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Triphenyl phosphate

MAK Value Documentation, supplement – Translation of the German version from 2021

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Keywords

triphenyl phosphate; liver; hepatocellular hypertrophy; thyroid; follicle cell hypertrophy; developmental toxicity; maximum concentration at the workplace; MAK value; peak limitation

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated triphenyl phosphate [115-86-6] considering all toxicological end points. Triphenyl phosphate is not neurotoxic in hens and rats and not irritating to the eyes and skin of rabbits. In a 13-week toxicity study with rats, hepatocellular hypertrophy and follicle cell hypertrophy in the thyroid gland started to be not adversely induced at a triphenyl phosphate dose of 105 mg/kg body weight and day. On the basis of the NOEL of 20 mg/kg body weight and day, a maximum concentration at the workplace (MAK value) of 10 ml/m^3 has been established. As its critical effect is systemic, triphenyl phosphate has been assigned to Peak Limitation Category II. The default excursion factor of 2 has been set because its half-life is not known. Triphenyl phosphate is not genotoxic in vitro. In vivo genotoxicity tests and lifetime carcinogenicity studies have not been performed with triphenyl phosphate. In a one-generation study in rats, triphenyl phosphate did not induce any effects on the offspring up to 690 mg/kg body weight and day. In a developmental toxicity study in rabbits, an increased proportion of foetuses per litter with absent accessory lung lobes occurred at 200 mg/kg body weight and day. Thus, the NOAEL for developmental toxicity is 80 mg/kg body weight and day. As there is a sufficiently large margin between this NOAEL and the MAK value, triphenyl phosphate has been assigned to Pregnancy Risk Group C. There are no data demonstrating that triphenyl phosphate is sensitizing to the skin or airways or that it penetrates the skin in toxicologically relevant amounts.

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MAK value (2020)	**10 mg/m³ I (inhalable fraction)**
Peak limitation (2020)	**Category II, excursion factor 2**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2020)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–
Synonyms	phosphoric acid triphenyl ester
Chemical name (IUPAC)	triphenyl phosphate
CAS number	115-86-6
Structural formula	$(C_6H_5O)_3PO$
Molecular formula	$C_{18}H_{15}O_4P$
Molar mass	326.29 g/mol
Melting point	50 °C (ECHA 2019)
Boiling point	decomposes at 410 °C (ECHA 2019)
Vapour pressure at 25 °C	0.00001 hPa (calculated; ECHA 2019)
log K_{OW} at 20 °C	4.63 (ECHA 2019)
Solubility at 20 °C	1.9 mg/l water (ECHA 2019)
Stability	thermal decomposition, formation of phenol and phenyl phosphoric acid esters (Henschler 1991)
Production	reaction of phosphorus oxychloride ($POCl_3$) with phenol at high temperature, purification by distillation (OECD 2002)
Purity	> 99.6% (OECD 2002)
Impurities	other aryl phosphates (Henschler 1991)
Uses	as plasticizer and flame retardant in plastics, as additive in heavy duty lubricants, metal-working fluids and hydraulic oils, in small amounts in adhesives, inks and coatings (OECD 2002)

For triphenyl phosphate, documentation from 1990 is available, in which the substance was assigned to Section IIb of the List of MAK and BAT Values (Henschler 1991). This supplement is based mainly on the publicly available registration data under REACH (ECHA 2019) and unpublished company studies.

According to information in safety data sheets, triphenyl phosphate is used in metal-working fluids or lubricating oils in concentrations of 0.1% to 1% (Exxon Mobil 2021; Hebro Chemie GmbH 2021; ROWE 2021); at these concentrations no irritation is to be expected.

1 Toxic Effects and Mode of Action

Triphenyl phosphate is not neurotoxic in cats and chickens after single oral doses of up to 10 000 mg/kg body weight.

In a 90-day feeding study in male rats, triphenyl phosphate induced dose-dependent centrilobular hepatocellular hypertrophy and hypertrophy of the follicular cells in the thyroid gland at 105 mg/kg body weight and day and above; at this dose, although these findings were regarded as not yet adverse, they were considered to be substance-related. In female animals, centrilobular hepatocellular hypertrophy was observed at about 600 mg/kg body weight and day. At this dose, also the absolute liver weights of male and female rats were increased and vacuolization occurred in cells of the adrenal cortex.

There are only few reliable findings in humans and animals for the skin sensitizing effects of triphenyl phosphate. These show the skin sensitization potential of triphenyl phosphate to be, at best, low. There are no data that indicate that the substance has respiratory sensitization potential.

Triphenyl phosphate is not irritating to the skin and eyes of rabbits.

In rabbits, gavage doses of 200 mg/kg body weight and day caused an increased incidence of foetuses with an absent accessory lobe of the lung.

In vitro genotoxicity studies did not reveal any mutagenic, clastogenic or aneugenic effects. In vivo genotoxicity studies or long-term carcinogenicity studies are not available.

2 Mechanism of Action

Neurotoxic effects, as known from other organophosphates, were not observed with triphenyl phosphate.

The mechanism by which triphenyl phosphate led to hypertrophy of hepatocytes and follicular cells of the thyroid gland in a 90-day feeding study in rats (WIL Research Europe B.V. 2015 a) is unknown. Enzyme induction is regarded as the probable cause. The findings in the thyroid are seen as secondary effects of the induction of UDP-glucuronosyltransferase resulting in increased degradation of T3/T4 and counter-regulation by thyroid-stimulating hormone (WIL Research Europe B.V. 2015 a).

H4IIE cells (rat hepatoma cell line) were used to investigate the scope of cytotoxic effects following exposure to triphenyl phosphate for 48 hours in the MTT assay (capacity to reduce 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide to a formazan), the induction of cytochrome P450 (CYP)1A1, and responses to oxidative stress in the *gpx1* (glutathione peroxidase 1), *gr* (glucocorticoid receptor), *gsta2* (glutathione *S*-transferase alpha 2) and *cat* (catalase) genes. Cell survival was decreased to about 75% in the MTT assay at all concentrations from 1 to 200 µM. In the EROD and MROD assays, enzyme activities were decreased in a statistically significant manner at the concentrations 1 µM and 50 µM, but not at 100 µM. The cyp1a1-mRNA was not increased in a statistically significant manner at the 3 concentrations. Only at 100 µM were gr-mRNA and cat-mRNA increased in a statistically significant fashion to less than 1.5-fold and 1.7-fold, respectively. The corresponding GR or CAT enzyme activities were unchanged. No statistically significant effects of triphenyl phosphate were seen at the other concentrations and for the other genes (Mennillo et al. 2019). The statistically significant changes that occurred in this study were not dose-dependent or were slight and of marginal biological relevance. The effects of triphenyl phosphate in these studies are thus not biologically relevant.

