Tributyl phosphate

(CAS No: 126-73-8)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of tributyl phosphate by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

The evaluation of the toxicity of tributyl phosphate has been based on the reviews by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG99), the Advisory Committee on Existing Chemicals of Environmental Relevance of the Society of German Chemists (BUA95), the German Commission for the Investigation of Health Hazards of Chemical compounds in the Work Area (Gre02), and the World Health Organization/ International Programme on Chemical Safety (WHO/IPCS) (WHO91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. However, many data presented in the afore-mentioned reviews were from unpublished studies that were not available to the committee. In addition, in June 1999, literature was searched in the databases Medline, Toxline, and Chemical Abstracts, starting from 1966, 1981, and 1937, respectively, and using the following key words: tributyl phosphate; phosphoric acid, tributyl ester; and 126-73-8. The final literature search was carried out in Toxline and Medline in October 2004.

In December 2004, the President of the Health Council released a draft of he document for public review. No comments were received.

2 Identity

name	: tributyl phosphate
synonyms	: tri-*n*-butyl phosphate; phosphoric acid, tri-*n*-butyl ester
molecular formula	: $C_{12}H_{27}O_4P$
structural formula	: $O=P(O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_3)_3$
CAS number	: 126-73-8

3 Physical and chemical properties

molecular weight	: 266.3
melting point	: <-80°C
boiling point	: 289°C (decomposes)
flash point	: 146°C (open cup)
vapour pressure	: at 20°C: 0.8 Pa
solubility in water	: insoluble (at 20°C: 0.04 g/100 mL)
log $P_{octanol/water}$	: 4.00 (experimental); 3.82 (estimated)
conversion factors	: at 20°C and 101.3 kPa: 1 mg/m^3 = 0.09 ppm 1 ppm = 11.1 mg/m^3

Data from ACG99, BUA95, Gre02, NLM03, WHO91, http://www.syrres.com/esc/est_kowdemo.htm.

Tributyl phosphate is a non-flammable, non-explosive, colourless, viscous, practically odourless liquid. Its vapour mixes well with air. It is thermally unstable and begins to decompose at temperatures below its boiling point, forming butene and phosphoric acid. Upon combustion, corrosive and toxic phosphor oxide fumes are formed. With an excess of oxygen, complete combustion to carbon dioxide and water occurs at about 700°C. The compound is thought to hydrolyse rapidly in acidic, neutral, or alkaline solution, forming phosphoric acid and butanol. It behaves as a weak alkylating agent and reacts vigorously with oxidants (ACG99, Che98, WHO91).

4 Uses

Tributyl phosphate is used as a solvent for cellulose esters, lacquers and natural gums, as a herbicide, and as a defoaming agent for concrete and oil well drilling. It is used as a plasticiser in the manufacture of plastics and vinyl resins, in the manufacture of brushable paper pulp, printing inks, and emulsion paints, and as an extractant in the dissolution process in nuclear fuel processing. Its major use is as a base stock in the formulation of fire-resistant aircraft hydraulic fluids (ACG99, Arn97, Aul98a, Aul98b, BUA95, WHO91).

5 Biotransformation and kinetics

In vitro studies

In a human skin model, the maximum steady state rate of penetration for tributyl phosphate through isolated stratum corneum conjunctum was 0.18 µg/cm^2/min

(95% confidence interval: 0.05 - 0.31 µg/cm^2/min) (Mar65). Based on its physical chemical properties, the dermal fluxes of tributyl phosphate through human skin were - converted - 2.6 (Guy93) or 3.3 µg/cm^2/min (Fis90).

The rate of metabolism of tributyl phosphate and the nature of the metabolites produced were determined in *in vitro* tests with rat liver microsomes. Tributyl phosphate was rapidly metabolised in the presence of added NADPH, but only slight breakdown was observed in the absence of NADPH. Dibutyl(3-hydroxybutyl) phosphate was obtained as a first metabolite, while extended incubation yielded 2 further metabolites: butyl di(3-hydroxybutyl) phosphate and dibutyl phosphate (Sas84).

Human studies

In 3 human subjects, the average maximum steady state rate of penetration of tributyl phosphate was 0.10 µg/cm^2/min. No further details were given (Mar65).

Animal studies

The committee did not find information on the absorption of tributyl phosphate following inhalation. The dermal penetration rate of tributyl phosphate *in vivo* in pigs was 0.35 µg/cm^2/min (Tre61).

After administration of oral doses of tributyl phosphate of 156 mg/kg bw, the parent compound was detected in the gastrointestinal tract, the blood, and the liver within 30 to 60 minutes. Following a single dose, the highest amount was found in the gastrointestinal tract (not quantified), and 5.7% of the dose was detected in the other tissues (no further information given). No tributyl phosphate was detectable in the tissues anymore after 3 days. During repeated administration for 7 days, no accumulation of tributyl phosphate occurred (Kha86).

When rats were given [^{14}C]-labelled tributyl phosphate as a single oral dose of 14 mg/kg bw, 50, 10, and 6% of the radioactivity were excreted in urine, exhaled air, and faeces, respectively, within 24 hours. The total elimination after 5 days was 82%. After a single intraperitoneal dose of [^{14}C]-labelled tributyl phosphate of 14 mg/kg bw, 70, 7, and 4% of the radioactivity were excreted in urine, exhaled air, and faeces, respectively, after 24 hours; the total elimination after 5 days was 90%. The metabolism of tributyl phosphate was studied in rats following single intraperitoneal doses of [^{14}C]-labelled tributyl phosphate of 50 or 250 mg/kg bw. In urine collected during 3 days after application, 11 phosphorus-containing metabolites were identified, which were excreted in total

amounts of 12.8 or 28.8% of the applied doses, respectively. The major metabolites were dibutyl phosphate, monobutyl phosphate, and butyl 3-carboxypropyl 3-hydroxybutyl phosphate, which were excreted in amounts of 5.1-17.8, 3.8-3.9, and 1.5-3.1% of the applied doses, respectively (Suz84a). In addition, several S-containing metabolites were identified, such as (3-oxobutyl)- and (3-hydroxybutyl) mercapturic acids, which were excreted in amounts of 8.9% and 5.2% of the dose of 250 mg/kg bw, respectively (Suz84b).

