The MAK Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

O,O,O-Triphenyl monothiophosphate

MAK Value Documentation – Translation of the German version from 2021

A. Hartwig[1,*] MAK Commission[2,*]

1 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

2 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords

O,O,O-triphenyl monothiophosphate; liver; hepatocellular hypertrophy; thyroid; thyroid follicle cell hypertrophy; thyroid colloid; maximum concentration at the workplace; MAK value; peak limitation

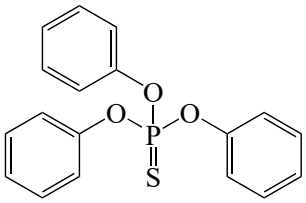
Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated *O,O,O*-triphenyl monothiophosphate [597-82-0] considering all toxicological end points. *O,O,O*-Triphenyl monothiophosphate is not neurotoxic in hens and rats and not irritating to the eyes and skin of rabbits. In an oral 13-week toxicity study with rats, increased liver weights and hepatocellular hypertrophy in addition to follicle cell hypertrophy and altered colloid in the thyroid gland were observed at 200 mg/kg body weight and day. On the basis of the NOAEL of 39.5 mg/kg body weight and day, a maximum concentration at the workplace (MAK value) of 20 mg/m^3 has been established. As its critical effect is systemic, *O,O,O*-triphenyl monothiophosphate has been assigned to Peak Limitation Category II. The default excursion factor of 2 has been set because its half-life is not known. *O,O,O*-Triphenyl monothiophosphate was not found to be mutagenic in 2 tests with Salmonella and a mixture of triphenyl thiophosphate with butylated derivatives was not found to be clastogenic or mutagenic in vitro. In vivo genotoxicity tests and carcinogenicity studies have not been performed with *O,O,O*-triphenyl monothiophosphate. A screening study carried out according to OECD Test Guideline 421 to investigate the reproductive toxicity and toxicity of *O,O,O*-triphenyl monothiophosphate did not report any effects on perinatal reproduction; studies specifically investigating developmental toxicity are not available. The substance has therefore been assigned to Pregnancy Risk Group D. There are no studies which demonstrate that *O,O,O*-triphenyl monothiophosphate is sensitizing to the skin or airways. The substance does not penetrate the skin in toxicologically relevant amounts.

Citation Note:
Hartwig A, MAK Commission. O,O,O-Triphenyl monothiophosphate. MAK Value Documentation – Translation of the German version from 2021. MAK Collect Occup Health Saf. 2023 Sep;8(3):Doc061. https://doi.org/10.34865/mb59782e8_3or

Manuscript completed:
16 Apr 2020

Publication date:
29 Sep 2023

MAK value (2020)	**20 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 D**
Germ cell mutagenicity	–
BAT value	–
Synonyms	phosphorothioic acid, O,O,O-triphenyl ester O,O,O-triphenyl thiophosphate triphenyl phosphorothioate
Chemical name (IUPAC)	triphenoxy(sulfanylidene)-λ5-phosphane
CAS number	597-82-0
Structural formula	
Molecular formula	$C_{18}H_{15}O_3PS$
Molar mass	342.349 g/mol
Melting point	53 °C (ECHA 2020)
Boiling point	> 255 °C, decomposes before boiling (ECHA 2020)
Vapour pressure at 25 °C	3.01×10^{-7} hPa (ECHA 2020)
log K_{OW}	5.0 at 23 °C and pH 6.4 (ECHA 2020)
Solubility	0.02 or 0.038 mg/l water at 20 °C and pH 7 (ECHA 2020)
Stability	stable at room temperature, not easily inflammable (ECHA 2020)
Production	no data
Purity	90% to 99% (Molbase 2020)
Impurities	no data
Uses	in lubricants in open systems or machines (ECHA 2020)

For certain end points, data for the mixture of *O,O,O*-triphenyl thiophosphate and its *tert*-butylphenyl derivatives (CAS Number 192268-65-8) are included.

