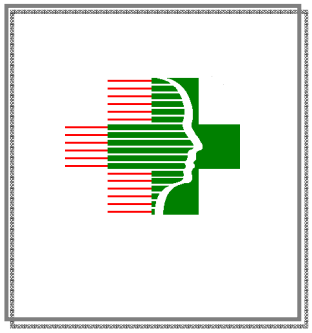


SUBSTANCE EVALUATION REPORT

Public Name: Tributyl phosphate

EC Number(s): 204-800-2

CAS Number(s): 126-73-8

Submitting Member State Competent Authority:

National Institute of Chemical Safety, Hungary

H-1097 Budapest, Nagyvárad tér 2.

tel: +361 476 1195

Year of evaluation (as given in the CoRAP): 2012

VERSION NUMBER: 1 **DATE: 15.01.2013**

Conclusions of the most recent evaluation step*	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	X
Concern clarified; Need for risk management measures; RMO analysis to be performed	
Other:	

Executive summary

Grounds for concern

Tributyl phosphate is produced in high volumes and has a wide, dispersive use (worker, professional, and consumer). However, there seem to be differences in the classification and labelling of the substance around the world, suggesting that the hazards relating to this substance are not appropriately justified. The following concerns have been identified:

Concern 1: Based upon several studies epithelial hyperplasia of the urinary bladder was evident and urinary bladder papillomas or carcinomas also appeared. As all the mutagenicity tests were negative, tributyl phosphate may be considered a non-genotoxic carcinogenic substance. However, in relation to the carcinogenicity, the re-assessment of potential genotoxic potential of tributyl phosphate might be useful.

Concern 2: The repeated dose studies suggest that the primary target organs of toxicity of tributyl phosphate are the liver and the urinary bladder. Absolute and relative liver weight elevation, hepatocyte hypertrophy, changes of clinical chemistry parameters and hepatocellular adenomas could be observed. Further to this, some studies suggest that tributyl phosphate might have adverse effects on kidney, spleen and testes as well.

Concern 3: Data available in the literature on the neurotoxic potential of tributyl phosphate seem to be contradictory. The studies submitted in the registration dossiers indicate no neurotoxic effects. However there are studies in which cholinesterase inhibition, cholinergic effects and other neurotoxic symptoms were described.

Concern 4: Tributyl phosphate might have teratogenic properties as long-term treatments resulted in decreased pup weights and delayed ossification coupled with underdeveloped, rudimentary ribs in rabbits.

Procedure

Tributyl phosphate has been selected for substance evaluation according to Article 44 of REACH Regulation for 2012, based upon the Justification Document prepared by the Hungarian REACH Competent Authority. The Justification Document identified the above listed initial concerns which

warranted a targeted substance evaluation of tributyl phosphate. The evaluating Member State was Hungary and the evaluation was executed by the Hungarian REACH Competent Authority.

In the course of the evaluation, the evaluating Member State concentrated on the above listed concerns and related end-points, and due to a precautionary approach, with additional focus on other possible target organs of toxicity as part of assessment of possible STOT properties and reproductive toxicity in relation to assessment of teratogenicity. While most of the end-points were evaluated separately, the findings were aligned in the course of the evaluation.

The core document used for the evaluation was the registration dossier, including the chemical safety report, but also other relevant scientific studies were assessed, as well as a robust study summary referenced in the registration dossier. In some cases the scientific papers cited in the registration dossier were outdated, have been published 3 decades ago. This was also a reason for searching additional, more recent scientific data.

The relevant studies used during the substance evaluation were mostly conducted in the 90's and after the year 2000 with the latest ones originating from 2009, but there is some literature from the 80's or earlier years as well.

This was the first time that tributyl phosphate was subject of substance evaluation. The targeted substance evaluation can be concluded with a report, based upon the following conclusions.

Conclusions

The targeted substance evaluation of tributyl phosphate carried out by the evaluating Member State, which based on existing and available information, led to the following conclusions.

Based upon the detailed evaluation of available information (aggregated registration dossier, Chemical Safety Report, other scientific evidence described in studies and literature), the evaluating Member State was in the position to clarify all the above listed concerns. It could be established that none of the above listed concerns are warranted. The available information is sufficient and reliable to conclude on these concerns, and there is no need of further studies or other information on these end-points. Further to this, no new concern was raised during the current substance evaluation.

Consequently, there is no need to take any additional risk management measures concerning the evaluated end-points, and the current CLP classification of the substance (followed by the registrant) is appropriate.

The observed changes in urinary bladder following repeated exposure to tributyl phosphate are considered as appropriately covered by the Carcinogenic category 2 classification. The STOT RE classification based on the effects of tributyl phosphate on urinary tract is not necessary if the substance is classified for carcinogenicity.

Concerning the various end points where concern was raised the registrant has also made sufficiently detailed investigations and came to similar conclusions on the hazard properties. These conclusions of the registrant can be supported by the evaluating Member State.

Statement of reasons

The concerns originally raised in the justification document and summarized above may be rejected due to the following reasons.

Concern 1: Carcinogenicity and genotoxicity

There were three available studies in rodents (mice and rats) which are considered reliable (Klimish reliability factor 1), but also sufficient to evaluate carcinogenicity. In two studies only pro-carcinogenic alterations (i.e. transitional cell carcinoma) were observed by the highest dose (3000 ppm) dietary intake in rats, in the urinary bladder of both sexes. Other alterations as bladder hyperplasia and papillomas in the urinary bladder were also found in female rats only at a lower concentration (700 ppm). Similar changes were not found in the same rat strain in an earlier reliable study. No suspicions referring to human carcinogenicity have ever been published. Since no similar effects have been found in mice, these effects might be species specific to rats.

Based on the available and reliable experimental data the concerns on possible more serious carcinogenic properties of tributyl phosphate can be rejected.

The genotoxic properties of the substance were also examined by the evaluating Member State and the reasoned opinion shows that no mutagenic activity of it can be demonstrated. All acceptable tests (bacterial mutagenicity, *in vitro* gene mutation, *in vivo* cytogenicity) gave negative results.

Concern 2: Specific Target Organ Toxicity – Urinary bladder, liver, kidney, spleen and testes

During the classification of specific target organ toxicity arising from a repeated exposure to a substance or mixture all significant health effects that can impair function, reversible and irreversible, immediate and/or delayed should be considered. Where possible secondary effects are observed in other organs, they should be carefully considered for the classification. The most appropriate data on repeated dose toxicity used in hazard characterization and risk assessment are primarily obtained from animal studies conforming to internationally agreed test guidelines. The evaluating Member State has examined the possible adverse effects of tributyl phosphate in urinary bladder, liver, kidney, spleen and testes; although in the toxicokinetic studies it was revealed that the major excretory route for the radio label of tributyl phosphate was the urine.

Based on the observed effects in the experiments described in relevant literature the following conclusions can be drawn.

Urinary bladder

In case of urinary bladder alterations observed in the short term repeated dose toxicological studies, namely different epithelial hyperplasias, postulate the non-genotoxic mode of action that can lead to neoplastic lesions observed in longer term toxicological studies. Numerous agents have been identified that produce superficial or deep cytotoxicity and regeneration, and are associated with increased incidences of bladder tumors in rodents. Similar toxic and regenerative processes appear to be involved with bladder carcinogenesis in humans related to chronic inflammation, such as schistosomiasis and calculi. Based on the findings it can be concluded that the effect observed in urinary bladder is due to a target organ toxicity of tributyl phosphate.

Liver

Animal studies have shown no significant accumulation of tributyl phosphate in the liver. Results from most of the repeated dose studies consistently showed increased liver weight of rats and mice, but it should be noted, that the dose was in all of these studies high. Some of these studies described elevated liver enzymes activity, a part of these enzymes are connected to the metabolism of the tributyl phosphate. The studies provide adequate basis for evaluating the repeated dose toxicity. The findings indicate that tributyl phosphate is not hepatotoxic.

Kidney, spleen and testes

As the main excretory route for the radio label of tributyl phosphate is the urine, the role of the excreted substance or metabolites in the development of kidney changes cannot be excluded.

However, the effective dose of kidney alterations in various relevant studies is well above the guidance value described in Guidance on the Application of the CLP Criteria.

Spleen alterations, namely the changes of the organ weight were observed in two studies at dose levels above the guidance values.

No effects on testes were observed either in the conclusive majority of longer term repeated dose studies or in 2-generation reproduction study. In addition no effect on male fertility was observed in the reproduction toxicity study.

Considering the evidences overviewed above, the concerns on the possible target organ toxicity for kidneys, spleen and testes are not warranted.

The purpose of STOT RE is to identify the primary target organ(s) of toxicity (CLP Annex I, 3.9.1.4) for inclusion in the hazard statement. As it is stated in the Guidance on application of CLP criteria, STOT RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class. The observed changes in urinary bladder following repeated exposure to tributyl phosphate can be considered as covered appropriately by the Carcinogenic category 2 classification.

Concern 3: Specific Target Organ Toxicity – Nervous system

The generally recommended strategy for neurotoxicity testing (Costa, 1998; OECD, 2004) was followed in the relevant studies. The observed symptoms were non-specific, consequently no further specific tests of motor and sensory functions were carried out. Therefore, only few publications exist about additional specific investigation of tributyl phosphate. Nevertheless, neurotoxicity of tributyl phosphate has been tested in all relevant fields: neurobehavioral, neuropathological, neurophysiological and neurochemical techniques were all applied to complete the knowledge about tributyl phosphate.

Based on the available scientific publications it can also be concluded that cholinesterase inhibition by tributyl phosphate is weak. Substantial cholinesterase inhibition in exposed animals was reported in one study only from rats that received a lethal dose of tributyl phosphate, however, this study was deemed unreliable in several available evaluations.

