

## TRIBUTYL PHOSPHATE

**CAS number:** 126-73-8

**Synonyms:** Phosphoric acid tributyl ester, TBP, tri-n-butyl phosphate

**Chemical formula:**  $C_{12}H_{27}O_4P$

### Workplace exposure standard (retained)

**TWA:** 0.2 ppm (2.2 mg/m<sup>3</sup>)

**STEL:** —

**Peak limitation:** —

**Notations:** Carc. 2

**IDLH:** 30 ppm

**Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques.

### Recommendation and basis for workplace exposure standard

A TWA of 0.2 ppm (2.2 mg/m<sup>3</sup>) is recommended to protect for irritation of the bladder, skin and mucous membranes in exposed workers.

### Discussion and conclusions

Tributyl phosphate is used as a flame retardant and solvent in mineralogical applications.

Critical effects of exposure are irritation of bladder, skin and mucous membranes.

Human exposure data are limited and no quantitative data on local irritation are available (ACGIH, 2018; DFG, 2012). Low systemic availability following dermal absorption is reported but no information on subsequent toxicity is available (DFG, 2002; HCOTN, 2005). Reversible bladder epithelial hyperplasia is reported at a LOAEL of 42 mg/kg/day with a corresponding NOAEL of 12 mg/kg/day in sub-chronically fed rats (ACGIH, 2018). These data are consistent with endpoints reported in a chronic feeding study with rats, in which a LOAEL of 33 and 42 mg/kg/day and NOAEL of 9 and 12 mg/kg/day are reported for males and females, respectively (ACGIH, 2018). However, it is inconsistent with a LOAEL of 15 mg/kg/day for low incidence of microscopic bladder epithelial hyperplasia reported in a multigenerational feeding study (HCOTN, 2005). Carcinogenicity is demonstrated in chronic feeding studies at relatively high concentrations and associated with chronic inflammation or irritation of the target organs rather than a genotoxic mechanism of action (ACGIH, 2018; HCOTN, 2005). The absence of mutagenic potential is further supported by negative results in the available genotoxicity database (ACGIH, 2018). Chronic exposure *via* the diet causes significant increases in hepatocellular adenomas above 24 mg/kg/day in mice (ACGIH, 2018; DFG, 2012; HCOTN, 2005).

The available data indicate that bladder epithelial irritation and hyperplasia are the critical endpoint in animals and that the observed carcinogenicity is likely caused by chronic irritation of the target

organs. However, variability in the chronic LOAEL between 15 and 42 mg/m<sup>3</sup> for this effect complicates selection of an appropriate point of departure (POD) to derive a TWA. Based on the NOAEL of 9 mg/kg/day, ACGIH (2018) and DFG (2012) estimate an inhalational equivalent dose of 63 mg/m<sup>3</sup> to derive respective TWA equivalents of 5 and 11 mg/m<sup>3</sup>. However, both these primary agencies do not consider the chronic LOAEL of 15 mg/kg/day for microscopic bladder hyperplasia from another study. Based on this LOAEL, HCOTN (2005) derives a HBROEL of 2 mg/m<sup>3</sup>. In view of this uncertainty, the TWA of 0.2 ppm (2.2 mg/m<sup>3</sup>) is retained and expected to be protective of bladder irritation and carcinogenicity, which is supported by the health-based recommendation presented by HCOTN (2005). This value is also expected to be protective of local irritation based on analogy to other organic acids (DFG, 2012).