In an unpublished study, rats given [^{14}C]-labelled tributyl phosphate as single or repeated oral doses of 10 and 350 mg/kg bw or as single intravenous injections of 5 mg/kg bw excreted approximately 65 - 85% of the dose in the urine within 48 hours. Major metabolites were dibutyl phosphate, monobutyl phosphate, butyl 2-hydroxybutyl phosphate, and 3-carboxypropyl dimethyl phosphate (BUA95).

6 Effects and mechanism of action

Human data

In an occlusive skin irritation test, tributyl phosphate was irritating when tested as a 75% solution in lanoline for 3 hours. When applied as a 50% and 25% solution in lanoline for 24 hours, mild irritation and no irritation were reported, respectively (BUA95). Tributyl phosphate has shown to be irritating to the skin, the eyes, the mucous membranes, and the respiratory tract (WHO91).

Patches with a solution containing less than 25% tributyl phosphate were applied 15 times on alternate days on the skin of 53 volunteers. No reactions were observed 24 hours after the final patch, therefore there is no evidence of sensitisation (Mon80). Workers exposed to air concentrations 15 mg/m^3 of tributyl phosphate have complained of nausea and headache (ACG99).

In order to investigate the association between exposure to tributyl phosphate and monocyte non-specific esterase (MNSE) staining activity, the mean monocyte count (number of monocytes per 100 leucocytes) was measured in a group of 12 plant workers (10 males, 2 females), potentially exposed to tributyl phosphate for 7 to 30 hours during a workweek (no further details given). Blood samples were drawn at the end of a workweek and analysed by 4 different methods, 2 enzymatic and 2 morphological. No statistically significant difference in monocyte count or non-specific esterase staining was found between the tributyl phosphate group and the plant controls, or general population controls, with any of the 4 methods used, indicating that tributyl phosphate does not inhibit non-specific monocyte esterase in humans (Man89).

Animal data

Irritation and sensitisation

In rats, exposure to a concentration of tributyl phosphate of 1500 mg/m^3 for 6 hours caused severe skin and respiratory irritation (BUA95).

A single dermal application of 500 mg tributyl phosphate to the intact or abraded skin of 6 rabbits produced severe irritation, including erythema and oedema in all animals (FMC85). When tested according to OECD guidelines, tributyl phosphate was slightly irritating to the skin of rabbits (4-hour exposure) (Bay86a). Application of a single dose of tributyl phosphate of 200 mg/kg to the skin of rats, rabbits, and guinea pigs (4 hour exposure) for 2 weeks, elicited severe inflammations in all animals (Kal70). In an open epicutaneous sensitisation test, tributyl phosphate was applied to the skin of guinea pigs once weekly for 3 weeks. After a 14-day rest period, followed by dermal challenge, no sensitisation was observed (FMC90). However, in another study, 6 out of 15 guinea pigs were sensitised. No further details were given (Eas86).

The instillation of 100 mg in the conjunctival sac of rabbits gave rise to mild irritation, which was noted 1, 2, 3, and 7 days following application (FMC85). When tested according to OECD guidelines, tributyl phosphate was slightly irritating to the eyes of rabbits (Bay86a).

Acute toxicity

The results of acute lethal toxicity tests are summarised in Table 1.

Table 1 Summary of acute toxicity studies for tributyl phosphate in experimental animals.

exposure route	species (sex)	LC_{50}/LD_{50} (duration)	reference
inhalation	rat	>4242 mg/m^3 (4 hours)	Bay90
	rat	28,000 mg/m^3 (1 hours)	FDRL76
	rat	>42,000 mg/m^3 (6 hours)	Eas86
dermal	rabbit	>3100 mg/kg bw	Joh77
	rabbit	>10,000 mg/kg bw	BUA95
	guinea pig	9700-19,400 mg/kg bw	Eas86
oral	rat	1400 mg/kg bw	Joh77
	rat (male)	1390 mg/kg bw	Mit80
	rat (female)	1530 mg/kg bw	Mit80
	rat	1552 mg/kg bw	Bay86b
	rat	1600-3200 mg/kg bw	Eas86
	rat	3000 mg/kg bw	Dav78
	rat	3350 mg/kg bw	Kal70

	rat	11,265 mg/kg bw	BUA95
	mouse	400-800 mg/kg bw	Eas86
	mouse (female)	900 mg/kg bw	Mit80
	mouse (male)	1240 mg/kg bw	Mit80
	mouse	1189 mg/kg bw	Kal71
intraperitoneal	rat	800-1600 mg/kg bw	Eas86
	rat	251 mg/kg bw	Kal71
	mouse	100-200 mg/kg bw	Eas86
	mouse	158 mg/kg bw	Kal71
	mouse	1000 mg/kg bw	Dav78
intravenous	rat	100 mg/kg bw	Van57

In summary, tributyl phosphate has a low acute toxicity in all species tested, except when the compound is administered intravenously. Clinical symptoms were mild anaesthesia, pronounced weakness, incoordination, and respiratory failure (Van57).