The conclusions of short-term and long-term, single dose and repeated dose toxicity studies were that nervous system is not target organ of tributyl phosphate. If neurotoxic effects were detected in

some studies they appeared only after exposure to very high doses, they were unspecific, transient, probably caused indirectly by other organ damages and/or general toxicity of tributyl phosphate.

Concern 4: Teratogenicity, reproductive toxicity

The teratogenicity studies for the developmental toxicity of tributyl phosphate were performed in two species (two strains of rats and one strain of rabbits). The studies involved range-finding experiments. Embryotoxic and foetotoxic effects, such as ossification disturbances (delayed ossification and rudimentary ribs) occurred only at maternally toxic doses. The studies were reliable and sufficient to conclude that teratogenic effect of tributyl phosphate could not be substantiated, therefore it can be stated that the hazard concern regarding teratogenicity of tributyl phosphate is not justified.

Further to the above, no specific adverse effects of tributyl phosphate on the reproduction were reported in the literature as yet. Any effects noted were sporadic and without any clear correlation with the treatment. Consequently, the available data do not suggest any specific, selective effects of tributyl phosphate on reproductive parameters or fertility. Reproductive organs were not identified as target organs of tributyl phosphate in the available studies.

CONTENTS

TABLES

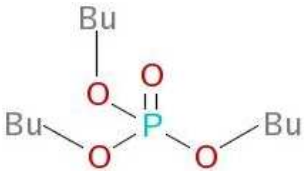
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1. Substance identity

Public Name:	tributyl phosphate
EC number:	204-800-2
EC name:	tributyl phosphate
CAS number (in the EC inventory):	126-73-8
CAS number:	126-73-8
CAS name:	tributyl phosphate
IUPAC name:	tributyl phosphate
Index number in Annex VI of the CLP Regulation	015-014-00-2
Molecular formula:	C12H27O4P
Molecular weight range:	266.3141
Synonyms:	Butyl phosphate, ((BuO)3PO) Phosphoric acid tributyl ester

Structural formula:



1.2 Composition of the substance

Name: tributyl phosphate

Details on the composition of the substance can be found in the Annex of the Report (confidential information)

1.3 Physico-chemical properties

Table 2. Overview of physicochemical properties

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	Colourless liquid	-
Melting/freezing point	<-80°C	-
Boiling point	289°C	Decomposes
Vapour pressure	0.003 mm Hg	at 25 °C
Surface tension	-	-
Water solubility	280 mg/L	at 25 °C
Partition coefficient n-octanol/water (log value)	4	log Kow/ log Pow
Flash point	146 deg C	Open cup
Flammability	Not Flammable	-
Explosive properties	Not Explosive	Contains no groups associated with explosive properties
Self ignition temperature	345 deg C	-
Oxidising properties	Not oxidizing	-
Granulometry	Not applicable	Liquid substance
Stability in organic solvents and identity of relevant degradation products	-	not critical
Dissociation constant	-	tributyl phosphate lacks the relevant functional groups required for dissociation
Viscosity	38.6	at 29.4 °C
Auto flammability	>482°C	-
Reactivity towards container material		
Thermal stability		
Relative density	0.97	relative density at 25 deg C

The substance has a long history of use as a flame retardant and can therefore justifiably be considered to be non-flammable, non-explosive and without oxidising properties. Testing for these end-points is not proposed and is not considered to be justified on scientific grounds. The viscosity of tributyl phosphate is reported to be 38.6s at 29.4°C (Saybolt Viscosity).

2 MANUFACTURE AND USES

2.1 Quantities

Tonnage band of the evaluated (joint) registration dossier is 1000-10,000 tonnes per annum.

2.1.1 Manufacturing processes

Details on manufacturing process can be found in the Annex of the Report (confidential information).

2.2 Identified uses

2.2.1 Uses by workers in industrial settings

- Manufacture of substance
- Formulation and use of hydraulic fluids, lubricants and greases
- Formulation and use of antifoam agents
- Formulation of pigments and use of paints
- Formulation and use of PUR coatings and adhesives
- Laboratory use in industrial settings

2.2.2 Use by professional workers

- Wide dispersive professional use of concrete containing antifoaming agent
- Use of paints
- Use of PUR coatings and adhesives
- Laboratory use as reagent
- Servicing hydraulic fluids and use of hydraulic fluids, lubricants and greases

2.2.3 Uses by consumers

- Service life of paints, coatings, adhesives and articles containing antifoam agents
- Use of paints
- Use of PUR coatings and adhesives

2.3 Uses advised against

No information on uses advised against.

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

CLP:

	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
	Hazard Class and Category Code(s)	**Hazard statement Code(s)**	**Pictogram, Signal Word Code(s)**	**Hazard statement Code(s)**	**Suppl. Hazard statement Code(s)**		
tributyl phosphate Index No.: 015-014-00-2	Carc. 2	H351	GHS08 GHS07 Wng	H351 H302 H315			
	Acute Tox. 4*	H302					
	Skin Irrit. 2	H315					

H351: Suspected of causing cancer

H302: Harmful if swallowed

H315: Causes skin irritation

DSD:

	Classification	Labelling	Concentration Limits	Notes
tributyl phosphate Index No.: 015-014-00-2	Carc. Cat. 3; R40	Xn R: 22-38-40 S: (2-)36/37-46		
	Xn; R22			
	Xi; R38			

R22: Harmful if swallowed.

R38: Irritating to skin.

R40: Limited evidence of a carcinogenic effect.

S(2): Keep out of the reach of children.

S36/37: Wear suitable protective clothing and gloves.

S46: If swallowed, seek medical advice immediately and show this container or label.

3.2 Self classification

The self classification in the registration dossiers is the same as the harmonised classification.

However, in the C&L Inventory the following additional hazard classes can be found:

- STOT RE 2, H373 (May cause damage to organs (*state all organs affected, if known*) through prolonged or repeated exposure (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard*))
- Eye irrit. 2, H319 (Causes serious eye irritation.)
- Aquatic Chronic 2, H411 (Toxic to aquatic life with long lasting effects.)

4 ENVIRONMENTAL FATE PROPERTIES

Not relevant for this evaluation.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not relevant for this substance evaluation.

5.2 Acute toxicity

Not relevant for this substance evaluation.

5.3 Irritation

Not relevant for this substance evaluation.

5.4 Corrosivity

Not relevant for this substance evaluation.

5.5 Sensitisation

Not relevant for this substance evaluation.

5.6 Repeated dose toxicity

5.6.1 Non-human information

5.6.1.1 Repeated dose toxicity: oral

Effected organs according to toxicological studies on tributyl phosphate following repeated exposure are the liver, kidney, urinary bladder, testes, spleen and the nervous system. The findings concerning the nervous system are discussed in detail under Chapter 5.11.1.1. on Neurotoxicity.

Hepatotoxicity

Based on the data submitted in the registration dossier accumulation in the liver was not detected after 1h during repeated administration study (for 7 days) via stomach (Khalturin et al. 1986). Some of the animal studies have shown an increased ß-glucuronidase activity (90 -fold of control activity after 1 and 2 hr, respectively). Cholinesterase activity was slightly inhibited (21% inhibition) (Suzuki et al. 1977).

The major metabolic pathways include oxidation of the butyl chains, dealkylation and glutathione conjugation. It was found that rat liver microsomal enzymes rapidly metabolized tributyl phosphate in the presence of NADPH (within 30 min), but only slight metabolic breakdown occurred in the absence of NADPH. Dibutyl(3 -hydroxybutyl) phosphate was obtained as a metabolite in the first stage of the test. The extended incubation time in the second stage of the test yielded 2 further metabolites, butyl di(3 -hydroxybutyl) phosphate and dibutyl hydrogen phosphate, which were produced from the primary metabolite dibutyl(3 -hydroxybutyl) phosphate (Sasaki et al. 1984).

Dietary feeding studies have shown an increased liver weight (Mitomo et al. 1980). Increased liver weights were seen in rats and mice exposed to tributyl phosphate from the lowest dose, and after higher doses centrilobular liver cell hypertrophy, eosinophilic hepatocellular changes (only in mice) and increased levels of liver-specific enzymes (70-700mg/kg/day) could be observed. Studies of the mechanism of the effects of tributyl phosphate on the liver are not available, but according to documentation not referred in the registration, the type of findings in the low dose range

hypertrophy, eosinophilic changes) suggest an adaptive process (MAK Value Documentation, 2002).

Based upon the available studies the evaluating Member State could establish that tributyl phosphate has no hepatotoxic properties.

Table 3. Overview of studies with medium and long-term oral administration and the findings related to liver

Species, strain, number of animals per sex and dose	Duration, dose	Findings	References
rat, SD, 10 ♂, 10 ♀	**14 days,** 0, 136, 407 mg/kg body weight	**from 136 mg/kg body weight**: relative liver weights increased (♂), potassium increased (♀);	Laham et al. 1984.
		407 mg/kg body weight: absolute and relative liver weights increased (♂, ♀), amylase activity increased (♂, ♀), bilirubin increased, AChE activity increased (♂), triglycerides increased (♂)	
rat, Wistar, 6–8 ♂	**9 weeks**, 0, 5000 mg/kg diet (about 0, 375 mg/kg body weight and day)	**5000 mg/kg diet**: relative weight increased	Oishi et al. 1982.
rat, Wistar, 10 ♂	**10 weeks**, 0, 5000, 10000 mg/kg diet (about 0, 375, 750 mg/kg body weight and day)	**from 5000 mg/kg diet**: liver weight increased, glucose decreased, coagulation time, liver enzymes and urea nitrogen increased;	Oishi et al. 1982.
		10000 mg/kg diet: protein and cholesterol increased	
rat, SD (no other details)	**3 months**, 0, 500, 2000,	"dose-dependent": body weight gains and liver weight increased	Mitomoto, 1980.