Triphenyl phosphate was tested in various in vitro test systems in comparison with 3,3′,5,5′-tetrabromobisphenol A and 2,2′,4,4′-tetrabromodiphenyl ether, substances known to cause effects in these systems. These studies were used to

distinguish whether triphenyl phosphate causes developmental toxicity or neurotoxicity. Triphenyl phosphate did not have any effects on embryonic stem cell differentiation in mice, neural stem cell proliferation in humans or neuronal growth in rats. At 15.9 µM, triphenyl phosphate inhibited the growth of human nerves and had an acute neurotoxic effect (inhibition of nerve action potentials) in rat nerves at 16.3 µM (Behl et al. 2015). In the oral 13-week study in rats, there were no specific findings in the nerves (WIL Research Europe B.V. 2015 a).

The effect of triphenyl phosphate (0 to 50 µM) and its metabolite, diphenyl phosphate (0 to 100 µM), on 3T3-L1 adipocytes was investigated in vitro. Triphenyl phosphate increased pre-adipocyte proliferation and subsequent differentiation coinciding with increased transcription of regulators of adipogenesis (CEBP alpha, beta, delta, PPARγ). When matured adipocytes were treated with triphenyl phosphate, basal uptake and insulin-stimulated uptake of glucose increased in a way similar to that of 2-deoxy-2-[(7-nitro-2,1,3-benzoxadiazol-4-yl)amino]-D-glucose (2-NBDG). When phosphoinositide 3-kinase, a kinase of the insulin signalling pathway, was inhibited, this effect did not occur. Diphenyl phosphate had no significant effect on cell proliferation and a much lesser effect on adipocyte differentiation and 2-NBDG uptake. Diphenyl and triphenyl phosphate probably induced isoproterenol-induced lipolysis during and after cell differentiation by increasing gene expression. It is suggested that the effect on the cells was the result of endocrine and noradrenergic mechanisms (Cano-Sancho et al. 2017). In the oral 13-week study in rats, there were no specific findings in adipocytes (WIL Research Europe B.V. 2015 a).

In an in vitro study, the effect of 0, 0.1, 1, 10, 50 or 100 µM triphenyl phosphate on the activity and maturation of dendritic cells isolated from the bone marrow of Balb/c mice, which are precursor cells of immune cells, was examined. The expression of histocompatibility complex class II (MHCII) was measured after 24-hour incubation with triphenyl phosphate (purity > 99%). In addition, co-stimulatory molecules and cytokine production were examined. Concentrations of 50 and 100 µM had a cytotoxic effect on dendritic cells (60% and about 15% alive, respectively). At and above 50 µM triphenyl phosphate, there was a statistically significant increase in the expression of MHCII and in the number of the markers CD80, CD86 and CD40 at the cell surface. Triphenyl phosphate induced IL-6 at and above 50 µM, but not IL-10. At cytotoxic concentrations, the enzyme haemoxigenase-1 (measured as mRNA) was induced, which is a marker of oxidative stress. However, this was not statistically significant. The authors concluded that triphenyl phosphate is immunotoxic only at cytotoxic concentrations, which may lead to different effects depending on the maturation state of the dendritic cells. The significance of the evidence of an immunocytotoxic or even immunostimulatory effect in vitro requires further clarification in vivo (Canbaz et al. 2017).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

There are no specific studies of the toxicokinetics and metabolism of triphenyl phosphate. The studies with repeated oral administration indicate that triphenyl phosphate is absorbed.

Triphenyl phosphate is contained in some nail varnishes at up to about 1.68% by weight. The concentration of diphenyl phosphate, a metabolite of triphenyl phosphate, was determined in the urine of 16 female volunteers. They then applied a nail polish containing 0.97% triphenyl phosphate to their nails, and the urinary diphenyl phosphate levels were determined over 24 hours. Ten to 14 hours after the nails were painted these levels were 7 times as high as prior to exposure. To determine the relative contributions of inhalation and dermal absorption, on 2 separate occasions 10 participants painted their nails and synthetic nails adhered to gloves, respectively. Urine was collected beforehand and for 24 hours following applications. When wearing gloves, the urinary levels of diphenyl phosphate were practically unchanged compared with the background levels. The authors concluded from this that the primary exposure route is dermal (Mendelsohn et al. 2016).

An estimation of the amount of triphenyl phosphate absorbed through the skin from nail polish using the ConsExpo model yielded 200 ng/kg body weight and day for the 5th percentile, and 1700 and 5000 ng/kg body weight and day for

the 50th and 95th percentiles, respectively. Compared with other sources (inhalation and ingestion of dust deposited during inhalation and eating), this suggests that dermal absorption is a significant uptake pathway. The modelled permeability coefficient was 0.089 cm per hour, and the log K_{OW} was 4.59 (Tokumura et al. 2019).

Another study, using skin wipe samples, yielded an estimated uptake of 0.3 ng/kg body weight and day (Liu et al. 2017).

Using the IH SkinPerm model according to Tibaldi et al. (2014), a flux of 0.07 µg/cm^2 and hour or a total absorbed amount of 0.14 mg triphenyl phosphate can be calculated for the exposure of 2000 cm^2 of skin to a saturated aqueous triphenyl phosphate solution for 1 hour. The model of Fiserova-Bergerova et al. (1990) yields a considerably higher flux of 4.5 µg/cm^2 and hour or a total absorbed amount of 9 mg triphenyl phosphate.

3.2 Metabolism

The incubation of triphenyl phosphate with rat liver homogenate in the presence and absence of NADPH "and other enzymes" showed that triphenyl phosphate is decomposed to diphenyl phosphate as the major metabolite by the mixed function oxidase system and arylesterase. The metabolic reactions were inhibited almost completely by carbon monoxide in the absence of NADPH, whereas the addition of potassium cyanide, sodium azide, dipyridyl and EDTA had little effect (ECHA 2019).

Seven different conjugates were detected after the incubation of triphenyl phosphate with rat liver microsomes in the presence of glutathione (Figure 1). They were formed via epoxides and monohydroxylated or dihydroxylated compounds. In addition, diphenyl phosphate was formed as a metabolite (Chu and Letcher 2019).