The possible neurotoxicity of tributyl phosphate was investigated in several studies. In rats, no symptoms were observed following the dermal application of tributyl phosphate. Laboured breathing and hypersalivation were observed after a single oral dose of 1030 mg/kg to rats; the animals recovered within 24 hours. Laboured breathing, pallor, and paralysis were seen after a single intraperitoneal or intramuscular injection of 515 mg/kg (Sab52). Rats (n=12/sex/group) were given single oral (gavage) doses of tributyl phosphate (purity:>99%) of 0, 100, 325 or 1000 mg/kg bw. Motor activity was measured before dosing, at approximately 11 hours after treatment, and on days 7 and 14. Functional observational battery (FOB) evaluations were conducted pre-exposure, at approximately 1, 6, and 24 hours, and days 7 and 14 post-dosing. At the high dose, one female died and a transient decrease in forelimb grip strength and in motor activity was found in both sexes. The 2 highest dose levels caused a transient decrease in body weight in males and a transient staining or discharge at the muzzle and/or nares in males and females. No treatment-related gross pathological findings were reported (Hea95).

Following acute lethal oral or intraperitoneal doses of tributyl phosphate, cholinesterase activities in brain, erythrocytes, serum, or liver were decreased by 35% (Kal71). When rats were treated with single intraperitoneal doses of tributyl phosphate of 16 to 266 mg/kg bw, 21% inhibition of plasma ChE activity was found. The activity of plasma β-glucuronidase was increased twice at 20 mg/kg bw and 50-fold at 266 mg/kg bw (Suz77).

In an acute neurotoxicity study, 20 adult hens were given 2 oral doses of tributyl phosphate (purity: 98%), equivalent to the LD_{50} (1863 mg/kg bw), 21 days apart. Hens were treated with atropine sulphate (15 mg/kg bw) 3 times daily for 5 days following dosing to protect against cholinergic effects. The animals were killed 21 days after the second dose. None of the hens exhibited treatment-related clinical signs, or peripheral nerve, spinal cord, or brain injury. The activity of brain neurotoxic esterase (NTE), or of brain acetyl cholinesterase (AChE) in the treated group was not statistically significantly different from the controls. The conclusion was that tributyl phosphate did not produce organophosporous compound-induced delayed neurotoxicity (OPIDN) (Car96). In another study, hens given an oral dose of 1840 mg/kg bw/day for 2 days did not develop behavioural changes or nerve damage (Joh77).

In an *in vitro* study, tributyl phosphate did not cause biologically significant changes in the activity of human red blood cell acetylcholinesterase (AChE) or human plasma cholinesterase (ChE) (Sab52). This was confirmed in a later study with brain AChE, liver ChE, or serum ChE of rats (Ois80).

A single intratracheal instillation of 5 µl of a 20% solution of tributyl phosphate in rats resulted in moderate injury of the lung parenchyma. The lactate dehydrogenase activity, the total protein content, and the total cell number in bronchoalveolar lavage fluid were increased mainly on day 1 after the treatment. The malondialdehyde content in lung tissue was elevated up to day 14 after the treatment, and the activities of superoxide dismutase and catalase were decreased up to day 7, and those of glutathione peroxidase and glutathione reductase on day 1 only. The authors concluded that inhibition of key antioxidant enzymes and the elevated lipid peroxidation are probably important mechanisms of the lung damage (Sal98).

Short-term toxicity

When groups of Wistar rats (group size not given) received tributyl phosphate at oral (gavage) doses of approximately 0, 140, or 200 mg/kg bw/day for 7 consecutive days, marked increases in the relative liver and kidney weights and in blood urea concentration and tubular degeneration was observed. No further data were given (Mit80).

In another study, Sprague-Dawley rats (n=10/sex/group) were given oral (gavage) doses of tributyl phosphate (purity: 98.4%) of approximately 0, 140, and 420 mg/kg bw/day for 14 days. No overt signs of toxicity were observed, and

there were no significant differences in body weight between the test groups and the control group. Absolute and relative liver weights were significantly increased in the high-dose group for both sexes. In the high-dose females, decreased haemoglobin levels and absolute and relative spleen weights were seen. Microscopic examination revealed an increased incidence of degenerative changes of the seminiferous tubules in 1 out of 4 high-dose males (Lah84).

In a 4-week toxicity study, Wistar rats (group size not given) that received oral (gavage) doses of tributyl phosphate (purity: not specified) of 0, 130, and 460 mg/kg bw/day showed 20% and 40% mortality. Marked depression of body weight gain and tubular damage were also observed (not further specified) (Mit80).

In a 10-week toxicity study, male Wistar rats (n=10-11/group) were given tributyl phosphate (purity: >97%) via the diet at doses equivalent to approximately 0, 375, or 750 mg/kg bw/day. The body weights and food consumption of the treated groups were significantly lower than those of the controls. In both treatment groups, increased relative brain, liver, and kidney weights and decreased absolute brain and kidney weights were found compared with the control group. Clinical chemistry analysis showed statistically significantly decreased serum glucose and increased urea concentrations at both dose levels, and increased total protein and cholesterol concentrations at the high dose. The activities of serum aminotransferase enzymes ALAT and ASAT and of alkaline phosphatase were significantly decreased at both dose levels. The activity of brain AChE was statistically significantly increased in both treatment groups, but no significant changes were observed in the activity of serum or liver ChE, compared with the control group. The blood coagulation time of the treated groups was significantly prolonged at both dose levels (Ois80).