1 Toxic Effects and Mode of Action

O,O,O-Triphenyl monothiophosphate is not neurotoxic. In a 90-day gavage study in Wistar rats, doses of 200 mg/kg body weight and day and above led to increased liver weights and centrilobular hepatocellular hypertrophy, in addition to hypertrophy of the follicular cells and altered colloid in the thyroid gland.

In a study in rats carried out according to OECD Test Guideline 421 with daily gavage doses of *O,O,O*-triphenyl monothiophosphate of 1000 mg/kg body weight, the number of nipples and the mean number of nipple areolae observed in male pubs were increased on postnatal day 13.

O,O,O-Triphenyl monothiophosphate is not irritating to the skin and eyes of rabbits and there is no evidence of a sensitizing potential of the substance. *O,O,O*-Triphenyl monothiophosphate is not mutagenic in the Salmonella typhimurium strains TA98 and TA100 in vitro. In vivo genotoxicity or carcinogenicity studies are not available.

2 Mechanism of Action

In an in vitro test, no inhibition of acetylcholinesterase activity was observed at *O,O,O*-triphenyl monothiophosphate concentrations of 39 to 5000 µg/ml. At concentrations of 2500 µg/ml and above, the substance precipitated in the medium. The positive control yielded the expected result (RCC Cytotest Cell Research GmbH 2002).

Triphenyl phosphate, presumably the main metabolite of *O,O,O*-triphenyl monothiophosphate, was not neurotoxic in cats and chickens (Hartwig and MAK Commission 2023).

In a 90-day gavage study in rats, liver hypertrophy and hypertrophy/hyperplasia of thyroid follicular cells were reported (BASF SE 2019). The findings in the thyroid gland are considered to be secondary effects of the liver hypertrophy, the induction of UDP-glucuronosyltransferase and the subsequently increased breakdown of T3/T4 (thyroxine/tetraiodothyronine) and counter-regulation by TSH (thyroid-stimulating hormone). This was confirmed by corresponding investigations (BASF SE 2018).

O,O,O-Triphenyl monothiophosphate did not exhibit androgenic or antiandrogenic activities in yeast expressing the human androgen receptor and β-galactosidase reporter gene in the yeast antiandrogen screening assay at concentrations of 10^{-10} to 10^{-4} M. The positive controls dihydrotestosterone and dihydrotestosterone with hydroxyflutamide yielded the expected result (BASF SE 2012 a).

In the yeast oestrogen screening assay using yeast cells expressing the human oestrogen receptor (no other data) and β-galactosidase reporter gene, *O,O,O*-triphenyl monothiophosphate did not exhibit oestrogenic or antioestrogenic activities at concentrations of 10^{-10} to 10^{-4} M. The positive controls 17β-oestradiol and hydroxytamoxifen yielded the expected result (BASF SE 2012 b).

O,O,O-Triphenyl monothiophosphate caused significant direct inhibition of antigen presentation in human monocytes from blood donations at concentrations of 1 µM and above (Esa et al. 1988).

3 Toxicokinetics and Metabolism

There are no specific studies of the toxicokinetics of *O,O,O*-triphenyl monothiophosphate. The substance is poorly soluble in water and can presumably be hydrolytically cleaved to form phenol (ECHA 2020). However, this has not been proven in experiments.

The toxic effects that occurred with repeated administration to rats suggest oral absorption.

There are no studies of dermal absorption of the substance. Using the IH SkinPerm model (Tibaldi et al. 2014), a flux of 2×10^{-3} µg/cm^2 and hour and a total absorbed amount of about 4 µg can be calculated for the exposure of 2000 cm^2 of

skin for 1 hour to a saturated solution of *O,O,O*-triphenyl monothiophosphate. A corresponding estimation according to Fiserova-Bergerova et al. (1990) yields a flux of 0.2 µg/cm^2 and hour and a total absorbed amount of 0.3 mg.