## **Recommendation for notations**

Classified as a category 2 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: 0.2 ppm (2.2 mg/m<sup>3</sup>)</b>
<b>ACGIH</b>	<b>2013</b>	<b>TLV-TWA: 0.5 ppm (5 mg/m<sup>3</sup>) (Inhalable fraction and vapor)</b>
<p>TLV-TWA intended to protect for bladder irritation and irritant effects on skin, eyes, and URT. Value should be measured as both particulate and vapour phases to account for evaporative losses during sampling.</p> <p>Non-mutagenic carcinogenicity demonstrated in chronically fed mice; unknown relevance to humans (A3).</p> <p>Summary of information:</p> <p>TLV-TWA is based on animal data in the absence of sufficient quantitative human exposure data. NOAEL for irritation and hyperplasia of the bladder epithelium are 9 and 12 mg/kg/d in male and female rats, respectively. Inhalational equivalents of these NOAEL estimated at 63 and 84 mg/m<sup>3</sup>, respectively, assuming a respiratory volume of 10 m<sup>3</sup> during an 8 h shift in a 70 kg worker. Absorbed dose at the TLV-TWA is approximately 0.7 mg/kg/d and therefore expected to be protective.</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>• Irritation with erythema and oedema when applied to skin (no further details provided)</li> <li>• Average dermal flux of 0.1 µg/cm<sup>2</sup>/min in 3 volunteers, flux of 2.6–3.3 µg/cm<sup>2</sup>/min when calculated from physicochemical properties</li> <li>• Non-sensitising in patch test with 15 applications of 25% solution (n=53)</li> <li>• Positive patch test in 1 patient with furniture-related dermatitis (n=42).</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>• Dermal LD<sub>50</sub> of &gt;3,100 mg/kg (rabbits); 9,700–19,400 mg/kg (guinea pigs)</li> <li>• LC<sub>50</sub> of &gt;4,200 mg/m<sup>3</sup> (rats, 4 h); highly variable, skin and respiratory irritation observed</li> <li>• NOAEL: 90 mg/kg/d (males) and 120 mg/kg/d (females) for increased liver weight and hepatocellular hypertrophy and bladder epithelial hyperplasia in sub-chronic feeding study (mice, 90 d):             <ul style="list-style-type: none"> <li>○ LOAEL of 360 (males) and 480 mg/kg/d (females)</li> </ul> </li> <li>• NOAEL of 12 mg/kg/d for reversible hyperplasia of bladder epithelium in sub-chronic feeding study (rats, 10 wk):             <ul style="list-style-type: none"> <li>○ LOAEL of 42 mg/kg/d, AHCIGI considers reversible nature of effects as evidence for non-genotoxic mechanism of carcinogenicity</li> </ul> </li> <li>• NOAEL of 24 mg/kg/d (females) and 29 mg/kg/d (males) for increased incidence of hepatocellular adenomas in chronic feeding study (mice, 18 mo):             <ul style="list-style-type: none"> <li>○ LOAEL of 169 mg/kg/d (females) and 206 mg/kg/d (males), no neoplastic or pre-neoplastic lesions observed in bladder</li> </ul> </li> <li>• NOAEL of 9 (males) and 12 mg/kg/d (females) for epithelial hyperplasia in bladder in chronic feeding study (rats, 2 yr):             <ul style="list-style-type: none"> <li>○ LOAEL of 33 mg/kg/d (males) and 42 mg/kg/d (females), significant increase of bladder papillomas at 143 mg/kg/d (males) and 182 mg/kg/d (females)</li> </ul> </li> </ul>		

Source	Year set	Standard
		<ul style="list-style-type: none"> <li>○ significant increase in transitional cell carcinomas also observed in males at 143 mg/kg/d</li> <li>• Based on results of sub-chronic and chronic feeding studies with mice and rats, agency concludes that carcinogenic mechanism of action is related to chronic irritation/inflammation of bladder epithelium caused by formation of calculi: <ul style="list-style-type: none"> <li>○ effect considered high-dose phenomenon only</li> </ul> </li> <li>• No evidence for mutagenicity in several <i>in vitro</i> with bacteria and mammalian cells: <ul style="list-style-type: none"> <li>○ no evidence for increased micronuclei <i>in vivo</i> with rats at up to 1,200 mg/kg</li> <li>○ no increase in sex-linked recessive lethal mutations in <i>Drosophila melanogaster</i></li> </ul> </li> <li>• Agency concludes that substance is non-mutagenic <i>in vitro</i> and <i>in vivo</i>.</li> </ul> <p>Insufficient data to recommend a TLV-STEL or notations for skin absorption or sensitisation.</p>