In a more recent study, groups of male Sprague-Dawley rats were given tributyl phosphate (purity: 99.97%) via the diet at levels equivalent to approximately 0, 10, 35, or 150 mg/kg bw/day for 10 weeks. The control and the high-dose group contained 20 animals each and the other groups 10. During week 11 of the study, 10 rats in each group were euthanised. The remaining 10 animals in the control and the high-dose group were fed only control diets for 10 additional weeks to evaluate reversibility of possible effects on the bladder epithelium. In addition, 2 groups of 10 rats each received either ammonium chloride (12,300 mg/kg feed) without tributyl phosphate or ammonium chloride plus tributyl phosphate (150 mg/kg bw) to evaluate the effect of urinary acidification on possible effects on the bladder epithelium. At the high dose, slight decreases in osmolality (without ammonium chloride) and in creatinine excretion (with and without ammonium chloride) were found, probably resulting

from a dilution effect. In the other groups, no changes were observed. X-ray energy dispersive spectroscopy of the urine of tributyl phosphate-treated rats showed no increased or abnormal crystalluria, urinary precipitate, or calculi. Microscopic examination (light and scanning electron microscopy) revealed dose-related urothelial hyperplasia at the 2 highest doses, with simple bladder hyperplasia and diffuse papillary and nodular hyperplasia. The hyperplasia was a consequence of focal necrosis, which was sufficiently severe in some sites to result in ulceration with acute inflammation and haemorrhage. When co-administered with tributyl phosphate, dietary ammonium chloride did not totally inhibit the proliferative changes in the bladder epithelium, but the hyperplastic effects were milder. In the recovery group, the bladder epithelial changes were reversible, but the ulcer repair process was accompanied by submucosal fibrosis. The NOAEL was 10 mg/kg bw/day. Arnold et al. concluded that high doses of tributyl phosphate appear to produce urothelial cytotoxicity with marked regenerative hyperplasia that is reversible upon cessation of tributyl phosphate treatment. According to Arnold et al., the cytotoxicity is likely due to a direct effect of tributyl phosphate or its metabolites rather than an indirect consequence of abnormal crystalluria, urinary precipitate, or calculi (Arn97).

In a 3-month feeding study, Wistar rats (no numbers given) received tributyl phosphate (purity not specified) at doses equivalent to approximately 0, 37.5, 150, or 750 mg/kg bw/day. Effects were a dose-dependent decreased body weight gain, accompanied by increments of liver, kidney, and testis weights, and a decrease in uterus weight. In the high-dose group, an increased blood urea concentration was found. No further data were given (Mit80).

In another study, Sprague-Dawley rats (n=15/sex/group) were given tributyl phosphate via the diet at levels equivalent to approximately 0, 0.6, 3, 15, 75, or 375 mg/kg bw/day for 13 weeks. Effects in the high-dose group were a decrease in red blood cell count and increases in prothrombin time in males and in serum γ-glutamyl transpeptidase levels and in absolute and relative liver weights in both sexes. No changes in cholinesterase levels in tributyl phosphate-treated groups were found. Microscopic examination revealed treatment-related transitional cell hyperplasia in the urinary bladders of both sexes at the high dose, and of males also at 75 mg/kg bw/day. No changes in nerve tissues, bone marrow, or liver were seen (Cas85).

In an 18-week toxicity study, groups of 12 male and 12 female Sprague-Dawley rats received tributyl phosphate by gavage once a day (5 days/week) at doses of 0, 200, or 300 to 350 mg/kg bw/day. The high-dose animals were given 300 mg/kg bw/day during the first 6 weeks, followed by 350 mg/kg bw for the remaining 12 weeks, since no signs of toxicity other than a slight body weight

reduction were observed in the first 6 weeks. The high-dose males had decreased body weights, starting from the 3rd week of the study. Effects in the high-dose females were a significant decrease in red blood cell AChE activity and significant increases in relative kidney, absolute and relative liver, absolute spleen weights. The high-dose males had significant increased relative kidney weights only. Microscopic examination revealed that both low- and high-dose male and female rats developed diffuse epithelial hyperplasia and subepithelial capillary hyperplasia of the urinary bladder. Males also had focal nodular epithelial hyperplasia and slight mononuclear cell infiltration. No macroscopic or microscopic changes were observed in the urethra, kidney, and prostate of tributyl phosphate-treated animals (Lah85).

In a neurotoxicity study, Sprague-Dawley rats (n=10/sex/group) received tributyl phosphate by gavage at doses of 0, 270, or 400 mg/kg bw/day for 14 consecutive days. In the high-dose males, a statistically significant reduction of caudal nerve conduction velocity was observed accompanied by morphological changes in the sciatic nerve. Electron microscopic examination of sciatic nerve sections showed a retraction of Schwann cell processes in unmyelinated fibres that, according to Laham et al., may be interpreted as an early response to a tributyl phosphate-caused insult. No axonal degeneration was observed in these animals (Lah83).

In another study, Wistar rats (n=12/sex/group) were given tributyl phosphate (purity: >99%) at oral (gavage) doses of 0, 32.5, 100, or 325 mg/kg per day, 7 days/week, for 13 weeks. Effects were dose-related increased mortality, salivation, and muzzle staining in the high- and mid-dose groups, and reduced food intake and body weight loss in the high-dose group. Motor activity, evaluated pre-study, and on days 28, 62, and 90 prior to dosing, or FOB tests, performed pre-study, on day 1 at 1, 6, and 24 hours post-dosing, and on days 7, 14, 35, 63, and 91 prior to dosing, did not show differences between tributyl phosphate-treated groups and the control group. Macroscopic examination did not reveal abnormalities in nerve tissues related to tributyl phosphate exposure (Hea95).