The substance is probably metabolized to triphenyl phosphate, which is epoxidized, hydrolysed, conjugated with glutathione and eliminated primarily in the urine. Also diphenyl phosphate has been detected as a metabolite (Hartwig and MAK Commission 2023).

4 Effects in Humans

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no data available.

5.1.2 Oral administration

The LD_{50} for *O,O,O*-triphenyl monothiophosphate dissolved in polyethylene glycol found in a study with groups of 5 male and 5 female Tif RAIf rats was greater than 10 000 mg/kg body weight. Within 2 hours of dosing, sedation, dyspnoea, exophthalmos, hunched posture and ruffled fur were observed in all dose groups. The animals recovered within 8 days. After 14 days, 1 female animal of the middle dose group died (Ciba-Geigy Limited 1976 a).

5.1.3 Dermal application

There are no data available for the effects of dermal application of *O,O,O*-triphenyl monothiophosphate.

In a study carried out according to OECD Test Guideline 402 with a mixture of ***O,O,O*-triphenyl thiophosphate and its *tert*-butylphenyl derivatives**, the undiluted application of 2000 mg/kg body weight did not cause mortality in HanIbm:Wistar rats. There were no signs of systemic or clinical toxicity and no gross-pathological findings. The LD_{50} was thus greater than 2000 mg/kg body weight (RCC Cytotest Cell Research GmbH 1997 a).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available.

5.2.2 Oral administration

In a study carried out according to OECD Test Guideline 421, groups of 10 male and 10 female Wistar rats were given daily gavage doses of *O,O,O*-triphenyl monothiophosphate as an aqueous solution at doses of 0, 100, 300 or 1000 mg/kg body weight per day (see Table 1 and Section 5.5.2). At and above 300 mg/kg body weight and day, centrilobular hepatocellular hypertrophy in the liver and increased relative ovarian weights were observed in the females. At the high dose, absolute and relative liver weights were increased in both sexes and, in addition, absolute and relative ovarian and thyroid weights in the females. At this dose, the male parents had increased TSH and decreased T4 levels and, in addition, minimal to slight hypertrophy/hyperplasia of the follicular cells (8 of 10 animals) and altered colloid (5 of

10 animals) were diagnosed in the thyroid gland. However, the thyroid weights of the male animals were not increased. The authors reported a NOAEL (no observed adverse effect level) of 300 mg/kg body weight and day for male animals and a NOAEL of 1000 mg/kg body weight and day for female animals because the liver findings were not considered to be adverse (BASF SE 2018). The Commission considers the NOAEL for females to be 100 mg/kg body weight and day, because of the increased relative ovarian weights and the slight hypertrophy in the liver at 300 mg/kg body weight and day. This thus indicates the onset of a dose–response relationship.

In a 90-day toxicity study according to OECD Test Guideline 408 in Wistar rats with daily gavage doses as an aqueous solution, increased relative liver weights, centrilobular hepatocellular hypertrophy and minimal hypertrophy/hyperplasia of thyroid follicular cells with a very slight change in the colloid were observed at and above 200 mg/kg body weight and day (Table 1). The number of affected animals and the severity of the findings are shown in Table 2. At the high dose of 1000 mg/kg body weight and day, the findings were more severe. Hypertrophy/hyperplasia of thyroid follicular cells are considered secondary effects of the liver hypertrophy (indication of enzyme induction). Thyroid hormones were not determined. The NOAEL was 39.5 mg/kg body weight per day (BASF SE 2019).