In experimental assays with human liver preparations, other phase I metabolites appeared, most notably a monohydroxylated metabolite, a dihydroxylated metabolite and a metabolite formed from triphenyl phosphate following hydroxylation and O-dearylation. In primary human hepatocytes, less than half of the triphenyl phosphate used was converted to diphenyl phosphate. Other metabolites were formed at amounts lower by a factor of 4 to 10 (Su et al. 2016; Van den Eede et al. 2013, 2016).

The morning urine from 4 male volunteers from Ottawa who were non-smokers was examined on 3 consecutive days. The presence of *p* and *m*-hydroxytriphenyl phosphate glucuronide was detected (Su et al. 2016).

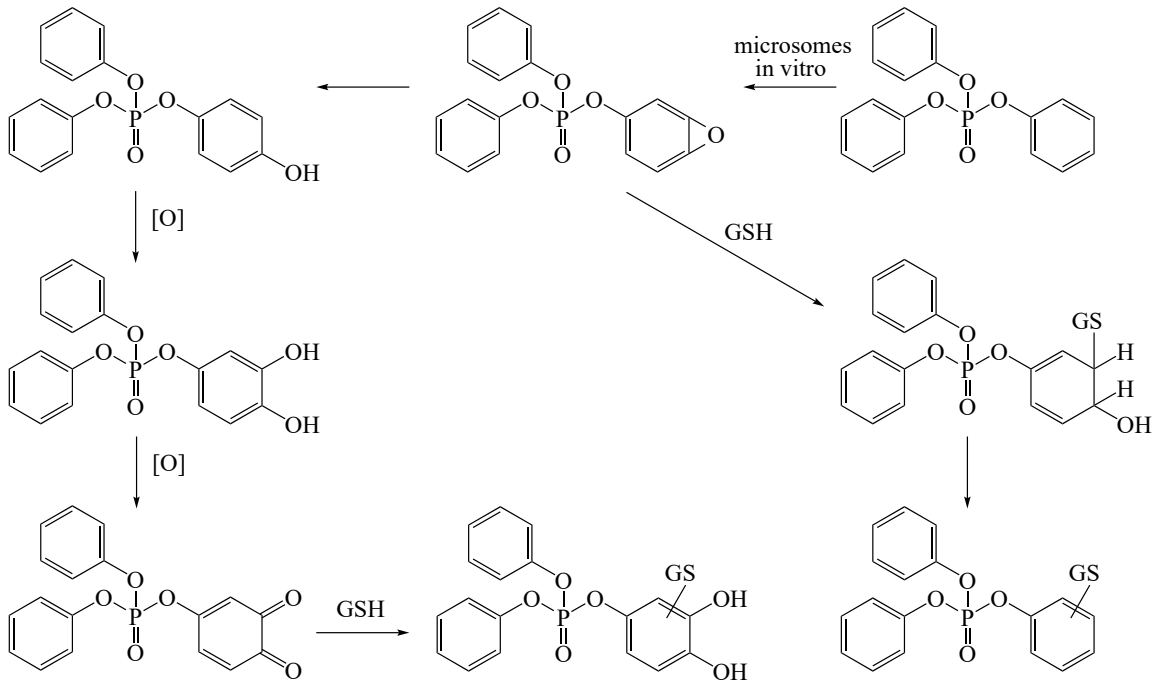

Fig. 1 Metabolites of triphenyl phosphate after incubation with rat liver microsomes (acc. to Chu and Letcher 2019)

4 Effects in Humans

Studies which have not yet been described are available only for the end point sensitization.

Allergenic effects

Sensitization caused by contact with triphenyl phosphate or with products containing triphenyl phosphate have been reported only in rare cases (Henschler 1991).

Between 1950 and 1962, 15 (0.07%) of a total of 23 192 patients examined at the Finsen Institute in Copenhagen were observed to react to the cellulose acetate film containing 7% to 10% triphenyl phosphate (and 3%–4% phthalic acid esters) used there for the patch test. The authors state that 3 of these patients who reacted to the cellulose acetate film were subsequently tested with 10% triphenyl phosphate and 2% tricresyl phosphate (both in acetone), and produced a reaction to both substances (no other details). In another case, skin reactions after contact with copy paper containing tricresyl phosphate were the reason for the patch test, in which the patient produced a 2+ reaction to 1% triphenyl phosphate and 1% tricresyl phosphate. In 487 other consecutively tested patients, no reactions to tricresyl phosphate occurred, and triphenyl phosphate was apparently not tested in these patients (Hjorth 1964).

A patient who reacted in a patch test to the PVC film containing tricresyl phosphate used in this test, and who had previously produced a reaction on the nose to her cellulose acetate spectacle frame containing triphenyl phosphate, was tested once more with both substances. 2+ reactions to 1% triphenyl phosphate both in arachis oil and in acetone and to 5% tricresyl phosphate in arachis oil were observed (no other details). When 16 control subjects were tested, there was 1 positive reaction (no other details) to tricresyl phosphate and 1 questionable reaction to triphenyl phosphate (Pegum 1966). Also, in another case, contact dermatitis on the bridge of the nose and temples was reported; this was attributed to a spectacle frame made from a polymerization product containing triphenyl phosphate. Patch tests with 5% and 0.5% triphenyl phosphate yielded a 2+ reaction after 72 hours, and a 1+ reaction with 0.05% triphenyl phosphate.

A 5% tricresyl phosphate preparation (mixture of *m* and *p*-isomers with 0.08% triphenyl phosphate) likewise induced a 2+ reaction. 2+ and 1+ reactions to preparations of 5% and 0.5% tri-*m*-cresyl phosphate, respectively, occurred, whereas 5% tri-*p*-cresyl phosphate did not produce any reaction (Carlsen et al. 1986).

In another publication, a positive patch test reaction to triphenyl phosphate and resorcinol monobenzoate was reported without further details. The reactions were found in a 12-year-old boy of impaired hearing who had suffered recurrent eczema on the ear for 3 years, caused by the earpieces of his hearing aids, which were replaced about every 6 months. The earpieces were made of a soft acrylate; information on its composition, however, could not be found (Spirig and Elsner 1995).