CD-1 mice (n=5/sex/group) received tributyl phosphate (purity: not given) dietary doses equivalent to 15, 150, 750, or 3000 mg/kg bw/day for 4 weeks. After 10 days, the lowest dose was changed from 15 to 1500 mg/kg bw/day. All high-dose animals died or were sacrificed moribund. Clinical signs were reduced food consumption, hypothermia, dyspnoea, lethargy, and tremors. The 750- and 1500-mg/kg bw/day groups showed reduced body weights. In male mice of all dose groups and in females given 750 or 1500 mg/kg bw/day, increased absolute

and relative liver weights were found. High-dose males had decreased absolute kidney weights (Bio90).

Groups of ddY mice (no numbers given) were administered tributyl phosphate (purity: not given) at dietary dose levels equivalent to 0, 75, 300, or 1500 mg/kg bw/day for 3 months. In all dose groups, dose-dependent decreases in body weight gain, accompanied by increases in liver, kidney, and testes weights and decreases in uterus weight were seen. At the high dose, blood urea concentration was increased. No further data were given (Mit80).

In another 3-month feeding study, CD-1 mice (n=17/sex/group) were given tributyl phosphate (purity: 99.7%) at doses equivalent to 0, 75, 300, or 1200 mg/kg bw/day. At the high dose, there were body weight loss, reduced body weight gain with reduced food consumption, increased absolute and relative liver weights with hepatocyte hypertropy, slight to moderate epithelial hyperplasia of the urinary bladder, some slight haematological alterations, and some changes of clinical chemistry parameters of liver function. At the mid dose, a slight decrease in body weight gain, elevated serum aminotransferase activities (in females only), moderately increased liver weights in both sexes, slight hepatocyte hypertropy, and minimal or slight epithelial hyperplasia of the urinary bladder were found. The NOAEL was 75 mg/kg bw/day (Bio91).

The results of the above short-term studies are summarised in Table 2.

Long-term toxicity and carcinogenicity

In a 2-year toxicity/carcinogenicity study, groups of Sprague-Dawley rats (n=50/sex/group) were given tributyl phosphate (purity: 99.7%) at dietary doses equivalent to 0, 9, 33, or 143 mg/kg bw/day for males and 0, 12, 42, or 182 mg/kg bw/day for females. Tributyl phosphate-related clinical effects at the high dose were a decreased body weight gain in males and females and an increased incidence of red discolouration of the urine in males. At the mid dose, body weight gain was decreased in females only. Mortality and haematology and urinalysis parameters were not significantly different between tributyl phosphate-treated and control groups. No treatment-related changes in absolute or relative organ weights were reported. Macroscopic and microscopic examination revealed a dose-related increase in the incidence and severity of urinary bladder hyperplasia and in the incidence of urinary bladder papillomas in mid- and high-dose male and female rats (males: 2/49 and 23/49, respectively vs. none in controls; females: 1/49 and 11/49 vs. none). The incidence of urinary bladder papillomas was statistically significant for both males and females in the

high-dose group. In addition, animals in this group showed an increased incidence of transitional cell carcinomas, which was statistically significant for males only (incidences: males: 6/49, females: 2/50 vs. 0/50 in controls, both sexes). In one high-dose male rat, a squamous cell carcinoma was found. The carcinogenic effects showed a clear threshold at doses of 33 or 42 mg/kg bw/day for males or females, respectively. According to Auletta et al., the mechanism for urinary bladder tumour formation by tributyl phosphate in rats appears to be a non-genotoxic proliferative process. No other tumours were associated with tributyl phosphate administration in this study. The NOAEL for long-term toxicity was 9 or 12 mg/kg bw/day for males or females, respectively (Aul98a).

Table 2 Summary of short-term oral toxicity studies for tributyl phosphate.

species (strain)	dose levels (mg/kg bw/day)	exposure duration	critical effect	NOAEL (mg/kg bw/day)	reference
general toxicity					
rat (Wistar; males)	0, 140, 200 (gavage)	7 days	increased liver, kidney weight; renal injury	LOAEL: 140	Mit80
rat (Sprague-Dawley; n=10/sex/group)	0, 140, 420 (gavage)	14 days	increased liver weight; testicular injury	140	Lah84
rat (Wistar; males)	0, 130, 460 (gavage)	4 weeks	increased mortality; renal injury	LOAEL: 130	Mit80
rat (Wistar; n=10-11 males/group)	0, 375, 750 (feed)	10 weeks	decreased bw; increased relative brain, liver, kidney weight; increased urea concentration; prolonged blood coagulation time	LOAEL: 375	Ois80
rat (Sprague-Dawley; n=10-20 males/group)	0, 10, 35, 150 (feed)	10 weeks	urothelial hyperplasia	10	Arn97
rat (Wistar; males)	0, 37.5, 150, 750 (feed)	3 months	decreased bw; increased liver, kidney weight	LOAEL: 37.5	Mit80
rat (Sprague-Dawley; n=15/sex/group)	0, 0.6, 3, 15, 75, 375 (feed)	13 weeks	urothelial hyperplasia	15	Cas85
rat (Wistar; n=12 sex/group)	0, 32.5, 100, 325 (gavage)	13 weeks	salivation; muzzle staining	32	Hea95
rat (Sprague-Dawley; n=12/sex/group)	0, 200, 300/350 (feed)	18 weeks	urothelial hyperplasia	LOAEL: 200	Lah85
mouse (CD-1; n=5/sex/group)	0, 150, 750, 1500, 3000 (feed)	4 weeks	decreased bw; increased liver weight	150	Bio90
mouse (ddY)	0, 75, 300, 1500 (feed)	3 months	decreased bw; increased liver, kidney weight	LOAEL: 75	Mit80

mouse (CD-1; n=17/sex/group)	0, 75, 300, 1200 (feed)	3 months	decreased bw; increased liver weight; urithelial hyperplasia	75	Bio91
neurotoxicity					
rat Sprague-Dawley; n=10/sex/group)	0, 270, 400 (gavage)	14 days	decreased nerve conduction velocity	270	Lah83
rat (Wistar; n=12 sex/group)	0, 32.5, 100, 325 (gavage)	13 weeks	motor activity and functional observational battery tests	325	Hea95