	10000 mg/kg diet (no other details)	**10000 mg/kg diet**: blood urea increased (no other details)	
rat, SD, 15 ♂, 15 ♀	**13 weeks**, 0, 8, 40, 200, 1000, 5000 mg/kg diet (about 0, 0.6, 3, 15, 75, 375 mg/kg body weight)	**from 8 mg/kg diet**: relative liver weights increased (♂);	Cascieri et al. 1985. FMC Corp. 1985.
		200 mg/kg diet: NOAEL;	
		from 1000 mg/kg diet: absolute liver weights increased, γ-GT increased (♂);	
		5000 mg/kg diet: body weight gains decreased, relative liver weight increased, γ-GT increased, cholesterol increased (♀), PTT and Ca^{2+} increased, albumin increased (♂)	
rat, SD, 12 ♂, 12 ♀	(from week 7 350 mg/kg body weight and day)	**300 mg/kg body weight**: body weight gains decreased (♂), absolute and relative liver weights increased	Laham et al. 1984; 1985.
rat, SD, 30 ♂, 30♀	**2-generation study,** 0, 200, 700, 3000 mg/kg diet (about 0, 10–20, 35–70, 160–330 mg/kg body weight and day)	**from 700 mg/kg diet**: body weight gains and food consumption decreased, centrilobular hypertrophy of the liver (♀: F_0, F_1)	Tyl et al. 1992**.** Tyl et al. 1997.

References:

Cascieri, T., Ballester, E.J., Seaman, L.R., McConnell, R.F., Thackara, J.W., Fletcher, M.J.: Subchronic toxicity study with tributyl phosphate in rats. Toxicologist 5:97. (1985).

FMC Corp: Thirteen week feeding study of tributyl phosphate in rats, FMC Corp Toxicology Laboratory No I82-705, FYI-OTS-0585-0380 (1985).

Khalturin GV, Andryuhkeeva NI: Tocicokinetics of tributyl phosphate following single and chronic intragastric intake by rats, Gig Sanit 1986(2):87. (1986).

Laham S, Long G, Broxup B.: Subacute oral toxicity of tri-n-butyl phosphate in the Sprague-Dawley rat, J. Appl. Toxicol. 4:150-154. (1984).

Laham S, Long G, Broxup B.: Induction of urinary hyperplasia in Sprague-Dawley rats orally administered tri-n-butyl phosphate, Arch. Environ. Health 40:301-306. (1985).

Mitomo T, Ito T, Terao K.: Toxicological Studies on TBP. I. Acute and Subacute Toxicities. J. Toxicol. Sci. 5:270-271. (1980).

Oishi H, Oishi S, Hiraga K.: Toxicity of several phosphoric acid esters in rats, Toxicol Lett. 13:29-34. (1982).

Sasaki K, Suzuki T, Takeda M, Uchiyama M.: Metabolism of phosphoric acid triesters by rat liver homogenate, Bull. Environ. Contam. Toxicol. 33:281-288. (1984). [cited in Environ Health Criteria 112, World Health Organization (1991).]

Suzuki Y, Kikuchi H, Kato C, Horiuchi Y, Tomita K, Hashimoto Y.: Effect of alkyl phosphates on ß-glucuronidase in rats: release of ß-glucuronidase from liver microsomes into serum, Biochem Pharm. 26:881-885. (1977).

Tributyl phosphate [MAK Value Documentation, 2002]. The MAK Collection for Occupational Health and Safety. 286–314. (published online: 31 January 2012)

Tyl RW, Marr MC, Myers CB: Two-generation reproductive toxicity study of tributyl phosphate administered in the feed to CD (Sprague-Dawley) rats, Research Triangle Institute, Project No. 60C-4652. (1992).

Tyl RW, Gerhart JM, Myers CB, Marr MC, Brine DR, Seely JC, Henrich RT.: Two-Generation Reproductive Toxicity Study of Dietary Tributyl Phosphate in CD Rats. Toxicol. Sci. 40(1):90-100. (1997).

Testes

Degenerative changes in seminiferous tubules were observed in one male animal in a 2-week feeding study in rats. The effective dose was 400 mg/kg bw/day, the NOAEL was 130 mg/kg bw/day. No effects on testes were observed either in other longer term repeated dose studies or in 2 generation reproduction study. In addition no effect on male fertility was observed in the reproduction toxicity study (Laham et al. 1985).

Considering these results the evaluating Member State can state that the classification of tributyl phosphate for STOT RE based on its effects on testes is not warranted

References:

Laham S, Long G, Broxup B.: Induction of urinary hyperplasia in Sprague-Dawley rats orally administered tri-n-butyl phosphate, Arch. Environ. Health 40:301-306. (1985).

Urinary bladder

In case of urinary bladder alterations observed in the short term repeated dose toxicological studies, namely different epithelial hyperplasias, postulate the non-genotoxic mode of action that can lead to neoplastic lesions observed in longer term toxicological studies.

As it is described in the paper of Cohen (2002), urothelial carcinogenesis in the rat proceeds through a sequence of morphologic changes beginning as simple hyperplasia, an increase in the number of cell layers in the urothelium. It then progresses to nodular and papillary hyperplasia, which resemble the Brunn's nests and papillary neoplasms with low-grade malignant potential in humans. In contrast the mouse commonly proceeds through a process of flat, nonpapillary dysplasia, carcinoma in situ, and invasive carcinoma with frequent metastases.

Numerous agents have been identified that produce superficial or deep cytotoxicity and regeneration, and are associated with increased incidences of bladder tumors in rodents. Similar toxic and regenerative processes appear to be involved with bladder carcinogenesis in humans related to chronic inflammation, such as schistosomiasis and calculi.

Based on these considerations the evaluating Member State can conclude that the observed changes in urinary bladder following repeated exposure to tributyl phosphate can be considered as covered appropriately by the Carcinogenic category 2 classification. The STOT RE classification based on the effects of tributyl phosphate on urinary tract is not necessary if the substance is classified for carcinogenicity.

As it is stated in the Guidance on application of CLP criteria, STOT RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class.

References:

Cohen SM.: Comparative Pathology of Proliferative Lesions of the Urinary Bladder. Toxicol Pathol 30:663. (2002).

Laham S, Long G, Broxup B.: Induction of urinary hyperplasia in Sprague-Dawley rats orally administered tri-n-butyl phosphate, Arch. Environ. Health 40:301-306. (1985).

Tyl RW, Marr MC, Myers CB.: Two-generation reproductive toxicity study of tributyl phosphate administered in the feed to CD (Sprague-Dawley) rats, Research Triangle Institute, Project No. 60C-4652. (1992).

Kidney

Kidney alterations were observed in the 2-generation reproduction study as renal pelvis epithelial hypertrophy and different tubular changes (dystrophy), organ weight increment or BUN level changes were observed in studies scored as not assignable. As the main excretory route for the radio label of tributyl phosphate was the urine, the role of the excreted substance or metabolites in the development of kidney changes cannot be excluded. The effective dose of these kidney alterations in the 9-week or 13-week repeated dose studies and in the 2-generation reproduction study is well above the guidance value (Tyl et al. 1992).

Considering the above facts the evaluating Member State can establish that the classification of kidney effects for STOT RE is not warranted.

References:

Tyl RW, Marr MC, Myers CB.: Two-generation reproductive toxicity study of tributyl phosphate administered in the feed to CD (Sprague-Dawley) rats, Research Triangle Institute, Project No. 60C-4652. (1992).

Spleen

Spleen alterations, namely the changes of the organ weight were observed in two studies at dose levels above the guidance values proposed in Guidance on the Application of the CLP Criteria. However, the direction of the observed changes was opposite in these studies (Laham et al, 1984; 1985).

Considering these inconsistencies the evaluating Member State could establish that no classification of TBP based on spleen effects is warranted for STOT RE.

References:

Laham S, Long G, Broxup B.: Subacute oral toxicity of tri-n-butyl phosphate in the Sprague-Dawley rat, J. Appl. Toxicol. 4:150-154. (1984).

Laham S, Long G, Broxup B.: Induction of urinary hyperplasia in Sprague-Dawley rats orally administered tri-n-butyl phosphate, Arch. Environ. Health 40:301-306. (1985).

Nervous system

Effects on nervous system were observed as decreased RBC (red blood cell) cholinesterase activity in one 18-week oral rat study and decrease of brain cholinesterase activity in one 4-month rabbit inhalation study. Furthermore in one 14-day rat study the decrease of conducting velocity and

morphological changes were observed. The effective dose in the oral studies were above the proposed guidance values for category 2 and the NOAEL values in these studies were close to the guidance value, but below it (Latham et al. 1984; 1985).

Detailed conclusions on the effects of tributyl phosphate on nervous are made under the respective chapter of this report.

References:

Laham S, Szabo J, Long G.: Effects of tri-n-butyl phosphate on the peripheral nervous system of the Sprague-Dawley rat, Drug Chem. Toxicol. 6:363-377. (1983).

Laham S, Long G, Broxup B.: Induction of urinary hyperplasia in Sprague-Dawley rats orally administered tri-n-butyl phosphate, Arch. Environ. Health 40:301-306. (1985).