A 29-year-old man with rhagadiform, psoriasis-like dermatitis on the palms of his hands after several months of hobby activities using an adhesive containing triphenyl phosphate, produced a 2+ reaction to 5% triphenyl phosphate in petrolatum in the patch test at the reading on day 4. No reaction to tricresyl phosphate was observed (Camarasa and Serra-Baldrich 1992). In contrast, a 48-year-old female patient with a vesicular erythematous reaction underneath a plastic prosthesis containing tricresyl phosphate produced a 2+ reaction to 5% tricresyl phosphate in petrolatum, but not to triphenyl phosphate in the patch test after 48 and 96 hours (Grimalt et al. 2009).

A 71-year-old woman, in whom wearing a respiratory mask led to an erythematous reaction after only 1 day and to facial eczema after 5 days, produced a 2+ reaction to 5% triphenyl phosphate in petrolatum in addition to a reaction to the plastic of the mask containing triphenyl phosphite. Testing with triphenyl phosphite was not carried out (Holden et al. 2006). In other cases of reactions to plastics containing triphenyl phosphite, positive reactions were observed to triphenyl phosphite but not to triphenyl phosphate (O'Driscoll et al. 1989; Sasseville and Moreau 2005; Suuronen et al. 2013; Vandevenne et al. 2013). In another publication describing a contact allergic reaction to a PVC plastic containing triphenyl phosphite, a positive patch test result to 5% tricresyl phosphate in petrolatum was reported. The substance was detected in a concentration of about 21 µg/g in addition to about 55 µg triphenyl phosphate/g and 116 µg triphenyl phosphite/g in the PVC gloves used. Patch tests with these 2 substances were apparently not performed (Crépy et al. 2014).

A total of 542 cases of occupational contact allergy were registered at the Finnish Institute of Occupational Health (FIOH) between 1974 and 1983. In 63 and 5 cases, this was caused by rubber and PVC gloves, respectively. Of the 5 patients with reactions to PVC gloves, 1 concrete worker produced a 1+ reaction to triphenyl phosphate and a 2+ reaction to tricresyl phosphate (no other details) and the glove materials in the patch test. Since the ingredients of the two makes of PVC gloves responsible were not known and were not tested, the relevance of these results is unclear (Estlander et al. 1986). The triphenyl phosphate tested at FIOH in a 5% preparation in petrolatum from 1991 to 1996 caused an allergic reaction in 1 of 358 persons tested and led to an irritant reaction in 3 persons. With tricresyl phosphate, likewise tested at a concentration of 5%, no positive reactions were found in 357 patients, but irritant reactions occurred in 6 cases (Kanerva et al. 1997, 1999). In the years from 1985 to 1992, a total of 10 280 patients were examined at the Helsinki University Dermatological Hospital; 343 and 839 were tested with 5% triphenyl phosphate and tricresyl phosphate, respectively. Allergic or irritant reactions were not observed in any case (Tarvainen 1995).

Conclusion: Only few clinical findings are available, some of which are well documented and some of which are not. The results do not provide any reliable evidence that triphenyl phosphate causes sensitization of the skin.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

Inhalation exposure to 200 000 mg triphenyl phosphate "dust"/m³ for 1 hour produced no signs of toxicity and no deaths in 5 male and 5 female Wistar rats. Data for how the exposure concentration was determined are not available (ECHA 2019).

In another insufficiently reported study, 5 CF1 mice were exposed whole-body to a triphenyl phosphate concentration of 363 mg/m³ for 6 hours and 7 mice were exposed to 757 mg/m³ for either 2 or 4 hours. Mortality and clinical toxicity did not occur (ECHA 2019).

5.1.2 Oral administration

In numerous acute toxicity studies, the oral LD_{50} could not be determined because no mortality occurred at doses up to 20 000 mg/kg body weight in rats, up to 5000 mg/kg body weight in mice, up to 4000 mg/kg body weight in guinea pigs, and up to 12 500 mg/kg body weight in chickens. Neurotoxic effects, as known from other organophosphates, were not observed in chickens up to 10 000 mg/kg body weight (ECHA 2019; Henschler 1991).

5.1.3 Dermal application

In rabbits, the dermal LD_{50} was above 7900 mg/kg body weight (OECD 2002).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are still no studies available.

5.2.2 Oral administration

The documentation from 1990 (Henschler 1991) describes 2 studies that are not suitable for the evaluation of triphenyl phosphate.

A 90-day feeding study from 2015, which was carried out according to OECD Test Guideline 408 with triphenyl phosphate (purity 99.5%) in Wistar rats, is now available. The results are presented in Table 1 and 2. Substance intake with the diet was 0, 20, 105 or 583 mg/kg body weight and day in male animals and 0, 22, 117 or 632 mg/kg body weight and day in female animals. No signs of clinical toxicity and no mortality occurred up to the high dose. Motor activity patterns at the beginning of exposure were increased in the males of the high dose group and decreased in the following weeks, but no morphological correlate in the nerves was found. There were no corresponding changes in clinical observations, functional tests or morphological examinations of neuronal tissue. At 105 mg/kg body weight and day, centrilobular hepatocellular hypertrophy occurred in 3 of 10 males (♂: 3 animals grade 1), and at 632 mg/kg body weight and day in all males and females (♂: 3 animals grade 1, 7 animals grade 2; ♀: 7 animals grade 1, 3 animals grade 2) without degenerative changes, which were therefore considered by the authors not to be adverse. The higher severity of hypertrophy of thyroid follicular cells observed only in male rats at 105 and 583 mg/kg body weight and day was evaluated as secondary to the hepatocellular hypertrophy and not adverse. The findings observed in the stomach of female rats at 117 mg/kg body weight and day and above and in the adrenal glands at 583/632 mg/kg body weight and day were also present in control animals at a similar incidence and severity, and were therefore considered not adverse (vacuolization of the limiting ridge between forestomach and glandular stomach, vacuolization of the zona fasciculata or zona glomerulosa of the adrenal gland). In addition, food intake was increased, body weight gains

were decreased (♂ –21%, ♀ –12%), and the liver weights were increased. Only the increased liver weights in the high dose group were regarded by the authors to be adverse (♂ +30% and ♀ +21%). At the high dose, the thyroid glands of male rats were enlarged and their weights increased (WIL Research Europe B.V. 2015 a). In male rats, centrilobular hepatocellular hypertrophy and hypertrophy of follicular cells in the thyroid gland occurred at 105 and 583 mg/kg body weight and day. At the high dose of 583/632 mg/kg body weight and day, the findings in the liver were observed in both male and female animals. The hypertrophy of follicular cells occurred with greater severity. Although the findings in the male animals at 105 mg/kg body weight and day according to different criteria (Hall et al. 2012; WHO 2015) were evaluated as not adverse, they nevertheless demonstrate an initial dose–effect relationship of an effect which is to be avoided. Therefore, the Commission considers the NOEL (no observed effect level) to be 20 mg/kg body weight and day. Vacuolization of adrenal cortical cells is a typical finding with similar organophosphates, for example tricresyl phosphate, isomers, "free of *o*-isomers" (Hartwig and MAK Comission 2023). A substance-specific effect is therefore probable.

