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Tricresyl phosphate, isomers, “free of *o*-isomers”

MAK Value Documentation – Translation of the German version from 2020

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Keywords

tricresyl phosphate; adrenal glands; ovaries; maximum workplace concentration; MAK value; toxicity; hazardous substance; peak limitation; developmental toxicity; reproductive toxicity

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated tricresyl phosphate, isomers [1330-78-5], “free of *o*-isomers” considering all toxicological end points. The para and meta isomers do not cause severe effects on the CNS. In a 90-day inhalation study with rats, 300 mg/m^3 did not induce neurotoxic effects. The critical effects of tricresyl phosphate, isomers, “free of *o*-isomers” in oral 2-year studies were higher grades of cytoplasmic vacuolation in the adrenal glands and hyperplasia of the interstitial cells of ovaries at 15 mg/kg body weight and day in female rats. The NOAELs were 13 mg/kg body weight and day for male rats (highest dose tested) and 7 mg/kg body weight and day for females. In male mice, the NOAEL was 7 mg/kg body weight and day based on ceroid pigmentation, foci and changes in the fat cells of the liver at 13 mg/kg body weight and day. In female mice, ceroid pigmentation in the adrenals occurred as from the lowest dose of 8 mg/kg body weight and day. Ceroid pigmentation in adrenals is common in older mice and therefore of questionable relevance for humans. A maximum concentration at the workplace (MAK value) of 5 mg/m^3 was derived for the inhalable fraction based on the NOAEL of 7 mg/kg body weight and day determined in female rats and male mice. As a systemic effect is critical, Peak Limitation Category II and the default excursion factor of 2 are assigned. A NOAEL of 100 mg/kg body weight and day was found in a developmental toxicity study in rats and a NOAEL of 62.5 mg/kg body weight and day in a 1-generation study in mice. Workplace concentrations of 175 and 88 mg/m^3 are calculated from these values. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and tricresyl phosphate, isomers, “free of *o*-isomers” are assigned to Pregnancy Risk Group C. Tricresyl phosphate, isomers, “free of *o*-isomers” were not mutagenic or clastogenic in vitro and did not increase tumour incidences in a 2-year study in rats or mice. Model calculations do not predict dermal uptake in toxicologically relevant amounts. There are no data that show that tricresyl phosphate, isomers, “free of *o*-isomers” are skin or airway sensitizers.

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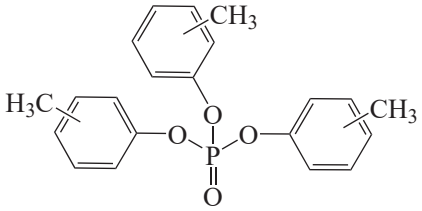
MAK value (2019)	**5 mg/m³ I (inhalable fraction)**
Peak limitation (2019)	**Category II, excursion factor 2**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2019)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
Synonyms	phosphoric acid tris(methylphenyl) ester tris(methylphenyl) phosphate tritolyl phosphate (in each case without *o*-isomers)
Chemical name	tris(4-methylphenyl) phosphate for the tri-*p*-isomer
CAS number	tri-*p*-isomer: 78-32-0 tri-*m*-isomer: 563-04-2 mixture including the *o*-isomers: 1330-78-5
Structural formula	 m-m-m, m-m-p, m-p-p, p-p-p
Molecular formula	$C_{21}H_{21}O_4P$
Molar mass	368.37 g/mol
Melting point[a)]	–33 °C (NCBI 2017 a)
Boiling point at 1013 hPa	> 400 °C (ECHA 2019)
Density at 20 °C	1.172 g/cm³ (ECHA 2019)
Vapour pressure at 25 °C	8×10^{-7} hPa (NCBI 2017 a)
log K_{OW}	5.11 (NCBI 2017 a)
Solubility	0.36 mg/l water at 25 °C (NCBI 2017 a)
Stability	no data
Production	reaction of cresols with phosphoroxychloride (NTP 1994)
Purity	> 99% (Sigma-Aldrich 2020)
Impurities	*o*-isomers, earlier up to 30%, today max. 1%, more probably 0.3% (ACGIH 2016), 0 to 2% tri-*o*-cresyl phosphate (Duarte et al. 2017)

Uses	among others, as a flame retardant in hydraulic fluids and lubricants, as a plasticizer in polyvinyl chloride and rubbers, as a petrol additive, in polyurethane foams, nitrocellulose lacquers, photochemicals, surface treatment products and synthetic resins (NICNAS 2017)

[a] The physico-chemical data refer to tricresyl phosphate containing an unspecified amount of *o*-isomers (CAS No. 1330-78-5).