Tab. 1 Effects of *O,O,O*-triphenyl monothiophosphate after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, Wistar, 10 ♂, 10 ♀	**about 65 days ♀, about 25 days ♂**, 0, 100, 300, 1000 mg/kg body weight and day, 7 days/week, gavage, purity 99.9%, OECD Test Guideline 421	**100 mg/kg body weight**: **NOAEL ♀**; **300 mg/kg body weight**: **NOAEL ♂**; **300 mg/kg body weight and above**: centrilobular hepatocellular hypertrophy ♀; relative ovarian weights 17% ↑; **1000 mg/kg body weight**: absolute liver weights ↑, relative liver weights ♀ 19% ↑ and ♂ 21% ↑, absolute and relative ovarian weights ↑ (relative 20%), absolute and relative thyroid weights ↑ (relative 23%), TSH ♂ ↑, T4 ♂ ↓, thyroid follicular cell hypertrophy/hyperplasia, colloid in thyroid changed	BASF SE 2018
rat, Wistar, 10 ♂, 10 ♀	**90 days**, 0, 39.5, 200, 1000 mg/kg body weight and day, 7 days/week, gavage, purity 99.9%, OECD Test Guideline 408	**39.5 mg/kg body weight**: **NOAEL**; **200 mg/kg body weight**: relative liver weights ↑ (♂, ♀), centrilobular hepatocellular hypertrophy (5/10 ♀, minimal), minimal to slight thyroid follicular hypertrophy/hyperplasia (6/10 ♂) with minimal to slight changes in the colloid, see Table 2; **1000 mg/kg body weight**: relative and absolute liver weights ↑ (♂, ♀), centrilobular hepatocellular hypertrophy (4/10 ♂ minimal to slight, all ♀ minimal to moderate), minimal to slight thyroid follicular hypertrophy/hyperplasia (7/10 ♂) with minimal to slight changes in the colloid; FOB at the end of the study did not yield substance-related findings	BASF SE 2019

FOB: functional observational battery; T4: tetraiodothyronine; TSH: thyroid-stimulating hormone

Tab. 2 Findings in the 90-day gavage study with daily administration of *O,O,O*-triphenyl monothiophosphate to rats (BASF SE 2019)

		Dose [mg/kg body weight and day]			
		0	**39.5**	**200**	**1000**
liver					
weight changes relative to controls	♂		+4.17%	+6.8%*	+20.9%**
	♀		–3.84%	+5.6%*	+18.6%**
centrilobular hepatocellular hypertrophy					
grade 1	♂	0/10	0/10	0/10	2/10
	♀	0/10	0/10	5/10	5/10
grade 2	♂	0/10	0/10	0/10	2/10
	♀	0/10	0/10	0/10	4/10
grade 3	♀	0/10	0/10	0/10	1/10

Tab. 2 *(continued)*

		Dose [mg/kg body weight and day]			
		0	**39.5**	**200**	**1000**
thyroid gland					
hypertrophy/hyperplasia follicular cells					
grade 1	♂	2/10	1/10	5/10	6/10
	♀	0/10	1/10	0/10	2/10
grade 2	♂	0/10	0/10	1/10	1/10
changed colloid					
grade 1	♂	1/10	1/10	6/10	4/10
	♀	0/10	1/10	0/10	0/10
grade 2	♂	1/10	1/10	1/10	3/10

*$p \leq 0.05$; **$p \leq 0.01$

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

O,O,O-Triphenyl monothiophosphate applied as dry substance was not irritating to the intact rabbit skin but slightly irritating to the scarified skin with a primary irritation index of 1.2 (on a scale with a maximum of 8) after occlusive application for 24 hours. Three male and 3 female animals were treated. After removal of the patch after 24 hours, erythema was observed on the intact dorsal skin with a score of 1 in 3 animals and a score of 2 in 2 animals; oedema with a score of 1 was found in 2 animals (maximum score of 4 in each case). After 72 hours, there were no more findings at the application site in the animals with intact skin, but erythema with a score of 1 was still apparent in 4 animals with scarified skin (Ciba-Geigy Limited 1976 c).

5.3.2 Eyes

An amount of 0.1 g of *O,O,O*-triphenyl monothiophosphate instilled into one eye of 6 rabbits was not irritating. In 3 animals the exposed eye was rinsed 1 minute after application of the substance. There were no unusual findings in the cornea, iris or conjunctivae in any of the animals (Ciba-Geigy Limited 1976 b).

5.4 Allergenic effects

There are no data available for *O,O,O*-triphenyl monothiophosphate alone.