Tab. 1 Effects of triphenyl phosphate in rats after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 5 ♂	**4 days**, 0, 55, 110, 220, 441, 881 mg/kg body weight and day, gavage, purity > 99%	gene expression investigations in the liver on day 5 (Affymetrix microarray); most sensitive end points for which BMD and BMDL median values could be obtained: HDL cholesterol (BMD 79 mg/kg body weight; BMDL 39 mg/kg body weight) and total cholesterol (BMD 142 mg/kg body weight; BMDL 90 mg/kg body weight) in serum, absolute and relative liver weights (BMD 136 and 103 mg/kg body weight; BMDL 48 and 71 mg/kg body weight, respectively); at all doses: serum cholinesterase 35%–70% ↓ (no BMD calculable); free thyroxine at and above 220 mg/kg body weight ↓ (BMD 178 mg/kg body weight; BMDL 139 mg/kg body weight); **gene expression examination**: 14 gene sets with altered transcription with BMD median values below the extrapolation limit of 18.3 mg/kg body weight, also including regulator genes of the cholesterol metabolism (GO:0090181) and hormone transport (GO:0009914); gene sets with reliably calculable BMD median: cellular polysaccharide biosynthesis process (GO:0033692) and oligodendrocyte development (GO:0014003) each BMD 19 mg/kg body weight and BMDL 11 mg/kg body weight; single genes: markedly increased transcription: Ces2c and Cyp2b1 with maximum increase by a factor of 16.3 and 10.5, respectively (BMD median values below the extrapolation limit of 18.3 mg/kg body weight); particularly decreased transcription: Scd and G6pc with maximum decrease by a factor of 11.1 and 5.1 (BMD median values below the extrapolation limit of 18.3 mg/kg body weight, BMDL 16 mg/kg body weight); **conclusion**: most sensitive BMD for gene sets: 19 mg/kg body weight (BMDL 11 mg/kg body weight) and for systemic effect HDL cholesterol (BMD 79 mg/kg body weight; BMDL 39 mg/kg body weight) and serum cholinesterase inhibition at and above 55 mg/kg body weight	NTP 2018
rat, Wistar, 5 ♂, 5 ♀	**28 days**, 0, 250, 1000, 4000 mg/kg diet, ♂: 0, 23, 104, 508 mg/kg body weight and day, ♀: 0, 39, 161, 701 mg/kg body weight and day, purity 99.6%, OECD Test Guideline 407	**range-finding study** with FOB and MA examination as tests for neurotoxicity; **23 mg/kg body weight: NOAEL (♂);** **104 mg/kg body weight:** body weight gains ↓ (♂), swollen eosinophilic appearance and hypertrophy of periportal hepatocytes (♂), ASAT activity ↓ (♂), cholesterol level ↑ (♂); **161 mg/kg body weight: NOAEL (♀);** **508/701 mg/kg body weight:** food intake ↑, absolute (♂: 22%, ♀: 13%) and relative liver weights ↑, swollen eosinophilic appearance and hypertrophy of periportal hepatocytes (♀), ASAT activity ↓ (♀), cholesterol concentration ↑ (♀)	Bayer HealthCare AG 2007

Tab. 1 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 10 ♂, 10 ♀	**90 days**, 0, 300, 1500, 7500 mg/kg diet, ♂: 0, 20, 105, 583 mg/kg body weight and day, ♀: 0, 22, 117, 632 mg/kg body weight and day, purity 99.5%, OECD Test Guideline 408	in week 12–13 FOB examinations also of hearing, pupillary and righting reflex, grip strength fore and hind limbs, motor activity test; **20 mg/kg body weight: NOEL**; **20/22 mg/kg body weight and above**: no changes in clinical observations or functional tests or morphological examinations of neuronal tissue, slight dose-related decrease in body weights (♂); **105/117 mg/kg body weight and above**: morphological changes in liver, thyroid (♂), adrenal glands, stomach (♀) (Table 2); enlarged and reddish-brown liver with centrilobular hepatocellular hypertrophy (♂), severity of hypertrophy of follicular cells of thyroid ↑ (♂), cholesterol ↑ (♂) without histopathological correlate, findings at this dose not adverse but substance-related; **583/632 mg/kg body weight**: motor activity not significantly ↑ (♂) decreased by habituation, food intake ↑ (♂ 16%, ♀ 12%), body weight gains ↓ (♂ 21%, ♀ 12%), absolute and relative liver weights ↑ (♂ absolute 30%, ♀ absolute 21%), enlarged (1/10 ♂) reddish-brown (17/20) liver with centrilobular hepatocellular hypertrophy (♀), thyroid gland enlarged and absolute and relative thyroid weights ↑ (♂ absolute 28%) – possibly secondary to liver hypertrophy, clinical biochemistry – not adverse since no histopathological correlates: cholesterol ↑, total protein ↑ (♂), calcium ↑ (♂), prothrombin time ↓ (not considered adverse since elevated values would be toxicologically relevant), haemoglobin and MCV and MCH ↓ (♀) without further haematological changes	WIL Research Europe B.V. 2015 a

ASAT: aspartate aminotransferase; BMD: benchmark dose with a benchmark response of one standard deviation from the control value; BMDL: benchmark dose lower confidence limit; FOB: functional observational battery; MA: motor activity; MCH: mean corpuscular haemoglobin; MCV: mean corpuscular volume (of an erythrocyte)

Tab. 2 Findings in the 90-day feeding study with triphenyl phosphate in rats (WIL Research Europe B.V. 2015 a)