Table 4. Observed target organs in repeated dose toxicity studies of tributyl phosphate

Target organ	**Observed effect**	**LOEL of the effect (mg/kg bw/day)**	**NOAEL (mg/kg bw/day)**	**Reference**
Urinary bladder	epithelial hyperplasia (mouse, 90 day)	300	75	Reference included in the Annex (Confidential information)
Nervous system	reduction in conduction velocity and morphological changes (rat, 14-day)	0.42 ml/kg bw/day (400 mg/kg bw/day)	270	Laham et al. 1983.
Urinary bladder	diffuse urothelial hyperplasia (rat,18 weeks)	200	Not determined	Laham et al. 1985.
Nervous system	RBC acetylcholine-esterase activity decrease (rat,18 weeks)	300-350	200	
Spleen	organ weight elevation (rat,18 weeks)	300-350	200	
Testicles (in one	degenerative changes in seminiferous	400	130	

Target organ	Observed effect	LOEL of the effect (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Reference
animal)	tubules (rat, 2 weeks)			
Spleen	organ weight decrease (rat, 2 weeks)	400	130	Laham et al. 1984.
Kidney	renal pelvis epithelial hypertrophy (rat, 16 weeks)	225	53	Tyl et al. 1992.

Table 5. Observed target organs in repeated dose toxicity studies scored as not assignable

Target organ	Observed effect	LOEL of the effect (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Reference
Urinary bladder	transitional cell hyperplasia (rat, 13 weeks)	75	Not determined	Cascieri et al. 1985.
Kidney	tubular changes (rat, 1 month)	No details, (applied dose levels were 130 and 460)	Not determined	Mitomo et al. 1980.
Kidney	increased BUN activity (rat, 9-week study)	5000 ppm (375 mg/kg bw/day)	Not relevant, one dose level was used	Oishi et al. 1982.
Kidney	tubulus dystrophia, increased weight long term (rat 5 mg/kg bw/day)	not determined	Not determined	Pupysheva, Peresedov, 1989.
Kidney	relative weight increment, BUN activity increase (rat 7 day)	no details, 140 and 200 mg/kg were applied for 7 days	Not determined	Mitomo et al. 1980.

References:

Cascieri T, Ballester EJ, Seaman LR, McConnell RF, Thackara, Fletcher MJ.: Subchronic toxicity study with tributyl phosphate in rats (13 weeks), Toxicologist 5:97. (1985).

Mitomo T, Ito T, Ueno Y, Terao K, Toxicological studies on tributyl phosphate. (I) Acute and subacute toxicities (1 month) J. Tox. Sci 5:270-271. (1980).

Oishi H, Oishi S, Hiraga K: Toxicity of several phosphoric acid esters in rats, Toxicol Lett. 13:29-34. (1982).

Pupysheva GJ, Peresedov VP: cited in Berufsgenossenschaft der chemischen Industrie. Toxikologische Bewertung Ausgabe 02/89, Nr. 170. (1989).

5.6.1.2 Repeated dose toxicity: inhalation

Nervous system

The effective dose in an inhalation study was well below the proposed guidance value, but the study was evaluated as not assignable, as few details were published.

Table 6. Repeated dose toxicity, inhalation route, not assignable study

Target organ	Observed effect	LOEL of the effect (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Reference
Nervous system	Decrease of brain ChE activity (rabbit 4 months)	13.6 mg/m^3	4.8 mg/m^3	Kalinina 1971.

References:

Kalinina, N.I.: Toxicity of the organophosphorus softening agents tributyl phosphate and di-(2-ethylhexyl)-phenylphosphate.(in Russian) Gig Tr Prof Zabol 15:30-33. (1971).

5.6.2 Human information

No human data are available.

5.6.3 Summary and discussion of repeated dose toxicity

In the toxicological studies performed with tributyl phosphate the liver, testes, kidney, urinary bladder, spleen and nervous system were affected. After a detailed evaluation of the presented

studies and publications the repeated dose toxicity of tributyl phosphate can be concluded by the evaluating Member State as it follows.

Animal studies have shown no significant accumulation of the tributyl phosphate in the **liver.** Results from most of the repeated dose studies consistently showed increased liver weight of rats and mice, but it should be noted that the dose was in all of these studies high. Some of these studies described elevated liver enzymes activity, a part of these enzymes are connected to the metabolism of tributyl phosphate. The available studies provide adequate basis for evaluating repeated dose toxicity. These findings indicate that tributyl phosphate has no hepatotoxic properties.

No effects on **testes** were observed either in other longer term repeated dose studies or in 2-generation reproduction study. In addition no effect on male fertility was observed in the reproduction toxicity study. Considering these results the classification of tributyl phosphate for STOT RE based on its effects on testes, is not warranted.

The observed changes of **urinary bladder** following repeated exposure to tributyl phosphate can be considered as appropriately covered by the Carcinogenic category 2 classification. The STOT RE classification based on the effects of tributyl phosphate on urinary tract is not necessary if the substance is classified for carcinogenicity.

The effective dose of **kidney** alterations in the 9-week or 13-week repeated dose studies and in the 2-generation reproduction study is well above the guidance value. Considering the above facts classification of specific target organ toxicity of tributyl phosphate for kidney is not triggered.

Spleen alterations, namely the changes of the organ weight were observed in two studies at dose levels above the guidance values proposed in Guidance on the Application of the CLP Criteria, so it can be stated that no reason for classification of tributyl phosphate for spleen can be found.

The conclusion of effects on **nervous system** of short term and long-term, single dose and repeated dose toxicity studies is that nervous system is not a target organ of tributyl phosphate. If neurotoxic effects were detected in some studies they appeared only after exposure to very high doses, they were unspecific, transient, probably caused indirectly by other organ damages and/or general toxicity of tributyl phosphate. (See also under Chapter 5.11.3 on Summary and discussion of specific investigations)

The registrant has examined duly this concern and arrived to the same conclusion concerning the toxicological properties of the substance.

5.7 Mutagenicity

5.7.1 Non-human information

5.7.1.1 In vitro data

Ames' tests were performed on various strains of Salmonella typhimurium (TA102, TA2638, TA1535, TA100, TA1537, TA98, hisC117, hisG46, TA1530, hisD3052, TA1531, TA1532, TA1538) and Escherichia coli (WP2/pKM101, WP2 uvr/pKM101). No mutagenic activity was observed in all but one test. However, in the latter test no data on GLP and the administered doses are available, consequently the results are not reliable (Klimish reliability factor 4) (Hanna et al. 1975, Gafieva, Gudin, 1986, Watanabe et al. 1987).

Cytogenetic assay was performed on mouse embryos, 48 and 144 hours *post conceptionem* without metabolic activation with no observed induction of micronuclei. No data on GLP and the administered doses are available. The data are not reliable (Klimish reliability factor 4) (Muller et al. 1987).

Cytogenetic assay was performed on CHO-K1 Chinese hamster ovary cells by doses up to 0.15 µl/ml, with and without metabolic activation, according to GLP. No significant induction of chromosome aberrations was observed. The data are reliable (Klimish reliability factor 2) (Batt et al, 1992).

A further test on mammalian gene (HGPRT) mutation assay was performed on CHO-K1-BH4 Chinese hamster ovary cells with and without metabolic activation according to GLP. The administered doses were: 0.05, 0.07, 0.08, 0.09 and 0.11 µl/ml, and 0.06, 0.08, 0.1, 0.125 and 0.15 µl/ml with and without S9 mix, respectively. Results were negative in all doses tested. The data are reliable (Klimish reliability factor 1).

References:

Batt KJ, Healy CE, Kneiss JJ, Putnam DL, Jacobson-Kram D.: Weiner ML, Fletcher MJ; Genotoxicity testing of tributyl phosphate. Environ. Mol. Mutagen. 19(Suppl. 20):5. (1992).

Gafieva Z, Gudin V.: Evaluation of the mutagenic action of TBP on Salmonella typhimurium. Gig. Sanit. 9:81. (1986).

Hanna P, Dyer K.: Mutagenicity of organophosphorous compounds in Bacteria and Drosophila. Mutat. Res. 28:405-420. (1975).

Muller WU, Streffer C, Markoski L.: Does tributyl phosphate influence the radiation risk of a highly proliferating system - the early mouse embryo in vitro? Health Physics 53:667-671. (1987).

SIDS Dossier, SIDS Initial Assessment Report for 12th SIAM, Paris, France. (2001).

Watanabe K, Sasaki K, Sakamoto T.: Comparison of chemically induced mutagenicity among four bacterial strains. Mutat. Res. 361:143-155. (1996).

5.7.1.2 In vivo data

SLRL test was performed on Drosophila melanogaster by *per os* administration with negative results. No data are available on GLP and the administered doses, consequently the data are not reliable (Klimish reliability factor 4) (Hanna, Dyer, 1975).

Cytogenetic assay was performed on male and female rats (strain not given) according to GLP by *per os* administration of tributyl phosphate in doses of 0-300-600-1200 mg/kg bw. The high dose was the maximum tolerated dose, clinical symptoms appeared at 600 mg/kg bw. No sign of aberrant cells was observed in bone marrow after 12, 24 or 36 hours. The data are reliable (Klimish reliability factor 1).

References:

Hanna P, Dyer K.: Mutagenicity of organophosphorous compounds in Bacteria and Drosophila. Mutat. Res. 28:405-420. (1975).

SIDS Dossier, SIDS Initial Assessment Report for 12th SIAM, Paris, France. (2001).

5.7.2 Human information

No human data are available.

5.7.3 Summary and discussion of mutagenicity

Possible mutagenic properties of TBP were critically analyzed based upon the available relevant data published in scientific periodicals or referred in the relevant OECD-SIDS Dossier (SIDS Initial Assessment Report for 12th SIAM, Paris, France, June 2001). Accordingly, the evaluating Member State came to following conclusion on mutagenicity.

Studies presented in the registration dossier to investigate the genotoxic potential of tributyl phosphate in vitro and in vivo were negative.