However, a maximization test was performed in guinea pigs with a mixture of ***O,O,O*-triphenyl thiophosphate and its *tert*-butylphenyl derivatives** (exact concentrations not specified). Intradermal induction was performed with a 1% preparation of the mixture in Alembicol D (coconut oil product); topical induction with 0.4 ml of the undiluted mixture was carried out under occlusive conditions for 48 hours by fixation of a cloth soaked with the substance. Challenge treatment was performed occlusively for 24 hours with a 50% preparation in Alembicol D and with 0.2 ml of the undiluted mixture. None of the 5 control animals pretreated with Freund's complete adjuvant or the 10 male guinea pigs in the treatment group produced any reaction or displayed systemic effects 24 and 48 hours after the challenge treatment. The positive control, hexyl cinnamic aldehyde, yielded the expected result (ECHA 2020; Huntingdon Life Sciences Ltd 1995 b).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

Based on a 14-day preliminary study with daily gavage doses of *O,O,O*-triphenyl monothiophosphate of 0, 50, 100, 250, 500 or 750 mg/kg body weight and day given to groups of 3 male and 3 female rats, doses of 0, 25, 125 and 500 mg/kg body weight and day were chosen for the main study carried out according to OECD Test Guideline 422 with groups of 10 male and 10 female Sprague Dawley rats. The male animals were exposed for 35 days and the females until day 4 of lactation. At and above 25 mg/kg body weight and day, histopathological changes occurred in the adrenal glands (hypertrophy of the adrenal cortex) and thyroid gland (follicular epithelial cell hypertrophy) of the female parent animals, and at and above 125 mg/kg body weight and day in the mammary tissue (mammary gland hypertrophy) of the male animals and liver (centrilobular hepatocellular hypertrophy) of the male and female parent animals. At 500 mg/kg body weight and day, the body weight gains of the female parent animals were reduced. Decreased implantation and foetal survival were reported at and above 125 mg/kg body weight and day. The fertility index was 100%, 100%, 88.9% and 80% at 0, 25, 125 and 500 mg/kg body weight and day, respectively. The NOAEL was thus 25 mg/kg body weight and day for the dams and fertility (Charles River Laboratories 2011; ECHA 2020). The findings in the offspring of this study did not appear plausible, which is why a further study was carried out according to OECD Test Guideline 421 (see Section 5.5.2). In this study, no effects of *O,O,O*-triphenyl monothiophosphate on the offspring were found (BASF SE 2018). Therefore, the findings of the study according to OECD Test Guideline 422 are not included in the evaluation of *O,O,O*-triphenyl monothiophosphate.

5.5.2 Developmental toxicity

O,O,O-Triphenyl monothiophosphate was administered daily as an aqueous solution by gavage to groups of 10 male and 10 female Wistar rats at doses of 0, 100, 300 or 1000 mg/kg body weight and day in a study carried out according to OECD Test Guideline 421. The findings are described in Section 5.2.2 and shown in Table 1. At and above 300 mg/kg body weight and day, centrilobular hepatocellular hypertrophy in the liver and increased relative ovarian weights were observed in the female animals. At 1000 mg/kg body weight and day, increased absolute and relative liver weights and increased absolute and relative ovarian and thyroid weights were observed in the females. In the male offspring, more animals (90%; 44.7% in the control group) with nipples (mean 2.5; in controls 1.2) and areolae were found at day 13 of life; the numbers were increased in a dose-dependent manner compared with the numbers in the controls. This finding was statistically significant only at 1000 mg/kg body weight and day and was outside the range of variation in the historical control data. The authors reported a NOAEL of 300 mg *O,O,O*-triphenyl monothiophosphate/kg body weight and day for male offspring and a NOAEL of 1000 mg/kg body weight and day for the female parents and female offspring (see Table 1), as the liver findings were not considered adverse (BASF SE 2018). Since the relative weights of the liver, ovaries and thyroid gland increased in a dose-dependent manner in the females, and in the middle dose group the relative ovarian weight was increased by 17% compared with that in the control group, the NOAEL for the dams is considered to be 100 mg *O,O,O*-triphenyl monothiophosphate/kg body weight and day. The NOAEL for perinatal toxicity is the high dose of 1000 mg/kg body weight and day because only findings up to postnatal day 4 were included for this purpose. The NOAEL for postnatal toxicity is also 1000 mg/kg body weight and day for the female offspring and 300 mg/kg body weight and day for the male offspring, although developmental toxicity is not investigated fully in studies carried out according to OECD Test Guideline 421.