		Dose [mg/kg body weight and day]			
		0	**20/22 ♂/♀**	**105/117 ♂/♀**	**583/632 ♂/♀**
Body weights at the end of study (g)	♂	425 ± 32	413 ± 31 (97%)	407 ± 41 (96%)	386 ± 35 (91%)
	♀	230 ± 16	219 ± 19 (95%)	221 ± 17 (96%)	207 ± 15 (90%)
Liver weights					
absolute (difference in % to the control value)	♂		+3.7	+6.5	+30.3**
	♀		−3.1	−2.7	+21.4**
relative to body weight (difference in % to the control value)	♂		+6.9*	+1.3**	+43.3**
	♀		+1.7	+1.7	+35**
Thyroid gland weights					
absolute (difference in % to the control value)	♂		±0[a)]	±0[a)]	+27.8**
relative to body weight (difference in % to the control value)	♂		±0[a)]	±0[a)]	+50**
Liver					
centrilobular hepatocellular hypertrophy					
grade 1	♂	0/10	0/10	3/10	3/10
	♀	0/10	0/10	0/10	7/10
grade 2	♂	0/10	0/10	0/10	7/10
	♀	0/10	0/10	0/10	3/10

Tab. 2 *(continued)*

		Dose [mg/kg body weight and day]			
		0	**20/22 ♂/♀**	**105/117 ♂/♀**	**583/632 ♂/♀**
Thyroid gland					
hypertrophy of follicle cells					
grade 1	♂	8/10	6/10	6/10	3/10
	♀	2/10	1/10	3/10	2/10
grade 2	♂	0/10	0/10	2/10	6/10
grade 3	♂	0/10	0/10	0/10	1/10
Adrenal glands					
vacuolization in fasciculate zone					
grade 1	♂	1/10	2/10	1/10	3/10
grade 2	♂	0/10	0/10	0/10	2/10
vacuolization zona glomerulosa					
grade 1	♀	0/10	1/10	1/10	1/10
grade 2	♀	0/10	0/10	0/10	2/10
Stomach					
vacuolization of the limiting ridge					
grade 1	♀	0/10	0/10	1/10	4/10
grade 2	♀	0/10	0/10	1/10	1/10
hyperplasia/hyperkeratosis of the limiting ridge					
grade 1	♀	0/10	0/10	0/10	1/10

*$p \leq 0.05$; **$p \leq 0.01$
a) same mean weight as in controls

Groups of 10 male Sprague-Dawley rats were given triphenyl phosphate at doses of 0, 161, 345, 517 or 711 mg/kg body weight and day in their diet for 4 months. Before the start of treatment and every 4 weeks thereafter, neurotoxicity was examined by means of the open-field test (orientation ability) and the rotarod test (motor coordination and balance), and forelimb grip strength and negative geotaxis were examined. The standard parameters commonly used in repeated-dose toxicity studies were determined only in some cases. Slightly retarded body weight gains were observed in the 3 higher dose groups (ECHA 2019); therefore, the NOAEL (no observed adverse effect level) was 161 mg/kg body weight and day, but no effects occurred in the behavioural tests at any dose.

5.2.3 Dermal application

Triphenyl phosphate doses of 0, 100 or 1000 mg/kg body weight and day were applied non-occlusively to 5 male and 5 female New Zealand White rabbits per dose for 6 hours a day, 21 to 23 days, on 5 days per week. The substance was applied to the intact skin, and in another 5 animals per dose and sex to the abraded dorsal skin. The animals wore collars to prevent ingestion of the substance. The only substance-related observation was a reduction in the acetylcholinesterase activity in plasma, erythrocytes and brain (no other details; ECHA 2019).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Triphenyl phosphate was not irritating to the rabbit skin (ECHA 2019; Henschler 1991), including in a study conducted in 1990 in accordance with OECD Test Guideline 404 at a purity of 99.7% (ECHA 2019).

5.3.2 Eyes

Triphenyl phosphate was not irritating to the rabbit eye (ECHA 2019; Henschler 1991; OECD 2002), including in a study conducted in 1990 in accordance with OECD Test Guideline 405 at a purity of 99.7% (ECHA 2019; OECD 2002).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In a maximization test carried out according to OECD Test Guideline 406 in Dunkin Hartley guinea pigs, triphenyl phosphate was not sensitizing. No reaction was observed in any of the 10 animals at the challenge treatment. Intradermal induction was carried out with 5%, topical induction was performed with 75%, and the challenge treatment with 75% and 50% triphenyl phosphate in arachis oil in each case (ECHA 2019).

In a study from 1992, female B6C3F1 mice were pre-treated with Freund's complete adjuvant in a modified mouse ear swelling test, followed by the application of acetone solutions of 3% or 10% triphenyl phosphate. Animals pre-treated with the 3% and 10% preparations produced a statistically significant positive response (no other details) 2 days after the challenge treatment. The 10% preparation, but not the 3% preparation, also caused an increase in lymphocyte proliferation (no other details) (ECHA 2019). It is not clear from the documentation, which is available only as a summary, whether lymphocyte proliferation was determined after the induction or after the challenge phase.

5.4.2 Sensitizing effects on the airways

There are still no studies available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

Doses of 0, 100 or 300 mg triphenyl phosphate/kg body weight and day were administered with the diet to groups of 7 four-week-old male ICR mice for 35 days, and the body weights, weights and biochemical parameters of the liver as well as the weights and testosterone levels of the testis were determined. Also histopathological examination of the right testis was performed in 2 animals per dose group to determine the number of seminiferous tubules. In animals given 300 mg/kg body weight and day, the body weights were decreased to about 87.5% to 80% of the control values, the liver weights were unaffected, liver enzymes indicating oxidative stress were increased, and the absolute testis weights were decreased by about 20%. Likewise, at 300 mg/kg body weight and day, the testosterone level was reduced, the number of seminiferous tubules decreased, and the Sertoli cells were slightly disorganized (Chen et al. 2015). As only a few animals were examined, the findings were mild and not described in detail, and the amount of substance in the diet was not analytically confirmed, the relevance of the findings is unclear.

In a one-generation study, male and female Sprague Dawley rats were fed diets containing 0%, 0.25%, 0.50%, 0.75% or 1.00% triphenyl phosphate from 4 weeks after weaning, for 91 days before and during mating and gestation. During gestation, this corresponded to triphenyl phosphate doses of 0, 166, 341, 516 and 690 mg/kg body weight and day. There was no treatment-related systemic toxicity nor effects on fertility (Welsh et al. 1987).