In a toxicity/carcinogenicity feeding study with mice, CD-1 mice (n=50/sex/group) received tributyl phosphate (purity: 99.7%) at doses equivalent to 29, 169, or 585 mg/kg bw/day for males, and 24, 206, or 711 mg/kg bw/day for females for 18 months. Survival, clinical signs, and haematology parameters were unaffected by treatment at any dose level. Initial body weight losses and significant decreases in body weight gain occurred in males and females receiving the high dose. A significant dose-related increase in absolute and relative liver weights was seen in male and female mice receiving the 2 highest doses of tributyl phosphate. Following post-mortem macroscopic and microscopic examinations, the liver was the main target organ. Effects reported were an increased incidence in eosinophilic hepatocellular changes in high-dose animals, especially in males, and a statistically significant increase in the incidence of hepatocellular adenomas in high-dose males (10/50; vs. 3/50, 6/50, and 7/50 in controls, low dose, and mid dose, respectively; range historical control incidences: 2/59-10/60). Incidences of hepatocellular carcinomas were similar among treated and control groups. There were no tributyl phosphate-related lesions in the urinary bladder, or in any other organs or tissues. The NOAEL for long-term toxicity was 24 or 29 mg/kg bw/day for females or males, respectively (Aul98b).

Mutagenicity and genotoxicity

- *In vitro* tests
  Gene mutation assays. In various studies, tributyl phosphate did not induce reverse mutations in *S. typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, or TA1538, in the absence or presence of metabolic activation by a rat or hamster liver microsomal S9 fraction. More specifically, tributyl phosphate was tested in strains TA98, TA100, TA1535, TA1537, and TA1538 at concentrations up to 100 µL/plate using the plate incorporation technique

(Mic78). In other studies, using strains TA98, TA100, TA1535, and TA1537, dose levels were up to 500 µg/plate (Bay85), using strains TA98, TA100, TA1537, and TA1538, ranging from 97 to 97,000 µg/plate (FMC85), or, using strains TA97, TA98, TA100, TA1535, from 1 to 3333 µg/plate (Zei92). In the later study, incubations were with 10 and 30% rat and hamster liver S9 concentrations (Zei92). Tested in strain TA98 only, negative results were obtained with metabolic activation at 1 to 1000 µg/plate (Abe94). In a study using strains TA102 and TA2638, no increased mutation frequency was found at concentrations ranging from 31 to 1250 µg/plate without metabolic activation (Wat96). In one study, tributyl phosphate was reported to be mutagenic in *S. typhimurium* strains TA1535 and TA1538 at doses of 500 to 1000 µg/plate, but not at levels below 100 µg/plate (Gaf86). Tests on *E. coli* strains WP2/pKM101 and WP2*uvrA*/pKM101 without metabolic activation were also negative at dose levels in the range of 125 to 5000 µg/plate (Wat96).

Tributyl phosphate was not mutagenic when tested in the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) forward mutation assay in Chinese Hamster Ovary (CHO) cells, at concentrations of 0.05 to 0.11 µL/mL without metabolic activation and of 0.06 to 0.15 µL/mL with activation (Bat92).

Tributyl phosphate did not produce an increase in recessive lethal mutation tests using *D. melanogaster* (Han75).

Cytogenicity assays. Tributyl phosphate did not induce increases in chromosomal aberrations in CHO cells, at 0.01 to 0.15 µL/mL, with or without metabolic activation (Bat92).

- *In vivo* tests

  When male and female rats (no numbers given) were treated with a single oral dose of tributyl phosphate of 0, 300, 600, or 1200 mg/kg bw, no increase in the frequency of chromosomal aberrations in bone marrow cells harvested 12, 24, or 36 hours after administration (Bat92).

The committee concludes that tributyl phosphate is not mutagenic *in vitro* in bacterial and mammalian cell systems and in fruit flies, and does not induce chromosomal aberrations *in vitro* in CHO cells and *in vivo* rat bone marrow.