5.6 Genotoxicity

5.6.1 In vitro

O,O,O-Triphenyl monothiophosphate was not mutagenic in the presence or absence of a metabolic activation system in the Salmonella typhimurium strains TA98 and TA100. The test concentrations for this substance were not specified; other substances studied in this publication were tested up to 500 or 5000 µg/plate (Breau et al. 1985).

The mixture of ***O,O,O*-triphenyl thiophosphate and its *tert*-butylphenyl derivatives** was not mutagenic in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and in Escherichia coli WP2 *uvr*A up to the concentration of 5000 µg/plate in the presence and absence of a metabolic activation system from livers of Aroclor 1254-treated rats. The positive controls yielded the expected result; cytotoxicity was not observed (Huntingdon Life Sciences Ltd 1995 a).

The mixture of ***O,O,O*-triphenyl thiophosphate and its *tert*-butylphenyl derivatives** dissolved in DMSO did not cause chromosomal aberrations in Chinese hamster V79 cells up to the concentration of 1000 µg/ml. Treatment intervals were 4 hours in the presence, and 18 or 28 hours in the absence of a metabolic activation system. Cells were prepared 18 or 28 hours after the addition of the substance. Cytotoxicity in the form of a maximum of 50% surviving cells occurred in the absence of a metabolic activation system at concentrations of 100 µg/ml and above, and in the presence of an activation system at 1000 µg/ml. The substance precipitated at 300 µg/ml and above. A shift in osmolality or pH was not observed in the reaction solution. The mitotic index and cell number were decreased in the presence and absence of a metabolic activation system at 300 µg/ml and above (RCC Cytotest Cell Research GmbH 1997 b).

In a hypoxanthine guanine phosphoribosyl transferase (HPRT) gene mutation test in CHO cells (a cell line derived from Chinese hamster ovary) carried out according to OECD Test Guideline 476, the mixture of ***O,O,O*-triphenyl thiophosphate and its *tert*-butylphenyl derivatives** was not mutagenic in the presence or absence of a metabolic activation system from phenobarbital-induced rat liver. Exposure lasted for 4 or 24 hours to concentrations of up to 5000 µg/ml in the absence of the activation system or for 4 hours to 800 or 1250 µg/ml in the presence of the activation system. Cytotoxicity occurred only in the presence of the metabolic activation system (35% survival at 312 µg/ml and above compared with that in the controls). The positive and negative controls yielded the expected results (BASF SE 2011).

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

There are no data available.

6 Manifesto (MAK value/classification)

There are no data for the effects of *O,O,O*-triphenyl monothiophosphate in humans. The critical effects in gavage studies in rats were centrilobular hepatocellular hypertrophy, and follicular cell hypertrophy and slightly altered colloid in the thyroid.

MAK value. A NOAEL of 39.5 mg/kg body weight and day can be derived for the rat from a 90-day gavage study. Slightly increased liver weights, centrilobular hepatocellular hypertrophy, follicular cell hypertrophy and altered deposition of colloid in the thyroid gland were observed at and above 200 mg/kg body weight and day. The findings in the thyroid are regarded as secondary effects of the liver hypertrophy, the induction of UDP-glucuronosyltransferase and the subsequently increased breakdown of T3/T4 and counter-regulation by TSH (BASF SE 2019).