5.5.2 Developmental toxicity

In a one-generation study with investigation of teratogenicity, male and female Sprague Dawley rats were fed diets containing 0%, 0.25%, 0.50%, 0.75% or 1.00% triphenyl phosphate from 4 weeks after weaning, for 91 days before and during mating and gestation. During gestation, this corresponded to triphenyl phosphate doses of 0, 166, 341, 516 and 690 mg/kg body weight and day. The number of pregnant animals was in the range from 29 to 38 per group. The foetuses were delivered by Caesarean section on day 20 of gestation, and all foetuses were examined for external

malformations. Half of the foetuses were examined for visceral and half for skeletal malformations using the Wilson technique and Alizarin red, respectively. No developmental toxicity and no substance-related malformations occurred. At 690 mg/kg body weight and day, the body weights of the dams were marginally decreased. The NOAEL for maternal and developmental toxicity was 690 mg/kg body weight and day (ECHA 2019; Henschler 1991; Welsh et al. 1987). A very detailed study of the foetuses including a presentation of the results with regard to foetuses and litters was performed, as specified in the OECD test guidelines. Thus, triphenyl phosphate was not teratogenic in this study with rats.

In the range-finding study to a developmental toxicity study according to OECD Test Guideline 414, New Zealand White rabbits were given gavage doses of triphenyl phosphate of 0, 83, 250 or 750 mg/kg body weight and day. The animals in the high dose group and 1 animal in the middle dose group died or had to be killed in extremis. The remaining rabbits in the middle dose group and all animals in the low dose group survived the remainder of the preliminary study without signs of toxicity. On the basis of these results, triphenyl phosphate doses of 0, 32, 80 or 200 mg/kg body weight and day were selected for the main study from gestation days 6 to 28. At 200 mg/kg body weight and day, the incidence of foetuses with a specific malformation (lungs with absent accessory lobe) was increased. The incidences were 1/188 (1/19), 0/181 (0/19), 1/183 (1/20), 3/172 (3/20) for foetuses (litter) at the dose levels 0, 32, 80, 200 mg/kg body weight and day, respectively. The proportion per litter was 0.5 ± 2.09%, 0.0 ± 0.00%, 0.5 ± 2.24% and 1.6 ± 4.03%, respectively. At the high dose, this finding was detected in another litter of 2 foetuses delivered preterm. This increased the incidence to 5 (4) or the proportion per litter to 2.4%. The highest proportion per litter in the laboratory's historical controls from 2010 to 2014 with 2787 foetuses examined for visceral malformations from 315 litters was 1.7% (3 (3)). Because the incidence of lungs with absent accessory lobes observed at 200 mg/kg body weight and day, including foetuses delivered preterm, was only slightly higher than the incidence in historical controls, this malformation was regarded by the authors to be incidental and not toxicologically relevant. Otherwise, no substance-related findings occurred, so that the NOAEL for maternal and developmental toxicity was considered to be 200 mg/kg body weight and day, the highest dose tested (WIL Research Europe B.V. 2015 b). The finding "lung with absent accessory lobe" is evaluated in different ways, by some authors as a malformation, by some as a variation or also as a finding between variation and malformation ("absent lung lobe"; BfR 2021). According to the OECD test guideline, a thorough examination of preterm foetuses does not have to be performed. The Commission included all 5 foetuses with absent accessory lobes in their evaluation. The proportion per litter of 2.4% is thus above the value of the historical controls of 1.7%. Therefore, the NOAEL is considered to be 80 mg/kg body weight and day.

Pregnant UCE-T2DM rats were given 170 µg triphenyl phosphate per day with their diet from day 8 of gestation up to the end of the lactation period. UCE-T2DM rats are a strain whose pathophysiology and progression of type 2 diabetes mellitus (T2DM) is similar to that of humans. Metabolic phenotypes and leptin and cumulative energy (kcal) intake were determined after 3.5 months in the offspring. Male offspring and untreated weight-matched male UCE-T2DM rats were observed up to the age of 6 months and examined for signs of obesity and type 2 diabetes mellitus. Regardless of body mass, offspring exposed to triphenyl phosphate exhibited accelerated development of type 2 diabetes mellitus and increased plasma levels of non-esterified fatty acids during fasting (Green et al. 2017). This non-standardized study with a specific study end point and with only 1 dose is not suitable for assessing the developmental toxicity of triphenyl phosphate.

5.6 Genotoxicity

5.6.1 In vitro

In the Salmonella typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 and in Saccharomyces cerevisiae D4, triphenyl phosphate was not mutagenic up to 5000 and 10 000 µg/plate, respectively, in the presence and absence of a metabolic activation system. An assay for the induction of DNA repair synthesis in Syrian hamster fibroblasts yielded negative results. Triphenyl phosphate was not clastogenic in the chromosomal aberration test in Chinese hamster V79 cells. The result of a micronucleus test in Syrian hamster embryonic fibroblasts was weakly positive: control 18 ± 4.9 per 2000 cells, 28.7 ± 4.0 per 2000 cells as the highest value at 5×10^{-5} M (lower effects at other concentrations in the

range from 10^{-6} M to 10^{-4} M; ECHA 2019). Triphenyl phosphate yielded negative results in the $TK^{+/-}$ test (OECD Test Guideline 476) (ECHA 2019; Henschler 1991).

The following describes studies carried out since the documentation from 1990 (Henschler 1991):

In the Salmonella mutagenicity test according to OECD Test Guideline 471, triphenyl phosphate (purity 99.7%) was not mutagenic or bacteriotoxic in the strains TA98, TA100, TA102, TA1535 or TA1537 up to 5000 µg/plate with and without pre-incubation and in the presence and absence of a metabolic activation system. There was also no inhibition of growth, though slight precipitation did occur at 5000 µg/plate. The positive control yielded the expected result (Bayer HealthCare AG 2011).

In the chromosomal aberration test in V79 cells of the Chinese hamster according to OECD Test Guideline 473, triphenyl phosphate was investigated in the presence (up to 60 µg/ml) and absence (up to 21 µg/ml) of a metabolic activation system and with incubation times of 4 and 18 hours. No precipitation occurred, but cytotoxicity was observed: at and above 7 µg/ml after 4 hours and at 10 µg/ml after 18 hours of incubation in the absence of the metabolic activation system and at and above 20 µg/ml in the presence of the metabolic activation system. A clastogenic effect of triphenyl phosphate was not observed. The positive control yielded the expected result (Bayer HealthCare AG 2008).

5.6.2 In vivo

There are still no studies available.