Eight bacterial mutagenicity tests, one in vitro cytogenetic test, two in vitro gene mutation tests, two in vitro micronucleus tests and two in vivo cytogenetic tests on mammalian cells and a SLRL Drosophila test were performed with tributyl phosphate. All of them gave negative results except one bacterial mutagenicity test, which was positive. However, the study giving the positive result was not considered reliable.

Only two bacterial mutagenicity tests, an in vitro cytogenetic test on mammalian cells, an in vitro gene mutation test on mammalian cells and an in vivo cytogenetic test in rat cells were acceptable for the evaluation (Klimish reliability factor 1-2), and all of them gave negative results.

As a consequence, the evaluating Member State could establish that tributyl phosphate has no mutagenic activity, and a classification as mutagen is not justified.

Registrant has examined duly this concern and arrived to the same conclusion.

5.8 Carcinogenicity

5.8.1 Non-human information

5.8.1.1 Carcinogenicity: oral

In a study performed by Auletta et al. (1998a), tributyl phosphate was administered in the diet at concentrations of 0, 150, 1000 or 3500 ppm to groups of 50 male and 50 female CD-1 mice for 18 months. A significant dose-related increase in absolute and relative liver weights was found in male and female mice, which received the two highest dietary concentrations of TBP (1000 and 3500 ppm) and the incidence of the pro-carcinogenic hepatocellular adenomas was significantly increased in male mice treated with 3500 ppm tributyl phosphate in diet. However, tributyl phosphate had no similar effects on females.

A chronic 2 years carcinogenicity study was also performed by Auletta et al (1998b) applying 0, 200, 700 and 3000 ppm to groups of 50 male and 50 female Sprague-Dawley rats. They found no

liver effects but enhanced urinary bladder hyperplasia and papilloma formation as well as the appearance of transitional cell carcinoma in urinary bladder in both sexes at the highest administered dietary dose (3000 ppm) only. The transitional cell carcinoma formation was not significant in females. The hepatocellular carcinoma incidences were equal in the treated and control groups.

Earlier, on the same rat strain and administering similar doses, Arnold et al (1997) did not find any pro-carcinogenic changes. However, Cascieri et al. (1985), found transitional cell hyperplasia of the urinary bladders in males at 1000 and 5000 ppm and in females at 5000 ppm. Laham et al. (1985) dosed Sprague-Dawley rats orally for 18 weeks at 200 mg/kg/day or at 300 mg/kg/day for the first six weeks and 350 mg/kg/day for the remaining 12 weeks. They reported that all treated rats developed diffuse hyperplasia of the urinary bladder.

As tributyl phosphate was negative in genotoxicity tests, Auletta et al (1998b) suggested that the benign tumors are induced by non-genotoxic mechanisms.

In case of urinary bladder alterations observed in the short term repeated dose toxicological studies, namely different epithelial hyperplasias, postulate the non-genotoxic mode of action that can lead to neoplastic lesions observed in longer term toxicological studies.

As it is described in the paper of Cohen (2002) urothelial carcinogenesis in the rat proceeds through a sequence of morphologic changes beginning as simple hyperplasia, an increase in the number of cell layers in the urothelium. It then progresses to nodular and papillary hyperplasia, which resemble the Brunn’s nests and papillary neoplasms with low-grade malignant potential in humans. In contrast the mouse commonly proceeds through a process of flat, nonpapillary dysplasia, carcinoma in situ, and invasive carcinoma with frequent metastases.

Numerous agents have been identified that produce superficial or deep cytotoxicity and regeneration, and are associated with increased incidences of bladder tumors in rodents. Similar toxic and regenerative processes appear to be involved with bladder carcinogenesis in humans related to chronic inflammation, such as schistosomiasis and calculi.

Based on these considerations the evaluating Member State could conclude that the observed changes in urinary bladder following repeated exposure to tributyl phosphate can be considered as covered appropriately by the Carcinogenic category 2 classification. The STOT RE classification based on the effects of tributyl phosphate on urinary tract is not necessary if the substance is classified for carcinogenicity.

As it is stated in the Guidance on application of CLP criteria, STOT RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class.

References:

Auletta CS., Kotkoskie LA, Saulog T, Richter, WA.: A dietary oncogenicity study of tributyl phosphate in the CD-1 mouse. Toxicology 128:135–141. (1998a).

Auletta CS, Weiner ML, Richter WR.: A dietary toxicity: oncogenicity study of tributyl phosphate in the rat. Toxicology 128: 125–134. (1998b)

Arnold LA., Cohen SM., Christensen R., Cano M., St.John M, Wahle BS.: Tributyl phosphate (TBP) effects on urine and bladder epithelium in male Sprague-Dawley rats. Toxicologist 36:173. (1997).

Cascieri T, Ballester EJ, Seaman LR, McConnell RF, Thackara JW, Fletcher MJ.: Subchronic toxicity study with tributyl phosphate in rats. Toxicologist 5:97. (1985).

Cohen SM.: Comparative Pathology of Proliferative Lesions of the Urinary Bladder. Toxicol Pathol 30:663. (2002).

Laham S, Long G, Broxup B.: Induction of urinary hyperplasia in Sprague-Dawley rats orally administered tri-n-butyl phosphate, Arch Environ Health 40:301-306. (1985).

SIDS dossier, SIDS Initial Assessment Report for 12th SIAM, Paris, France (2001).

Tyl RW, Marr MC, Myers CB.: Two-generation reproductive toxicity study of tributyl phosphate administered in the feed to CD (Sprague-Dawley) rats, Research Triangle Institute, Project No. 60C-4652. (1992).

5.8.2 Human information

No human data are available.

5.8.3 Summary and discussion of carcinogenicity

Possible carcinogenic properties of tributyl phosphate critically analyzed by the evaluating Member State were based upon the available relevant data published in scientific periodicals or referred in the relevant OECD-SIDS dossier (SIDS Initial Assessment Report for 12th SIAM, Paris, France, June 2001).

Authors discuss that changes observed during the studies might be species specific as no tributyl-phosphate-related malignant lesions were seen on any treatment level on CD1 mice and in Sprague-Dawley rats, urinary bladder hyperplasia and papillomas were induced only at 700 and 3000 ppm dietary concentrations. At the highest concentration, bladder transitional cell carcinomas were also detected in the males in this species. No suspicions referring to human carcinogenicity have ever

been published. Since no similar effects have been found in mice, these effects might be species specific to rats.

Based on the above considerations the evaluating Member State could conclude that the observed changes in urinary bladder following repeated exposure to tributyl phosphate can be considered as covered appropriately by the Carcinogenic category 2 classification. Also, the STOT RE classification based on the effects of tributyl phosphate on urinary tract is not necessary as the substance is classified for carcinogenicity.

Based upon the available study data published in periodicals and in the OECD-SIDS dossier the evaluating Member State supports the present classification of TBP (DSD: Carc. Cat. 3, R40 or CLP: Carcinogenic Hazard Category 2, H 351),

Registrant has examined duly this concern and arrived to the same conclusion.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.1.1 Non-human information

A two-generation reproductive toxicity study of tributyl phosphate in CD rats (Gerhart et al. 1993) was submitted for the registration. The test material was administered in the diet *ad libitum* at dose levels of 0, 200, 700 and 3000 ppm (equivalent to approx. 15, 53 and 225 mg/kg bw/day according to the study report). Clinical signs, feed consumption and body weights were observed throughout the study. Adult reproductive organs were evaluated histologically.

No evidence of reproductive toxicity, of reproductive organ pathology, or of effects on gestation or lactation was noted at any dose tested. The NOAEL for reproductive toxicity was found to be at least 3000 ppm.

Adult toxicity was observed in both sexes and generations at 700 and 3000 ppm (Tyl et al. 1997). Observations included reduced body weights, body weight gain and feed consumption, urinary bladder epithelial hyperplasia (both sexes), renal pelvis epithelial hyperplasia only at 3000 ppm (male kidneys) and centrilobular hypertrophy (female livers). At 200 ppm, transient reductions in body weight were observed in F0 and F1 females, with urinary bladder epithelial hyperplasia in F0

males and females and in F1 males. Under the conditions of this study, a NOAEL was not determined for adult toxicity.

Postnatal toxicity was evidenced by consistent reductions in F1 and F2 pup body weights at 3000 ppm and by occasional weight reductions in F2 litters at 700 ppm, and was associated with maternal toxicity observed at these doses and times. The NOAEL for postnatal toxicity was at or below 200 ppm.

The study was adequate and reliable for assessing reproductive and fertility effects of tributyl phosphate (Klimish reliability factor 1), no further studies are considered necessary. The NOAEL for reproductive toxicity was shown to be 3000 ppm, however assigning an exact equivalent in mg/kg bw/day does not seem accurate as due to the differences in feed consumption the ranges of the achieved tributyl phosphate levels varied greatly within each dose level. Nevertheless the results of the test clearly suggest that tributyl phosphate does not have to be considered as a selective reproductive toxicant as no reproductive parameters were significantly affected at any dose level.

No specific adverse effects of tributyl phosphate on the reproduction were reported in the literature as yet. Any effects noted were sporadic and without any clear correlation with the treatment.

Consequently the available data do not suggest any specific, selective effects of tributyl phosphate on reproductive parameters or fertility. Reproductive organs were not identified as target organs of tributyl phosphate in the available studies.

Degenerative changes in seminiferous tubules were observed in one male animal in a 2-week feeding study in rats. The effective dose was 400 mg/kg bw/day, the NOAEL was 130 mg/kg bw/day. No effects on testes were observed either in other longer term repeated dose studies or in the 2-generation reproduction study. In addition no effect on male fertility was observed in the reproduction toxicity study (Laham et al. 1984).