Reproduction toxicity

In a 2-generation reproduction study, groups of weanling Sprague-Dawley rats (n=30/sex/group) were administered tributyl phosphate in the diet at levels equivalent to 0, 15, 53, or 225 mg/kg bw/day for 10 weeks pre-mating. Each female F0 animal was mated with a single male from the same dose group for 3 weeks, with continuing exposure to dietary tributyl phosphate. Male rats were sacrificed after mating. Female rats were treated during gestation and lactation. After weaning of their litters, the F0 females and 10 F1 weanlings/sex/dose level were necropsied. F1 weanlings (n=30/sex/dose level) were given tributyl phosphate for 11 weeks and were bred as described above. F1 parents and 10 F2 weanlings/sex/dose level were then euthanised. Microscopic examination was carried out on reproductive organs, urinary bladders, kidneys (males) and livers (females) of parental animals. No microscopic examination was conducted on F1 and F2 weanlings. Parental toxicity was observed in both sexes and generations at the high and mid doses. At both doses, effects included reduced body weights, body weight gain, and food consumption, a high incidence of urinary bladder hyperplasia (both sexes), renal pelvis epithelial hyperplasia (males), and hepatic centrilobular hypertrophy (females). At the low dose, isolated and transient reductions in body weight were observed in F0 and F1 females, with a low incidence of urinary bladder epithelial hyperplasia in F0 males and females and in F1 males (1-2 out of 29-30 animals, compared to 0 out of 29-30 control animals). There was no evidence of reproductive toxicity or of effects on gestation or lactation at any dose tested. Post-natal toxicity was demonstrated by consistent reductions of F1 and F2 pup body weights at the top dose and by occasional weight reductions in F2 litters at the mid dose, and was associated with maternal toxicity observed at these doses and times. A statistically significant reduced pup body weight in F2 litters was found at the low dose on post-natal day 14, but not on any of the other days of examination. Microscopic examination of reproductive organs did not show tributyl phosphate-related abnormalities. According to Tyl et al., the LOAEL for parental toxicity was 15 mg/kg bw/day, the approximate NOAEL for postnatal toxicity was 53 mg/kg bw/day and the NOAEL for reproductive toxicity was at least 225 mg/kg bw/day (Tyl97). The committee concludes that the critical effect in this 2-generation study in rats is the hyperplasia of the urinary bladder.

In a developmental toxicity study, groups of pregnant Wistar rats (n=24/group) received tributyl phosphate (purity: 100%) in corn oil at doses of 0, 188, 375, or 750 mg/kg bw/day by gavage on gestational days 6 to 15. On gestational day 20,

the animals were euthanised. Maternal mortality was significantly increased in the high-dose group. Maternal body weights and body weight gains were significantly decreased in all treatment groups. No treatment-related effects were observed in liver weights, gravid uterine weights, number of corpora lutea, and number of uterine implantations in any of the groups. Significant reduced fetal body weights and delayed ossification were observed in the offspring of the high-dose group. There was no evidence of fetotoxicity or teratogenetic effects. The NOAEL for developmental effects was 375 mg/kg bw/day, while 188 mg/kg bw, the lowest dose tested, was the LOAEL for maternal toxicity (Sch91).

In another study, pregnant Wistar rats (n=20/group) were given tributyl phosphate at dose levels of 0, 62.5, 125, 250, or 500 mg/kg bw/day by gavage on gestational days 7 to 17. At the 2 highest doses, maternal body weight gains were significantly reduced, and at the high dose, significant increases in absolute liver weight and significant decreases in absolute spleen weight were seen. Reproductive effects seen included statistically significant increases in the number of pups with a rudimentary lumbar rib at the high dose. No treatment-related effects were observed on numbers of dams with living fetuses or total resorptions, number of corpora lutea, implants or living fetuses, the incidence of dead or resorbed fetuses, the sex ratio, or the body weight of living pups in any of the groups. No skeletal malformatons or visceral anomalies were seen. The maternal and developmental NOAELs were 125 and 250 mg/kg bw/day, respectively (Nod94).

In a developmental toxicity study with rabbits, pregnant New Zealand white rabbits were given tributyl phosphate (purity: 100%) in corn oil at doses of 0, 50, 150, or 400 mg/kg bw/day by gavage on gestational days 6 to 18. The animals were sacrificed on gestational day 30. A decrease in mean body weight and a not statistically significant increase in resorptions were observed at the high dose. No treatment-related effects were observed in liver weights, gravid uterine weights, number of corpora lutea, and number of uterine implantations in any of the groups. No further maternal or fetal abnormalities were recorded. The maternal and developmental NOAELs were 150 and 400 mg/kg bw/day, respectively (Sch91).

The committee concludes that there is no evidence of reproduction toxicity of TBP in rats and rabbits.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for tributyl phosphate in the Netherlands is 5 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for tributyl phosphate in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Workers can be exposed to tributyl phosphate through inhalation or by skin contact. No human or animal data are available on the absorption of the compound through the lungs. Dermal penetration rates were obtained *in vitro* from a human skin model, *in vivo* in human volunteers and in pigs, and by calculation from physico-chemical data; they ranged from 0.1-0.35 µg/cm^2/min for the experimental values to ca. 3 µg/cm^2/hour for the calculated values. The committee notes that the experimental data were produced in the 1960s and that for the human *in vivo* data, experimental details were completely absent. Although the relevance and quality of these penetration data remains unclear, they suggest a significant penetration ability. In rats, absorption following oral intake is 82%, based on the amount of radioactivity excreted in the urine, the faeces, and exhaled air within 5 days after administration. Following absorption, the compound is metabolised into at least 11 P-containing metabolites. The major metabolite excreted in the urine is dibutyl phosphate (17.8% of the applied dose), followed by monobutyl phosphate (3.9% of the dose). In addition, several S-containing metabolites, such as 3-hydroxybutylmercapturic acid, have been identified in the rat.

In humans, tributyl phosphate is irritating to the skin, the eyes, the mucous membranes, and the respiratory tract. No cases of occupational diseases following exposure to tributyl phosphate have been reported.

In experimental animals, tributyl phosphate is irritating to the skin and the eyes. Data on skin sensitisation are conflicting. Based on the results of acute lethal toxicity studies in test animals, the committee considers the compound as unlikely to present an acute health hazard following inhalation or skin contact, but harmful via the oral route. Single oral administration of tributyl phosphate did not induce acute neurotoxic effects in rats (maximum dose tested: 1000 mg/kg bw).