This documentation uses the term tricresyl phosphate, isomers, "free of *o*-isomers", to refer to tricresyl phosphates that do not contain a cresyl moiety methylated at the *ortho* position. Specifically, these are the 4 isomers *m*-*m*-*m*-tricresyl phosphate, *m*-*m*-*p*-tricresyl phosphate, *m*-*p*-*p*-tricresyl phosphate and *p*-*p*-*p*-tricresyl phosphate. The CAS number 78-32-0 is used for both *p*-*p*-*p*-tricresyl phosphate and mixtures of tricresyl phosphate, "free of *o*-isomers" (Winder and Balouet 2002). Kronitex® tricresyl phosphate is one of the mixtures of tricresyl phosphate, free of *o*-isomers, that has been investigated by a number of studies. Triesters containing only *m*-isomers or *p*-isomers do not cause organophosphate-induced delayed neuropathy (OPIDN). This disorder is induced only if at least 1 of the 3 cresyl groups has a methyl group substituted at the *o*-position (NTP 1994). For the evaluation of *o*-tricresyl phosphate isomers, see Hartwig and MAK Commission (2023 a).

The studies evaluated for this documentation investigated commercially available mixtures of tricresyl phosphates containing the tri-*o*-isomer in concentrations of 0.07% (ECHA 2019) or < 0.1% (NTP 1994). Other sources found that commercial products today contain < 0.2% tri-*o*-cresyl phosphate (Wolkoff et al. 2016). However, the fraction of tri-*o*-cresyl phosphate determined in commercial mixtures of tricresyl phosphates by another source were much higher at up to 2% tri-*o*-cresyl phosphate (Duarte et al. 2017). There are no data available for the tricresyl phosphate concentrations used in hydraulic fluids. Aircraft engine oils contain *o*-tricresyl phosphate isomers in sum amounts of less than 50 mg/kg. An oil produced with 3% tricresyl phosphate would therefore contain about 1.7 mg of *o*-isomers per gram of tricresyl phosphate, which is equivalent to 0.17%. These are primarily mono-*o*-isomers, which are more neurotoxic than di-*o*-cresyl phosphate and tri-*o*-cresyl phosphate (De Nola et al. 2008; Winder and Balouet 2002). In the following, the term tricresyl phosphate, "free of *o*-isomers", is used for tricresyl phosphate, isomers, "free of *o*-isomers".

1 Toxic Effects and Mode of Action

All tricresyl phosphate isomers are readily absorbed after oral and dermal exposure and probably also after exposure by inhalation. Tricresyl phosphate, "free of *o*-isomers", has low acute toxicity in animals. There are no data in humans available that can be attributed with certainty to tricresyl phosphate, "free of *o*-isomers".

In rabbits, tricresyl phosphate, "free of *o*-isomers", was not irritating to the skin and, at most, slightly irritating to the eyes.

The studies investigating the induction of sensitizing effects did not provide data for the composition of the tricresyl phosphates examined. For this reason, it cannot be assumed that the tricresyl phosphates were "free of *o*-isomers". There are only few findings in humans for skin sensitizing effects; these findings are not regarded as reliable. A borderline positive result is available from a local lymph node assay (LLNA) in mice, which cannot be clearly interpreted and demonstrates, at best, a very slight skin sensitizing potential. There are no data for the sensitizing effects of tricresyl phosphate on the respiratory tract.

In a 90-day inhalation study with daily exposure of rats to the aerosol of a tricresyl phosphate mixture at concentrations up to 1000 mg/m^3, body weight gains were reduced at the high concentration of 1000 mg/m^3. This effect was not observed at the middle concentration of 300 mg/m^3. In a 2-year feeding study with a mixture of 79% tricresyl phosphate (21% tri-*m*-cresyl phosphate, 4% tri-*p*-cresyl phosphate, < 0.1% tri-*o*-cresyl phosphate, other unidentified tricresyl phosphates) and 18% dicresyl phosphate, a dose-dependent decrease in the serum cholinesterase activity was observed. Up to the highest doses tested of 15 mg/kg body weight and day in rats and 37 mg/kg body weight and day

in mice, slight effects on grip strength were observed, but only after 3 months, and not after 9, 15 and 24 months. At all time points, however, the serum cholinesterase activity was decreased to levels as low as 57% of the levels determined in the controls. In female rats, cytoplasmic vacuolation in the cells of the adrenal cortex and ovarian interstitial cell hyperplasia were observed at 15 mg/kg body weight and day. In female mice, the severity of ceroid pigmentation in the cells of the adrenal cortex increased at the lowest dose tested of 8 mg/kg body weight and day and above. Ceroid pigmentation and foci in addition to changes in the fat cells of the liver of male animals were found at doses of 13 mg/kg body weight and day and above.