Table 7. Overview of experimental two-generation studies on fertility

Method	Animal model	Findings	Reliability	Reference
EPA OTS 798.4700 (Reproduction and Fertility Effects) administration: oral/feed Doses: 0, 200, 700 and 3000 ppm (approx. 15, 53 and 225 mg/kg bw/day) Exposure: F0 generation: 10 weeks; F1 generation: 11 weeks	rat (Sprague-Dawley) male/female	NOAEL for reproductive toxicity: at least 3000 ppm (approx. 225 mg/kg bw) NOAEL for postnatal toxicity: at or below 200 ppm (approx. 15 mg/kg bw)	1 (reliable without restrictions)	Tyl et al. 1997. Gerhart et al. 1993.

Considering these results based on the effects on testes the evaluating Member State could conclude that the classification of tributyl phosphate for STOT RE is not warranted.

References:

Gerhart JM, Tyl RW, Myers CB, Marr MC, Brine DR, Seely JC.: Two generation study of dietary tributyl phosphate (TBP) in CD rats. Toxicologist 1993 Mar:13(1):76. (1993).

Laham S, Long G, Broxup B.: Subacute oral toxicity of tri-n-butyl phosphate in the Sprague-Dawley rat, J. Appl. Toxicol. 4:150-154. (1984).

Tyl RW, Gerhart JM, Myers CB, Marr MC, Brine DR, Seely JC, Henrich RT.: Two-Generation Reproductive Toxicity Study of Dietary Tributyl Phosphate in CD Rats. Toxicol. Sci. 40(1):90-100. (1997).

5.9.1.2 Human information

No human data are available.

5.9.2 Developmental toxicity

5.9.2.1 Non-human information

Three teratogenicity studies are available for tributyl phosphate with Klimish reliability factor 1, all of them involve range-finding experiments as well. The studies were performed in two species (two strains of rats and one strain of rabbits).

In a developmental toxicity study in CD rats (Schroeder et al. 1991) no embryotoxic effects were seen at any of the dose levels. A reduction in mean foetal weight and delayed ossification was seen only at the 750 mg/kg/day dose level. External, visceral and skeletal examination of the foetuses recovered from females in the treatment groups at day 20 of gestation revealed no teratogenic response at any of the dose levels evaluated. The NOAEL for teratogenicity and embryotoxicity was 150 mg/kg bw, for foetotoxicity and teratogenicity it was >400 mg/kg bw.

In the developmental toxicity study in rabbits (Schroeder et al. 1991) tributyl phosphate was administrated by gastric intubation (18 mated females/group) at dose levels of 50, 150 and 400 mg/kg/day during the day 6-18 gestation period. Dose levels 50 and 150 mg/kg bw were not found to be maternally toxic, embryotoxic, foetotoxic or teratogenic. At 400 mg/kg/day maternal toxicity and embryotoxicity were suggested, with no observations of foetotoxicity or teratogenicity. The NOAEL for maternal toxicity, embryotoxicity, foetotoxicity and teratogenicity was >150 mg/kg bw.

A developmental toxicity study in Wistar rats (Noda et al. 1994) also concluded that tributyl phosphate was not teratogenic. In this experiment, doses of 0, 62.5, 125, 250 or 500 mg/kg/day of tributyl phosphate were administered by gastric intubation. There were no significant differences between the groups in the incidence of dead or resorbed foetuses, the number of living foetuses and the body weights of living foetuses of both sexes. The incidence of rudimentary lumbar rib increased significantly at 500 mg/kg/day. There were two cases of malformation: a foetus with deformity of fore- and hind-limbs at 400 mg/kg/day in the dose-finding study and conjoined twins exhibiting three fore-limbs and four hind-limbs at 125 mg/kg/day in the main teratological study. These malformations were rare in the background data of teratology, and the incidence of foetuses with malformations was not increased significantly. NOAEL was found to be 62.5 mg/kg bw/day for maternal toxicity and 250 mg/kg bw/day for foetotoxicity.

All the above studies showed that embryotoxic and foetotoxic effects such as ossification disturbances (delayed ossification and rudimentary ribs) occured only at maternally toxic doses.

Based on the appropriately performed primary studies described, the evaluating Member States has found that teratogenic effect of tributyl phosphate could not be substantiated; therefore the hazard concern regarding teratogenicity of tributyl phosphate is not justified.

Table 8. Overview of experimental studies on developmental toxicity

Method	Animal model	Findings	Reliability	Reference
EPA OTS 798.4900 (Prenatal Developmental Toxicity Study) administration: oral/gavage//corn oil doses: 0, 188, 375, or 750 mg/kg bw exposure: day 6 to 15 of gestation (daily)	rat (Sprague-Dawley)	NOAEL for both teratogenicity and embryotoxicity: 750 mg/kg bw/day (actual dose received)	1 (reliable without restrictions)	Schroeder et al. 1991.
EPA OTS 798.4900 (Prenatal Developmental Toxicity Study) administration: oral/gavage//corn oil doses: 0, 50, 150 or 400 mg/kg bw exposure: day 6 to 18 of gestation (daily)	rabbit (New Zealand White)	NOAEL for maternal toxicity, embryotoxicity, foetotoxicity and also teratogenicity: >150 mg/kg bw/day	1 (reliable without restrictions)	Schroeder et al. 1991.
Range finding study administration: oral/gavage//corn oil doses: initial phase: 0, 80, 435, 790, 1145, and 1500 mg/kg bw second phase: 0, 600 and 790 mg/kg/day. exposure: day 6 to 15 of gestation (daily)	rat (Sprague-Dawley)	Considerable maternal mortality at dose levels of 790, 1145 and 1500 mg/kg bw. At 435 mg/kg/bw maternal toxicity but no effects on embryo. A dose of 80 mg/kg bw was not considered to be maternally toxic, embryotoxic or foetotoxic.	2 (reliable with restrictions)	Schroeder et al. 1991.
Range finding study administration: oral/gavage//corn oil doses: 0, 50, 250, 412, 775, 1137 and 1500 mg/kg bw exposure: day 6 to 18 of gestation (daily)	rabbit (New Zealand White)	Tributyl phosphate administered at dose levels of 775, 1137 and 1500 mg/kg/day proved extremely toxic to pregnant New Zealand White rabbits, as all animals in these groups died during the treatment. At a dose level of 50 mg/kg/day no maternal toxicity was indicated. At the 250 mg/kg/day dose level, no maternal toxicity was evident from body weight or food consumption data. At the 412 mg/kg/day dose level, the magnitude of weight loss seen over the day 6-30 gestation interval was suggestive of a treatment-related response.	2 (reliable with restrictions)	Schroeder et al. 1991.

Teratological study administration: oral/gavage//olive oil doses: 0, 100, 200, 400 or 800 mg/kg/day (dose finding study) 0, 62.5, 125, 250 or 500 mg/kg/day (main study) exposure: days 7-17 of gestation	rat (Wistar)	LOAEL at ≥200/250 mg/kg/day Tri-n-butyl phosphate was considered not to be teratogenic in this study.	1 (reliable without restrictions)	Noda et al. 1994.
Structure-activity and metabolism studies on organophosphate teratogens and their alleviating agents in developing hen eggs with special emphasis on bidrin Teratogenic signs of hen embryos were evaluated at day 21 from eggs injected on day 4 of incubation with tributyl phosphate Dose: 5 mg/egg Exposure: 17 days	hen	Weak teratogenic effects (decrease of survival, weight, length)	3 (not reliable)	Roger et al. 1969.

The submitted 2-generation reproductive toxicity study of tributyl phosphate in CD rats (Gerhart et al. 1993) further supports that the substance is not toxic for the offspring at doses that are not maternotoxic.

A developmental toxicity study in developing hen eggs of organophosphate teratogens including tributyl phosphate was also submitted in the dossier (Roger et al. 1969). The test species of this study is, however, inappropriate for drawing conclusions regarding effects of tributyl phosphate on humans; furthermore the experiment has several major deficiencies and thus cannot be considered reliable. The study was deemed irrelevant for the evaluation of the effects of tributyl phosphate.

The above presented range-finding and main teratogenicity studies (Schroeder et al. 1991; Noda et al. 1994) conducted in rabbits and two strains of rats have already been evaluated by several independent, recognized and reliable international scientific bodies. The reports concluded that tributyl phosphate does not produce developmental toxicity in offspring at levels that are not maternally toxic and does not have teratogenic activity, even at maternally toxic doses. This opinion is consistent with the conclusion of the evaluating Member State and further supports that no concern arises regarding teratogenicity of tributyl phosphate.

References:

Gerhart JM, Tyl RW, Myers CB, Marr MC, Brine DR, Seely JC.: Two-generation study of dietary tributyl phosphate in CD rats. Toxicologist 13:76. (1993).

Noda T. Yamano T. Shimizu M. Morita S.: Effects of tri-n-butyl phosphate on pregnancy in rats. Food Chem Toxicol., Nov; 32(11):1031-6. (1994).

Roger JC, Upshall DG, Casida JE.: Structure-activity and metabolism studies on organophosphate teratogens and their alleviating agents in developing hen eggs with special emphasis on bidrin. Biochem. Pharmacol. 18:373-392. (1969).

Schroeder RE, Gerhart JM, Kneiss J.: Developmental Toxicity Studies of Tributyl Phosphate in the Rat and Rabbit, Teratology 43:455. (1991).

Screening Assessment for the Challenge - Phosphoric Acid Tributyl Ester (Tributyl Phosphate) CAS: 126-73-8. Environment Canada - Health Canada. (2009).

SIDS dossier, SIDS Initial Assessment Report for 12th SIAM, Paris, France. (2001).