The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL of 39.5 mg *O,O,O*-triphenyl monothiophosphate/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 species-specific toxicokinetic 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 obtained from a NOAEL from experimental studies with animals (1:2), the extrapolated

workplace concentration is 24.2 mg/m^3. Using the preferred value approach, a MAK value of 20 mg *O*,*O*,*O*-triphenyl monothiophosphate/m^3 for the inhalable fraction can be derived.

Peak limitation. As the MAK value is derived from a systemic effect, *O*,*O*,*O*-triphenyl monothiophosphate has been classified in Peak Limitation Category II. Data for the half-life of the substance are not available. Therefore, the default excursion factor of 2 is set for *O*,*O*,*O*-triphenyl monothiophosphate.

Prenatal toxicity. A prenatal developmental toxicity study is not available.

In a study with male and female Wistar rats carried out according to OECD Test Guideline 421, the maternal NOAEL was 100 mg/kg body weight and day because the relative weights of the liver, ovaries and thyroid gland increased in a dose-dependent manner at and above 300 mg/kg body weight and day. The NOAEL for perinatal toxicity was 1000 mg/kg body weight and day (BASF SE 2018). In studies according to OECD Test Guideline 421, no histopathological examination of the offspring is performed, so that sufficient investigations of developmental toxicity are not available. Therefore, *O*,*O*,*O*-triphenyl monothiophosphate has been assigned to Pregnancy Risk Group D.

Carcinogenicity and germ cell mutagenicity. There are no studies of the carcinogenicity of *O*,*O*,*O*-triphenyl monothiophosphate. Mutagenicity tests in 2 Salmonella strains yielded negative results. The mixture of ***O,O,O*-triphenyl thiophosphate and its *tert*-butylphenyl derivatives** did not cause chromosomal aberrations in Chinese hamster V79 cells and yielded negative results in the HPRT assay in CHO cells. There are also no in vivo studies for this compound. In view of the structure of *O*,*O*,*O*-triphenyl monothiophosphate, genotoxic or carcinogenic effects are not to be expected. *O*,*O*,*O*-Triphenyl monothiophosphate has therefore not been classified in any of the categories for germ cell mutagens or carcinogens.

Absorption through the skin. There are no studies available for the absorption of *O*,*O*,*O*-triphenyl monothiophosphate through the skin. From the systemically tolerable concentration of 24.2 mg/m^3 derived above, a daily tolerable intake of 242 mg *O*,*O*,*O*-triphenyl monothiophosphate is calculated (10 m^3 respiratory volume per day, 100% absorption by inhalation). However, model calculations for the dermal absorption of *O*,*O*,*O*-triphenyl monothiophosphate under standard conditions (saturated aqueous solution, exposure of 2000 cm^2 of skin for 1 hour) yielded very low absorbed amounts of 0.004 mg or 0.3 mg. *O*,*O*,*O*-Triphenyl monothiophosphate is therefore not designated with an “H” (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no data for sensitizing effects in humans and no positive results from experimental studies in animals or from in vitro studies. *O*,*O*,*O*-Triphenyl monothiophosphate has therefore not been 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.

References

BASF SE (2011) In vitro gene mutation test in CHO cells (HPRT locus assay). Project No 50M0450/10M068, 18 Mar 2011, Ludwigshafen: BASF SE, unpublished

BASF SE (2012 a) O,O,O-Triphenylphosphorothioate testing for potential androgenic and antiandrogenic activity using the YAS-Assay [AR] (Yeast androgenic screening). Project No 11V0610/11M318, 01 Oct 2012, Ludwigshafen: BASF SE, unpublished

BASF SE (2012 b) O,O,O-Triphenylphosphorothioate testing for potential estrogenic and antiestrogenic activity using the YES-Assay [ERa] (Yeast estrogen screening). Project No 10V0610/11M317, 01 Oct 2012, Ludwigshafen: BASF SE, unpublished

BASF SE (2018) O,O,O-Triphenylphosphorothioate reproduction/developmental toxicity study screening test in Wistar rats, oral administration (gavage). Project No 80R0610/11R264, 22 Jan 2018, Ludwigshafen: BASF SE, unpublished