Source	Year set	Standard
<b>DFG</b>	<b>2000</b>	<b>MAK: 1 ppm (11 mg/m<sup>3</sup>)</b>
<p>Summary of additional information.</p> <p>In the absence of quantitative human exposure data, MAK based on NOAEL of 9 and 24 mg/kg/d for epithelial hyperplasia of bladder in rats and hepatocellular adenomas in mice, respectively (also cited by ACGIH, 2018). Allometric scaling factors of 4 (rats) and 7 (mice) are applied separately to inhalational equivalents and a factor of 7/5 is applied to account for continuous exposure to calculate NOAEC of 22 and 34 mg/m<sup>3</sup> in humans. The lowest of these is halved to account for increased exertion in the workplace to derive a MAK of 11 mg/m<sup>3</sup>.</p> <p>MAK expected to be protective of local irritation by analogy to MAK of other strong organic acids, e.g. formic acid and acetic acid.</p> <p>Mechanism of carcinogenicity not considered to be genotoxic based on liver cell hypertrophy and eosinophilic responses in chronic feeding studies, which suggest chronic inflammation/irritation is source of carcinogenicity (category 4).</p> <p>Skin notation recommended due to evidence for systemic availability following dermal absorption; low acute dermal toxicity noted.</p> <p>Sensitiser notation not recommended based on negative results in limited human and animal studies.</p> <p>Human data:</p> <ul style="list-style-type: none"> <li>Weak ChE inhibition (5–7%) <i>in vitro</i> in human RBC (no further details)</li> <li>Nausea and headaches in workers exposed at 15 mg/m<sup>3</sup> (documented only as personal communication without further data, agency considers this information of limited utility).</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>LC<sub>50</sub> of 380 ppm (rats, 4 h): <ul style="list-style-type: none"> <li>reduced motility, red tears, laboured breathing at 73 ppm,</li> <li>loss of myotactic reflexes at 194 ppm</li> </ul> </li> <li>Irritative effects on respiratory tract at 350 and 3,800 ppm (rats, 6 h): <ul style="list-style-type: none"> <li>no effect at 18.6 ppm</li> </ul> </li> <li>No effect on brain or plasma ChE activity</li> <li>No evidence for neurotoxic effects at 100, 325, or 1,000 mg/kg in single dose gavage study (rats)</li> <li>Negative dermal sensitisation with 10% solution in mineral oil (guinea pigs, n=20)</li> <li>Positive dermal sensitisation in standardised test (not specified) in 6 of 14 guinea pigs (no further details).</li> </ul>		
<b>SCOEL</b>	<b>NA</b>	<b>NA</b>
No report.		
<b>OARS/AIHA</b>	<b>NA</b>	<b>NA</b>
No report.		
<b>HCOTN</b>	<b>2005</b>	<b>TWA: 5 mg/m<sup>3</sup></b>
<p>Summary of additional information:</p> <p>Existing administrative OEL considered too high; HBROEL derived from results of sub-chronic and chronic feeding studies in mice and rats (also reported in ACGIH, 2018 and DFG 2002), indicating bladder hyperplasia is the critical effect. Maternal LOAEL of 15 mg/kg/d for epithelial bladder hyperplasia from a 2-generation reproductive feeding study in rats used as POD. Value adjusted</p>		