Tributyl phosphate; Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands, Committee on Updating of Occupational Exposure Limits; 2000/15OSH/158. (2005).

Tributyl phosphate [MAK Value Documentation, 2002]. The MAK Collection for Occupational Health and Safety. 286–314. (published online: 31 January 2012).

Tri/Dibutyl phosphate. BUA Report 108. p. 21. GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) (1992).

Tri-n-butylphosphat [MAK Value Documentation in German language, 2000]. The MAK Collection for Occupational Health and Safety. 1–30. (published online: 31 January 2012).

Tyl RW, Gerhart JM, Myers CB, Marr MC, Brine DR, Seely Jc, Heinrich RT.: Two-generation reproductive toxicity study of dietary tributyl phosphate in CD rats. Fundam Appl Toxicol. 40:90-100. (1997).

5.9.2.2 Human information

No human data are available.

5.9.3 Summary and discussion of reproductive toxicity

Effects on fertility

In the available two-generation studies (Gerhart et al. 1993, Tyl et al. 1997) no effects on reproductive toxicity were noted; treatment did not affect gestation or lactation. No pathological changes were found on reproductive organs. Postnatal toxicity was observed in the F1 and F2

generations, the pup body weights were consistently reduced at 3000 ppm and occasionally reduced in F2 litters at 700 ppm; these symptoms were however associated with maternal toxicity.

Under the conditions of these studies, a NOAEL was not determined for adult toxicity; the NOAEL for reproductive toxicity was at least 3000 ppm (approx. 225 mg/kg bw) and the NOAEL for postnatal toxicity was approximately 200 ppm (approx. 15 mg/kg bw).

The results of the tests clearly suggest that tributyl phosphate does not have to be considered as a selective reproductive toxicant as no reproductive parameters were significantly affected at any dose level.

No specific adverse effects of tributyl phosphate on the reproduction were reported in the literature as yet. Any effects noted were sporadic and without any clear correlation with the treatment.

The evaluating Member State concluded that the studies were sufficiently reliable and adequate for the assessment of the effects on fertility. The available data do not suggest any specific, selective effects of tributyl phosphate on reproductive parameters of fertility. Reproductive organs are not identified as target organs of tributyl phosphate. Classification of tributyl phosphate regarding this endpoint is not required.

Developmental toxicity

Based on the above mentioned studies performed in two strains of rats and rabbits, the respective range finding studies and the 2-generation studies in rats, classification of tributyl phosphate is not justified for developmental toxicity. All the above studies showed that embryotoxic and foetotoxic effects such as ossification disturbances (delayed ossification and rudimentary ribs) occurred only at maternally toxic doses. The available studies were considered sufficient for the evaluation of developmental toxicity. Further studies for reproductive or developmental toxicity are not required. Based on the appropriately performed primary studies described, the evaluating Member State considers that teratogenic effect of tributyl phosphate could not be substantiated; therefore the hazard concern regarding teratogenicity of tributyl phosphate is not justified.

The registrant has duly examined the reproductive toxicity of the substance and came to the same conclusion.

5.10 Endocrine disrupting properties

Not relevant for this evaluation.

5.11 Other effects

Not relevant for this evaluation.

5.11.1 Non-human information

5.11.1.1 Neurotoxicity

The generally recommended strategy for neurotoxicity testing (Costa, 1998; OECD, 2004) was followed in the relevant studies on tributyl phosphate. Tiered approach evaluation of neurotoxic potential of tributyl phosphate was usually started with qualitative and quantitative functional observation battery – a standardized screening battery for the assessment of many aspects of behavioral and neurological functions in rodents – and it was correctly chosen as a first line method according to the recommendations. The observed symptoms were non-specific, therefore no further specific tests of motor and sensory functions were carried out. Therefore, only few publications exist about additional specific investigation of tributyl phosphate. Nevertheless, neurotoxicity of tributyl phosphate has been tested in all relevant fields: neurobehavioral, neuropathological, neurophysiological and neurochemical techniques were all applied to complete the knowledge about tributyl phosphate. (Tributyl phosphate [MAK Value Documentation 2002]; OECD SIDS, 2001; ATSDR, 2009; Health Council of the Netherlands, 2005).

The conclusions of short-term and long-term, single dose and repeated dose toxicity studies were that nervous system is not a target organ of tributyl phosphate. Even where a NOAEL for neurotoxicity was determined (e.g., Beyrouty et al. 1991), it was higher than 325 mg/kg/day (rat, oral) whereas NOAELs from other aspects of toxicity were doubtlessly lower (such as ca. 25 mg/kg/day, repeated dose, carcinogenicity, rat and mouse). Even if neurotoxic effects were reported in some studies, these usually were unspecific symptoms (the authors declared that the observed effects are indirectly caused by other organ damages and/or general toxicity of tributyl phosphate), and tended to occur only at the highest dose levels, transiently, and without dose-effect relationship (Tributyl phosphate [MAK Value Documentation 2002], OECD SIDS, 2001; ATSDR, 2009; Health Council of the Netherlands, 2005).

The main exposure route for workers directly handling tributyl phosphate is inhalational or dermal. The substance is not accumulated and not volatile (low vapour pressure), but inhalation of mists is possible (although rare). An acute inhalation study (Bayer AG, 1990) gave clear evidence that signs

and symptoms of possible neurotoxicity in rats, exposed to aerosolized tributyl phosphate, developed only at very high concentrations of the substance (2140 mg/m^3, aerosol). Strong general toxicity and respiratory irritation were observed at much lower aerosol concentrations, which indicate (as it was concluded in the study referred to) that the nervous system effects were secondary to these. Consequently, neurotoxicity is not an appropriate base for determining human exposure limits.

Dermal route is another likely way of occupational exposure; neurotoxic studies carried out by dermal administration are, however, scarce. Despite that, there is no reason for concern as dermal toxicity of tributyl phosphate is much lower than inhalational toxicity. This is supported by the fact that no occupational disease has been reported so far. (Tributyl phosphate [MAK Value Documentation 2002], OECD SIDS, 2001; ATSDR, 2009; Health Council of the Netherlands, 2005). Even when humans were exposed to air concentration of 15 mg/m^3 tributyl phosphate, 6 x of REL by NIOSH, no specific neurotoxic symptoms (only nausea and headache) were observed.

Another toxicological evaluation (BG Chemie, 2000) also concluded that neurotoxic effects were detected only after oral exposure to very high doses and the symptoms were transient, but because of this way of administration this evaluation cannot be used to assess human exposure either.

Consumers and the general population are unlikely exposed by tributyl phosphate therefore no relevant neurotoxic effect can be characterized.

Cholinesterase inhibition was mentioned as an initial concern. Thoroughly examining the available scientific literature it could be concluded that cholinesterase inhibition caused by tributyl phosphate is weak (as stated in: Tributyl phosphate [MAK Value Documentation 2002]). Substantial cholinesterase inhibition in exposed animals – by 35%, i.e. to 65% of the non-exposed control – was reported in one study only (Kalinina, 1971) from rats that received a lethal dose of tributyl phosphate (this study was deemed unreliable in several available evaluations). And, compared to relevant human limits, like the biological exposure indicator for occupational tributyl phosphate exposure: blood acetyl- cholinesterase activity lowered to 70% of the original (OECD SIDS, 2001; Maroni et al., 2000); or to cholinesterase decrease up to 50-60%, defined in an article as “mild” (Maroni, Ferioli, 1998), even this 35% decrease does not seem dramatic. Of 15 papers, available *in extenso* or cited in detail in other documents (such as BUA, 1992; OECD SIDS, 2001; Health Council of the Netherlands, 2005), 6 reported cholinesterase activity decrease but it was mostly mild and transient. Other papers mentioned no change or increase. The available data are thus partly

contradictory, but it can be concluded that cholinesterase inhibition due to tributyl phosphate exposure is not a concern.

Significantly reduced nerve conduction velocity was mentioned in several publications, all referring to a single study (Laham et al. 1983). It is clear from this study that the effect was seen only in male rats, after a high dose (ca. 420 mg/kg daily, higher than the NOAEL mentioned above) and was borderline significant. No other animal study, and no report on cases of human exposure, has mentioned nerve damage.

Differently from other organophosphorus compounds tributyl phosphate does not cause organophosphate-induced delayed neuropathy (OPIDN) shown clearly in several studies (Beyrouty et al. 1991; Carrington et al. 1996; Johannsen at al. 1977).

On the base of the above mentioned findings the evaluating Member State could establish that no further experiments are needed to expand the knowledge about tributyl phosphate as sufficient data are available. Consequently, on the base of the above mentioned findings it can be stated that the initial concern about the possible neurotoxic effects of tributyl phosphate is not warranted.

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5.11.2 Human information

5.11.2.1 Neurotoxicity

The main exposure route for workers directly handling tributyl phosphate is inhalational or dermal. The substance is not accumulated and not volatile (low vapour pressure), but inhalation of mists is possible (although rare).

Dermal route is another likely way of occupational exposure; neurotoxic studies carried out by dermal administration are, however, scarce.

Despite that, there is no reason for concern as dermal toxicity of tributyl phosphate is much lower than inhalational toxicity. This is supported by the fact that no occupational disease has been reported so far. (Tributyl phosphate [MAK Value Documentation 2002], OECD SIDS, 2001; ATSDR, 2009; Health Council of the Netherlands, 2005). Even when humans were exposed to air concentration of 15 mg/m^3 tributyl phosphate, 6 x of REL by NIOSH, no specific neurotoxic symptoms (only nausea and headache) were observed. The above information supports that tributyl phosphate has no neurotoxic potential.

Consumers and the general population are unlikely exposed by tributyl phosphate, therefore no relevant neurotoxic effect can be characterized.