BASF SE (2019) O,O,O-Triphenylphosphorothioate repeated-dose 90-day oral toxicity study in Wistar rats administration by gavage. Project No 50C0610/11S274, 09 Jan 2019, Ludwigshafen: BASF SE, unpublished

Breau AP, Mitchell WM, Swinson J, Field L (1985) Mutagenic and cell transformation activities of representative phosphorothioate esters in vitro. J Toxicol Environ Health 16(3–4): 403–413. https://doi.org/10.1080/15287398509530750

Charles River Laboratories (2011) A combined repeated dose toxicity study with a reproduction/developmental toxicity screening test of O,O,O-Triphenylphosphorothioate administration by oral gavage in rats. LAS00033, 12 Apr 2011, Wickliffe, OH: Charles River Laboratories, unpublished

Ciba-Geigy Limited (1976 a) Acute oral LD50 in the rat. Project No Siss 5111, 14 Jan 1976, Basel: Ciba-Geigy Limited, unpublished

Ciba-Geigy Limited (1976 b) E.4 – Eye irritation in the rabbit. Project No Siss 5111, 07 May 1976, Basel: Ciba-Geigy Limited, unpublished

Ciba-Geigy Limited (1976 c) Skin irritation in the rabbit after single application. Project No Siss 5111, 07 May 1976, Basel: Ciba-Geigy Limited, unpublished

ECHA (European Chemicals Agency) (2020) O,O,O-Triphenyl phosphorothioate (CAS Number 597-82-0). Registration dossier. Joint submission, first publication 25 Jun 2013, last modification 24 May 2020. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/13644, accessed 04 Jun 2020

Esa AH, Warr GA, Newcombe DS (1988) Immunotoxicity of organophosphorus compounds. Modulation of cell-mediated immune responses by inhibition of monocyte accessory functions. Clin Immunol Immunopathol 49(1): 41–52. https://doi.org/10.1016/0090-1229(88)90093-1

Fiserova-Bergerova V, Pierce JT, Droz PO (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med 17(5): 617–635. https://doi.org/10.1002/ajim.4700170507

Hartwig A, MAK Commission (2023) Triphenyl phosphate. MAK Value Documentation, supplement – Translation of the German version from 2021. MAK Collect Occup Health Saf 8(3): Doc062. https://doi.org/10.34865/mb11586kske8_3ad

Huntingdon Life Sciences Ltd (1995 a) Bacterial mutation assay. CBG 731/952570, CG Test No 954069, 21 Dec 1995, Cambridgeshire: Huntingdon Life Sciences Ltd, unpublished

Huntingdon Life Sciences Ltd (1995 b) Skin sensitization in the guinea-pig. CBG 739/952772/SS954072, 01 Dec 1995, Cambridgeshire: Huntingdon Life Sciences Ltd, unpublished

Molbase (2020) Triphenyl phosphorothionate, CAS number 597-82-0. http://www.molbase.com/cas/597-82-0.html, accessed 10 Feb 2020

RCC Cytotest Cell Research GmbH (1997 a) Acute dermal toxicity study. RCC Project 666393, 27 Oct 1997, Roßdorf: RCC Cytotest Cell Research GmbH, unpublished

RCC Cytotest Cell Research GmbH (1997 b) In vitro chromosome aberration assay in Chinese hamster V79 cells. Project 593600, 01 Dec 1997, Roßdorf: RCC Cytotest Cell Research GmbH, unpublished

RCC Cytotest Cell Research GmbH (2002) Evaluation of an inhibitory effect of IRGALUBE TPPT on acetylcholinesterase. Project 758403, 15 Nov 2002, Roßdorf: RCC Cytotest Cell Research GmbH, unpublished

Tibaldi R, ten Berge W, Drolet D (2014) Dermal absorption of chemicals: estimation by IH SkinPerm. J Occup Environ Hyg 11(1): 19–31. https://doi.org/10.1080/15459624.2013.831983