Source	Year set	Standard
<p>with factor of 7/5 for continuous experimental exposure and oral absorption of 82% to calculate a NOAEL of 17 mg/kg/d. UF of 4 and 18 are applied to account for allometric scaling and inter- and intraspecies differences, respectively to extrapolate the proposed HBROEL of 0.18 ppm (2 mg/m<sup>3</sup>).</p> <p>Dermal fluxes from <i>in vivo</i> human and animal studies, and physicochemical calculations range between 0.1–0.35 µg/cm<sup>2</sup>/h (also reported in ACGIH, 2018 and DFG, 2002). A skin notation is proposed based on estimated dermal uptake being more than 10% of an effective dose from exposure at the HBROEL.</p> <p>Animal data:</p> <ul style="list-style-type: none"> <li>• LOAEL of 15 mg/kg/d for increased incidence of microscopic bladder epithelial hyperplasia reported in 2-generation reproductive feeding study with dose groups 0, 15, 53, and 225 mg/kg/d, pups received diets containing substance after weaning (rats, F<sub>0</sub>: 13 wk, F<sub>1</sub>: 11 wk): <ul style="list-style-type: none"> <li>○ NOAEL for reproduction &gt;225 mg/kg/d</li> <li>○ NOAEL of 53 mg/kg/d for post-natal toxicity based on reduced pup body weight in F2 litters.</li> </ul> </li> </ul>		

## Secondary source reports relied upon

Source	Year	Additional information
NICNAS	✓ 2019	<ul style="list-style-type: none"> <li>• Not considered genotoxic based on negative results of several <i>in vivo</i> and <i>in vitro</i> genotoxicity studies</li> <li>• Bladder tumours may be caused by direct cell damage leading to hyperplasia of the bladder epithelium based on available chronic carcinogenicity studies and negative genotoxicity studies: <ul style="list-style-type: none"> <li>○ carcinogenicity category 2 classification therefore appropriate</li> </ul> </li> <li>• Other serious health effects not expected in humans.</li> </ul>
ECHA	✓ 2020	<ul style="list-style-type: none"> <li>• NOAEL of 9 mg/kg/d for epithelial hyperplasia in bladder in chronically fed rats used as POD to calculate DNEL: <ul style="list-style-type: none"> <li>○ overall assessment factor of 20 applied to account for allometric scaling and intraspecies differences to arrive at DNEL of 3.13 mg/m<sup>3</sup>.</li> </ul> </li> </ul>
OECD	✓ 2001	<ul style="list-style-type: none"> <li>• Primary exposure path in occupational setting is dermal contact</li> <li>• Most likely effects of exposure are irritation of the skin and eyes.</li> </ul>
US NIOSH	✓ 1994	<ul style="list-style-type: none"> <li>• IDLH based on acute inhalation toxicity data in animals.</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	Carcinogenicity – category 2
NICNAS	—
EU Annex	Carcinogenicity – category 2
ECHA	Carcinogenicity – category 2
ACGIH	Carcinogenicity – A3
DFG	Carcinogenicity – 4, H (skin)
SCOEL	NA
HCOTN	—
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:		
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%:	no	
<b>a skin notation is not warranted</b>		

## IDLH

Is there a suitable IDLH value available? Yes

## Additional information

Molecular weight:	266.31
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 10.89 mg/m <sup>3</sup> ; 1 mg/m <sup>3</sup> = 0.092 ppm
This chemical is used as a pesticide:	<input type="checkbox"/>
This chemical is a biological product:	<input type="checkbox"/>
This chemical is a by-product of a process:	<input type="checkbox"/>

Molecular weight:	266.31
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 10.89 mg/m <sup>3</sup> ; 1 mg/m <sup>3</sup> = 0.092 ppm
This chemical is used as a pesticide:	<input type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input checked="" type="checkbox"/> ACGIH <input type="checkbox"/> DFG <input type="checkbox"/> SCOEL

## Workplace exposure standard history

Year	Standard
Click here to enter year	

## 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.

Deutsche Forschungsgemeinschaft (DFG) (2012) Tri-n-butylphosphat – MAK value documentation, German language edition.

Deutsche Forschungsgemeinschaft (DFG) (2002) Tributyl phosphate – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2005) Tributyl phosphate. Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/158.

European Chemicals Agency (ECHA) (2020) Tributyl phosphate – REACH assessment.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2019) Phosphoric acid, tributyl ester: Human health tier II assessment – IMAP report.

Tenth Adaptation to Technical Progress Commission Regulation (EU) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

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

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