5.7 Carcinogenicity

No evidence of carcinogenic effects of triphenyl phosphate (purity 95%–99.9%) was found in a mouse lung adenoma short-term test in A/St mice from 1977. These animals have a very high sensitivity to carcinogens resulting in a short latency period and higher tumour rate. For this purpose, 20 male animals per dose group were given intraperitoneal injections of 20 mg/kg body weight (18 doses, 3 per week), 40 mg/kg body weight (3 doses within 1 week) or 80 mg/kg body weight (a single dose) with a follow-up observation period of 18 to 24 weeks. The study was terminated on the same day for all dose groups, and the lung surface was examined for nodules. Some of these nodules were examined histopathologically to confirm that they were adenomas. Eighteen of 20 animals in the low dose group, 3 of 20 animals in the middle dose group and 12 of 20 animals in the high dose group survived. Adenomas occurred only in animals of the high dose group; the increase in the incidence was not statistically significant. The positive control urethane induced 19.6 tumours per mouse with 100% survival (no other details; ECHA 2019). There was no information about a negative control group.

6 Manifesto (MAK value/classification)

There are only few statements regarding effects in humans, such as questionable findings, which at best indicate a low skin sensitizing potential. The critical effect in oral studies with rats is centrilobular hepatocellular hypertrophy.

MAK value. In a 90-day feeding study, triphenyl phosphate caused centrilobular hepatocellular hypertrophy and hypertrophy of thyroid follicular cells in a dose-dependent manner at and above 105 mg/kg body weight and day in male rats. These findings were evaluated as not yet adverse but substance-related. In female animals, centrilobular hepatocellular hypertrophy occurred only at 632 mg/kg body weight and day. The findings indicate enzyme induction (WIL Research Europe B.V. 2015 a). In male animals, the onset of a dose–response relationship is thus evident at 105 mg/kg body weight and day and above, and the NOEL is 20 mg/kg body weight and day.

A benchmark calculation for the end point centrilobular hepatocellular hypertrophy (severity of grade 1 and 2) in the subchronic feeding study in rats results in a $BMDL_{10}$ of 21 mg/kg body weight and day (model averaging) and a $BMDL_{05}$ of 10 mg/kg body weight. Thus, a similar dose is obtained as starting point for the calculation of the MAK value.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOEL of 20 mg triphenyl phosphate/kg body weight and day to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding toxicokinetic species-specific correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. Due to a possible increase in effects over time (1:2) and as this value is derived from a NOEL based on experimental studies with animals (1:2), the concentration extrapolated for the workplace is 12.5 mg/m^3. From this, using the preferred value approach, a MAK value of 10 mg/m^3 for the inhalable fraction can be derived. Since the substance is not irritating to the skin and eyes of rabbits, an irritant effect on the respiratory tract is not to be expected for exposure at the level of the MAK value.

Peak limitation. The MAK value is derived from a systemic effect. Therefore, triphenyl phosphate has been assigned to Peak Limitation Category II. Since data for the half-life are not available, the default excursion factor of 2 has been set.

Prenatal toxicity. In a valid and well-documented one-generation feeding study with investigation of the teratogenicity of triphenyl phosphate in Sprague Dawley rats, the NOAEL for maternal and developmental toxicity was 690 mg/kg body weight and day, the highest dose tested. Triphenyl phosphate was not found to be teratogenic (ECHA 2019; Henschler 1991; Welsh et al. 1987).

In a prenatal developmental toxicity study in New Zealand White rabbits with gavage administration from gestation days 6 to 28, carried out according to OECD Test Guideline 414, an increased proportion of foetuses with an absent accessory lobe of the lung per litter was observed at 200 mg/kg body weight and day (see Section 5.5.2; WIL Research Europe B.V. 2015 b); the Commission therefore considers the NOAEL for developmental toxicity to be 80 mg/kg body weight and day, and that for maternal toxicity to be 200 mg/kg body weight and day.

The toxicokinetic extrapolation of the NOAEL for developmental toxicity of 690 mg triphenyl phosphate/kg body weight and day for the rat and of 80 mg/kg body weight and day for the rabbit results in concentrations in the air of 1691 mg/m^3 and 233 mg/m^3, respectively, using the assumptions described above (see Section "MAK value" above, species-specific correction values: rat: 1:4, with 7 days feeding of the rats in comparison with 5 days per week exposure at the workplace; rabbit: 1:2.4 without extrapolation to a 5-day working week in humans). As the 169-fold and 23-fold margins between the calculated concentrations in the air and the MAK value of 10 mg/m^3 I (inhalable fraction) are sufficiently large, triphenyl phosphate has been assigned to Pregnancy Risk Group C.

Carcinogenicity. There are no long-term carcinogenicity studies. A short-term study with intraperitoneal administration to investigate carcinogenic effects in the lung of mice provided no evidence of carcinogenic effects of triphenyl phosphate. Studies of genotoxicity and its structure likewise produced no evidence from which a carcinogenic potential could be suspected. Triphenyl phosphate continues not to be classified in one of the categories for carcinogens.

Germ cell mutagenicity. Mutagenicity tests in Salmonella typhimurium and a chromosomal aberration test in Chinese hamster V79 cells with triphenyl phosphate yielded negative results. These studies complement the previously described genotoxicity studies in vitro, the results of which were likewise negative (Henschler 1991). In vivo data are not available. Since genotoxic effects are not suspected also due to its structure, triphenyl phosphate continues not to be classified in one of the categories for germ cell mutagens.

Absorption through the skin. From the concentration of 12.5 mg/m^3 extrapolated for the workplace (see above), a daily tolerable intake of 125 mg triphenyl phosphate is calculated for 100% absorption by inhalation and a 10 m^3 respiratory volume. From model calculations, the dermal absorption of triphenyl phosphate under standard conditions (saturated aqueous solution, 2000 cm^2 of skin, exposure for 1 hour) results in absorbed amounts of 0.14 mg and 9 mg, respectively, that is a maximum of about 7% of the systemically tolerable amount. Therefore, triphenyl phosphate continues not to be designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Only few clinical findings are available, some of which are well documented, which do not provide reliable evidence for skin sensitization. A guinea pig maximization test performed according to test guidelines yielded a negative result. A modified mouse ear swelling test and a modified test for the measurement of lymphocyte transformation, which were not performed according to the test guidelines, yielded possibly positive results that cannot be included in the evaluation. Overall, a skin sensitization potential of triphenyl phosphate cannot be sufficiently inferred from the available, in some cases contradictory, data. Data for sensitization of the airways are not available. Therefore, triphenyl phosphate continues not to be designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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