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5.11.3 Summary and discussion of specific investigations

Neurotoxicity

Neurotoxicity of tributyl phosphate has been tested in all relevant fields: neurobehavioral, neuropathological, neurophysiological and neurochemical techniques were applied to have a general view on potential neurotoxic property of tributyl phosphate. Based upon the available information the evaluating Member State concluded to the followings.

The conclusion of short term and long term, single dose and repeated dose toxicity studies was that nervous system is not a target organ of tributyl phosphate. Even if neurotoxic effects were reported in some studies, these usually were unspecific symptoms (the authors declared that the observed effects are indirectly caused by other organ damages and/or general toxicity of tributyl phosphate) and tended to occur only at the highest dose levels, transiently and without dose-effect relationship.

The available data regarding cholinesterase inhibition of tributyl phosphate are judged to be slight, consequently it can be concluded that cholinesterase inhibition due do tributyl phosphate exposure is not a concern.

Human data also shows that after inhalation exposure to tributyl phosphate no specific neurotoxic symptoms (only nausea and headache) were observed. Dermal toxicity of tributyl phosphate is much lower than inhalational route of exposure, this is also supported by the fact that no occupational disease has been reported so far on dermal exposure of tributyl phosphate.

Consequently, the evaluating Member State could establish that tributyl phosphate has no neurotoxical property.

The registrant also made specific investigations about the neurotoxic properties of the substance and arrived at the same conclusion.

5.12 Combined effects

Not relevant for this evaluation.

5.13 Derivation of DNEL(s) / DMEL(s)

Not relevant for this evaluation.

5.14 Conclusions of the human health hazard assessment and related classification and labelling

In the course of the targeted substance evaluation, the evaluating Member State, in line with the initial concerns identified in the justification document has examined the following end-points: repeated dose toxicity, mutagenicity, carcinogenicity, toxicity for reproduction (fertility and developmental toxicity) and neurotoxicity.

Based upon the evaluation of available information the evaluating Member State can draw the following conclusions.

Toxicological studies performed with tributyl phosphate involved the liver, testes, kidney, urinary bladder, spleen and the nervous system. The available studies were reliable and sufficient to establish that liver, testes, kidney, spleen and the nervous system are not the target organs of tributyl phosphate.

However, in case of urinary bladder alterations observed in the short term repeated dose toxicological studies, namely different epithelial hyperplasias, postulate the non-genotoxic mode of action that can lead to neoplastic lesions observed in longer term toxicological studies.

Urothelial carcinogenesis in the rat proceeds through a sequence of morphologic changes beginning as simple hyperplasia, an increase in the number of cell layers in the urothelium. It then progresses to nodular and papillary hyperplasia, which resemble the Brunn's nests and papillary neoplasms with low-grade malignant potential in humans. In contrast the mouse commonly proceeds through a process of flat, non-papillary dysplasia, carcinoma *in situ*, and invasive carcinoma with frequent metastases.

Numerous agents have been identified that produce superficial or deep cytotoxicity and regeneration, and are associated with increased incidences of bladder tumors in rodents. Similar toxic and regenerative processes appear to be involved with bladder carcinogenesis in humans related to chronic inflammation, such as schistosomiasis and calculi.

As it is stated in the Guidance on application of CLP criteria, STOT RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class. Based on these considerations the evaluating Member State can conclude that the observed changes in urinary bladder following repeated exposure to tributyl phosphate can be considered as covered appropriately by the Carcinogenic category 2 classification (CLP). The STOT RE classification based on the effects of tributyl phosphate on urinary tract is not necessary if the substance is classified for carcinogenicity.

Evaluation of mutagenic properties of tributyl phosphate confirmed that the substance has no mutagenic activity. The available studies, which were reliable and sufficient, gave negative results.

Concerning the carcinogenic properties of tributyl phosphate there were three available studies in rodents (mice and rats) which can be considered reliable, but also sufficient to evaluate carcinogenicity. In two studies only pro-carcinogenic alterations (i.e. transitional cell carcinoma) were observed by the highest dose (3000 ppm) dietary intake in rats in the urinary bladder of both sexes. Other alterations as bladder hyperplasia and papillomas in the urinary bladder were also found in female rats only at a lower concentration (700 ppm). Similar changes were not found in the same rat strain in earlier reliable studies. No suspicions referring to human carcinogenicity have ever been published. Since no similar effects have been found in mice, these effects might be species specific to rats.

Based on the available and reliable experimental data and the CLP classification criteria, the concerns on possible more serious carcinogenic properties of tributyl phosphate can be rejected, and the current CLP classification as Carcinogenic category 2 can be supported.

The valid two-generation studies, which were adequate and reliable for assessing reproductive and fertility effects of tributyl phosphate, showed no evidence of reproductive toxicity, of reproductive organ pathology, or effects on gestation or lactation at any dose tested. Postnatal toxicity was evident by consistent reductions in F1 and F2 pup body weights at 3000 ppm and occasional weight reductions in F2 litters at 700 ppm, and was associated with maternal toxicity observed at these doses and times. The results of the tests clearly suggest that tributyl phosphate does not have to be

considered as a selective reproductive toxicant as no reproductive parameters were significantly affected at any dose level. No specific adverse effects of tributyl phosphate on the reproduction were reported in the literature as yet. Any effects noted were sporadic and without any clear correlation with the treatment.

Consequently, the available data do not suggest any specific, selective effects of tributyl phosphate on reproductive parameters of fertility. Reproductive organs are not identified as target organs of tributyl phosphate. Classification of tributyl phosphate regarding this end-point is not required.

Furthermore, based on key studies performed in two strains of rats and rabbits, the respective range finding studies and the 2-generation studies in rats, classification of tributyl phosphate is not justified for developmental toxicity either. All these studies, which were reliable and sufficient, showed that embryotoxic and foetotoxic effects such as ossification disturbances occurred only at maternally toxic doses. Further studies for reproductive or developmental toxicity are not required. Based on the appropriately performed primary studies described above, it can be declared that teratogenic effect of tributyl phosphate could not be substantiated; therefore the hazard concern regarding teratogenicity of tributyl phosphate is not justified and classification regarding this end-point is not required either.

Neurotoxicity of tributyl phosphate has been tested in all relevant fields: neurobehavioral, neuropathological, neurophysiological and neurochemical techniques were applied to have a general view on potential neurotoxic property of tributyl phosphate.

The conclusion of short term and long term, single dose and repeated dose toxicity studies was that nervous system is not a target organ of tributyl phosphate. Even if neurotoxic effects were reported in some studies, these usually were unspecific symptoms (the authors declared that the observed effects are indirectly caused by other organ damages and/or general toxicity of tributyl phosphate) and tended to occur only at the highest dose levels, transiently and without dose-effect relationship. The studies were sufficient and reliable. The available data regarding cholinesterase inhibition of tributyl phosphate are judged to be slight, consequently it can be concluded that cholinesterase inhibition due do tributyl phosphate exposure is not a concern.

Human data also shows that after inhalation exposure to tributyl phosphate no specific neurotoxic symptoms (only nausea and headache) were observed.

Based on the evaluation of the above studies for neurotoxicity of the substance the evaluating Member State could conclude that tributyl phosphate has no neurotoxical property. Classification of tributyl phosphate regarding this end-point is not required.

The registrant came to the same conclusions regarding the hazard properties of the substance.

Based on the above findings of substance evaluation, the evaluating Member State can state that the concerns initially identified are not warranted.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

Not relevant for this evaluation.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not relevant for this evaluation.

8 PBT AND VPVB ASSESSMENT

Not relevant for this evaluation.

9 EXPOSURE ASSESSMENT

Not relevant for this evaluation.

10 RISK CHARACTERISATION

Not relevant for this evaluation.

11 OTHER INFORMATION

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13 ABBREVIATIONS

AC	Article Category
AChE	acetylcholinesterase
ATSDR	Agency for Toxic Substances and Disease Registry
BG Chemie	Berufsgenossenschaft Chemie
BUA	Beratergremium für umweltrelevante Altstoffe
BUN	Blood Urea Nitrogen
CAESAR	Computer Assisted Evaluation of Industrial Chemical Substances According to Regulations
CAS	Chemical Abstracts Service
CHO	Chinese Hamster Ovary
CSR	Chemical Safety Report
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
DSD	Dangerous Substances Directive
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
ERC	Environmental Release Category
GLP	Good Laboratory Practice
HSDB	Hazardous Substances Data Bank
HGPRT	Hypoxanthine-Guanine Phosphoribosyltransferase
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
LOEL	Lowest Observed Effect Level
MAK	Maximale Arbeitsplatz-Konzentration
MSCA	Member State Competent Authority
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NIOSH	National Institute for Occupational Safety and Health

NOAEL	No Observable Adverse Effect Level
OPIDN	Organophosphate-Induced Delayed Neuropathy
PBT	Persistent Bioaccumulative and Toxic
PC	Chemical Product
PNEC	Predicted No Effect Concentration
PPE	Personal Protective Equipment
PTT	Partial Thromboplastin Time
PUR	Polyurethane
RBC	Red Blood Cell
REL	Recommended Exposure Limit
RMO	Risk Management Options
SD	Sprague-Dawley
SEV	Substance Evaluation
SIAM	SIDS Initial Assessment Meeting
SIDS	Screening Information Data Set
SLRL	sex-linked recessive lethal
STOT	Specific Target Organ Toxicity
STOT RE	STOT repeated exposure
SU	Sector of End Use
TBP	Tributyl Phosphate
UNEP	United Nations Environment Programme
vPvB	Very Persistent and Very Bioaccumulative
γ-GT	Gamma-Glutamyltransferase