup>)</b>
<p>Summary of additional data:</p> <p>OEL derivation is commensurate with MAK derivation presented in DFG (2013). No STEL proposed due to absence of irritation in tests of acute exposure. No skin notation warranted due to low dermal absorption rate relative to levels required for systemic toxicity. Not considered sensitising based on weight of evidence in human and animal studies.</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>Urinary concentration of monobutyl phthalate metabolite was not correlated with DNA damage in comet assay with human sperm (n=141)</li> <li>Several epidemiological studies indicate association between phthalate exposure (various phthalate esters discussed) and adverse male reproductive effects. However, due to inconsistencies and confounding co-exposures no evaluation as to the risk of DBP is made specifically.</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>LC<sub>50</sub>: 25,000 mg/m<sup>3</sup> (mice, 2 h), &gt;15,680 mg/m<sup>3</sup> (rats, 4 h)</li> <li>Oral LD<sub>50</sub>: between 6,300 and &gt;20,000 mg/kg (rats), 10,000 mg/kg (guinea pigs)</li> <li>LD<sub>50</sub>: 22,000 mg/kg (rabbits, dermal).</li> </ul>		
<b>OARS/AIHA</b>	<b>NA</b>	<b>NA</b>
No report.		
<b>HCOTN</b>	<b>NA</b>	<b>NA</b>
No report.		

## Secondary source reports relied upon

Source	Year	Additional information
HSE	✓ 2002	<ul style="list-style-type: none"> <li>8 h TWA: 5 mg/m<sup>3</sup>; 15 min STEL: 10 mg/m<sup>3</sup>.</li> </ul>
NICNAS	✓ 2016	<ul style="list-style-type: none"> <li>Grouped with other alkyl (C<sub>4</sub>-C<sub>6</sub>) phthalate esters based on American Chemical Council categorisation of alkyl phthalate esters by molecular weight of side-chains</li> <li>Phthalates are rapidly and almost completely absorbed following oral exposure; bioavailability is assessed as 100%</li> <li>Bioavailability from dermal absorption is unlikely to exceed 5% of dose in humans</li> <li>No evidence for bioaccumulation</li> <li>Not expected to have mutagenic or genotoxic potential in humans based on the weight of evidence.</li> </ul>
APVMA	✓ 2014	<ul style="list-style-type: none"> <li>Insect repellent for sheep, not to be used 14 d before slaughter or on females producing offspring or milk for human consumption.</li> </ul>
NTP	✓ 2000	<ul style="list-style-type: none"> <li>Concentrations in US plants ranged from below the detection limit (0.01–0.02 mg/m<sup>3</sup>) to 0.08 mg/m<sup>3</sup>.</li> </ul>

Source	Year	Additional information
OECD	✓ 2001	<ul style="list-style-type: none"> <li>Same rat inhalation study as cited in DFG (2013), which was used for MAK derivation: <ul style="list-style-type: none"> <li>NOAEC of 509 mg/m<sup>3</sup> for systemic and neurotoxic effects</li> <li>LOAEC of 1.18 mg/m<sup>3</sup> for local upper respiratory effects.</li> </ul> </li> </ul>
US NIOSH	✓ 1994	<ul style="list-style-type: none"> <li>IDLH based on acute inhalation toxicity data in animals. Due to its low volatility, the IDLH concentration can only be reached at elevated temperatures or if the liquid is misted.</li> </ul>

## Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?

No

The chemical is not a non-threshold based genotoxic carcinogen.

## Notations

Source	Notations
SWA	—
HCIS	—
NICNAS	—
EU Annex	—
ECHA	NA
ACGIH	—
DFG	Carcinogenicity – 3B
SCOEL	—
HCOTN	NA
IARC	NA
US NIOSH	NA

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

## Skin notation assessment

Calculation
Adverse effects in human case study: no
Dermal LD <sub>50</sub> ≤ 1000 mg/kg: no
Dermal repeat-dose NOAEL ≤ 200 mg/kg:
Dermal LD <sub>50</sub> /Inhalation LD <sub>50</sub> < 10:
<i>In vivo</i> dermal absorption rate > 10%:
Estimated dermal exposure at WES > 10%:
<b>a skin notation is not warranted</b>

## IDLH

Is there a suitable IDLH value available?

Yes

## Additional information

Molecular weight:	278.34
Conversion factors at 25°C and 101.3 kPa:	1 ppm = Number mg/m <sup>3</sup> ; 1 mg/m <sup>3</sup> = Number ppm
This chemical is used as a pesticide:	<input checked="" type="checkbox"/>
This chemical is a biological product:	<input type="checkbox"/>
This chemical is a by-product of a process:	<input type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input type="checkbox"/> ACGIH <input type="checkbox"/> DFG <input checked="" type="checkbox"/> SCOEL

## Workplace exposure standard history

Year	Standard
<a href="#">Click here to enter year</a>	

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7<sup>th</sup> Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the *TLVs® and BEIs® Guidelines section* on the ACGIH website.

Australian Pesticides and Veterinary Medicines Authority (APVMA) (2014) list of registered products, approval no. 39575/0614

Deutsche Forschungsgemeinschaft (DFG) (2015) Di-n-butyl phthalate – MAK value documentation.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2016) Recommendation from the Scientific Committee on Occupational Exposure Limits for Di-n-butyl phthalate. SCOEL/REC/143.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016) C4-6 side chain transitional phthalates: Human health tier II assessment – IMAP report.

National Toxicology Program (NTP) (2000) NTP-CERHR Expert Panel Report on Di-n-Butyl Phthalate. NTP-CERHR-DBP-00.

Organisation for Economic Cooperation and Development (OECD) (2001) SIDS initial assessment profile – Dibutylphthalate.

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – dibutyl phthalate.