In short-term toxicity studies in rats and mice, the urinary bladder, the liver, and the kidney were the target organs. The critical effect in both species was an

increased incidence of hyperplasia of the urinary bladder. The NOAELs for this effect were 10 and 15 mg/kg bw/day in a 10- and 13-week study, respectively, in rats, and 75 mg/kg bw/day in a 3-month study in mice. The NOAEL for neurotoxicity was >325 mg/kg bw/day in a 13-week study.

In a long-term (2-year) toxicity and carcinogenicity study in rats, the bladder was the target organ showing increased incidences of urinary bladder hyperplasia and papillomas at doses of 33 (males) and 42 mg/kg bw (females) and higher. Transitional cell carcinomas of the urinary bladder were observed at 143 (males) or 182 mg/kg bw (females) only. The carcinogenic effects showed a clear threshold at 33-42 mg/kg bw. The NOAEL for long-term toxicity was 9 and 12 mg/kg bw/day for males and females, respectively. In mice, the target organ was the liver showing increased incidences of eosinophilic hepatocelluar changes and of (benign) hepatocellular adenomas in male mice at 585 mg/kg bw. The NOAEL for long-term toxicity was 24 and 29 mg/kg bw/day for female and male mice, respectively, based on increased absolute and relative liver weights at the next higher doses of 169 (males) or 206 mg/kg bw/day (females). .

Tributyl phosphate was not mutagenic *in vitro* in bacterial and mammalian cell systems and in fruit flies and did not induce chromosomal aberrations *in vitro* in CHO cells and *in vivo* in rat bone marrow.

The committee concludes that tributyl phosphate is a non-genotoxic carcinogen in rats and mice and that tumours were only observed at dose levels, associated with toxic, proliferative effects.

In a 2-generation reproduction study in rats, the NOAEL for reproductive toxicity was at least 225 mg/kg bw/day and for post-natal toxicity 53 mg/kg bw/day, the latter on the basis of reduced pup body weights in F2 litters. The LOAEL for parental toxicity was 15 mg/kg bw/day, based on microscopic evidence of a very low incidence of urinary bladder epithelial hyperplasia. In developmental toxicity studies, no developmental effects were observed at dose levels that did not cause maternal toxicity. The committee concluded that the NOAELs for maternal and developmental toxicity were 115 and 250 mg/kg bw/day in the rat and 150 and 400 mg/kg bw/day in the rabbit.

Based on the above data, the committee takes the 2-generation rat study, demonstrating a parental LOAEL of 15 mg/kg bw/day, as starting point in establishing a health-based recommended occupational exposure limit (HBROEL). Adjusting for the percentage of oral absorption in rats (i.e., 82%) and exposure time (i.e., 7 days/week vs. 5 days/week for workers) results in a no-adverse-effect level (NAEL) of 17 mg/kg bw. For the extrapolation to an HBROEL, a factor of 4 for allometric scaling from rats to humans, based on

caloric demand, and an overall factor of 18, covering the absence of a NOAEL and inter-and intraspecies variation, are applied, resulting in a NAEL for humans of 0.24 mg/kg bw/day. Assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day and a retention of 100%, and applying the preferred value approach, a HBROEL of 2 mg/m^3 is recommended for tributyl phosphate.

The committee recommends a health-based occupational exposure limit for tributyl phosphate of 2 mg/m^3 (0.18 ppm), as an 8-hour time-weighted average (TWA).

Assuming a skin notation should be added when exposure to hands and forearms (2000 cm^2) to liquid tributyl phosphate during 1 hour leads to an additional uptake of 10% or more of the uptake by inhalation at the HBROEL during an 8-hour working day, the following calculation can be made. Exposure of 2000 cm^2 of skin for 1 hour may lead to an uptake of 12 mg (2000 (cm^2) x 0.1 ($\mu g/cm^2$/min) x 60 (min)). Uptake by inhalation amounts to 20 mg, assuming a worker inhales 10 m^3 of air during an 8-hour working day and a retention of 100%.

Since the amount that may be absorbed through the skin absorption is more than 10% of the amount taken up by inhalation, the committee recommends a skin notation.

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Annex

Occupational exposure limits for tributyl phosphate in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	5	8 h	administrative		SZW05
Germany						
- AGS	-	2.5	8 h		S, [d]	TRG04
- DFG MAK-Kommission	1	11	8 h		S, [d], [e]	DFG05
	4	44	15 min[c]			
Great Britain						
- HSE	-	5[f]	8 h	OES		HSE02
	-	5[f]	15 min			
Sweden	-	-				Swe00
Denmark	0.2	2.5	8 h			Arb02
USA						
- ACGIH	0.2	-	8 h	TLV		ACG05
- OSHA	-	5	8 h	PEL		ACG04
- NIOSH	0.2	2.5	10 h	REL		ACG04
European Union						
- SCOEL	-	-				EC05

[a] S = skin notation; which means that skin absorption may contribute considerably to the body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

[d] Classified in pregnancy group C: i.e., there is no reason to fear a risk of damage to the embryo or fetus when MAK and BAT values are observed.

[e] Classified in carcinogenicity category 4: i.e., listed among substances with carcinogenic potential for which genotoxicity plays no or at most a minor part. No significant contribution to human cancer risk is supported provided the MAK value is observed. The classification is supported especially by evidence that increases in cellular proliferation or changes in cellular differentiation are important in the mode of action. To characterise the cancer risk, the manifold mechanisms contributing to carcinogenesis and their characteristic dose-time-response relationships are taken into consideration.

[f] For all tributyl phosphate isomers; however, the CAS number assigned to this entry is that for tri-*n*-butyl phosphate.