Tricresyl phosphate, "free of *o*-isomers", was not mutagenic or clastogenic in the in vitro studies available for evaluation. There are no in vivo studies of genotoxicity available. In the 2-year feeding study mentioned above, a mixture of tricresyl phosphate containing less than 0.1% tri-*o*-cresyl phosphate was not carcinogenic in F344 rats and B6C3F1 mice up to the highest doses tested of 15 and 37 mg/kg body weight and day, respectively.

In a 1-generation study in rats, tricresyl phosphate containing less than 9% tri-*o*-cresyl phosphate induced morphological changes in the testes and ovaries, a reduced fertility index and reduced litter sizes. In a developmental toxicity study with tricresyl phosphate, "free of o-isomers", in rats, delays in ossification were observed in the foetuses with concurrent maternal toxicity.

2 Mechanism of Action

2.1 Adrenal glands/liver/testes/ovaries

Long-term oral studies with tricresyl phosphate, "free of *o*-isomers" found vacuolation and ceroid pigmentation in the cells of the adrenal cortex in rats and female mice, respectively, as well as ceroid pigmentation, foci and changes in the fat cells of the liver in male mice (NTP 1994). A possible explanation for this may be that this is the primary site for steroid hormone synthesis, which is catalysed by cytochrome P450 enzymes. As the findings were not associated with cytotoxicity, the biotransformation of tricresyl phosphate itself or one of its metabolites may lead to the competitive inhibition of steroid biosynthesis with the accumulation of lipids in the vacuoles. This may lead also to the liver findings in male mice. However, it is unclear why these effects are not observed in female mice (NTP 1994).

The substrate of steroid hormones, cholesterol, is stored as cholesteryl ester in the steroid hormone-synthesizing cells such as those in the adrenal cortex, the interstitial cells of the ovaries and the Leydig cells. Tricresyl phosphate, "free of o-isomers", given in daily oral doses of 0 or 400 mg/kg body weight and day in sesame oil to groups of 12 female Sprague Dawley rats for 40 days, led to increased weights in the adrenal glands and ovaries in comparison with those determined in the control animals. Lipidosis in the form of stored cholesteryl ester was determined in the adrenal glands and ovaries and cholesteryl ester hydrolase activity was inhibited by up to 97%. Also the enzyme that esterifies cholesterol, cholesterol acetyl transferase, was inhibited by 27%, increasing intracellular cholesterol levels. The accumulation of lipids in the cells has therefore been explained by the inhibition of cholesterol metabolism (Latendresse et al. 1993).

Certain forms of lipid deposition, so-called ceroid deposits, are found in humans and rodents and develop when changes occur in the metabolism of unsaturated fatty acids. These deposits always occur intracellularly. They begin as small globules, which then coagulate until, in some cases, they almost completely fill the cytoplasm. In the adrenal glands, this effect occurs only in the adrenal cortex and is influenced by oestrogens. It is a normal sign of ageing in the adrenal glands and testes (Alpert 1953), which is accelerated by tricresyl phosphate in the adrenal glands of female mice.

2.2 Nerves

The documentation "tricresyl phosphate, sum of all *ortho* isomers" (Hartwig and MAK Commission 2023 a) includes an in-depth evaluation of the role played by neurotoxic esterase (NTE) in the development of OPIDN, which was observed after exposure to tricresyl phosphates containing *o*-isomers.

Earlier studies, particularly those investigating the delayed neurotoxicity of "tricresyl phosphate" in chickens, attributed their findings to tri-*o*-cresyl phosphate. For this reason, the fraction of tri-*o*-cresyl phosphate used in the production of tricresyl phosphate mixtures was considerably reduced. OPIDN is not induced by triesters containing only *m*-isomers or *p*-isomers. The disorder develops only if at least 1 of the 3 cresyl moieties has a methyl group substituted at the *ortho* position (NTP 1994). Strong evidence for this was provided by the findings in chickens given one of the pure isomers into the crop (a single dose of *m*-*m*-*p*-tricresyl phosphate or *m*-*p*-*p*-tricresyl phosphate of 2975 mg/kg body weight; a single dose of *m*-*m*-*m*-tricresyl phosphate of 2000 mg/kg body weight or 15 doses of *p*-*p*-*p*-tricresyl phosphate of 500 mg/kg body weight and day). In vivo, neurotoxic effects were not induced by isomers that did not contain a cresyl moiety methylated at the *ortho*-position (Aldridge and Barnes 1961; Henschler 1958). However, 24 hours after a single dose of these isomers was administered in vivo, serum cholinesterase activity was inhibited by a maximum of 21% (Aldridge and Barnes 1961).

In an oral 2-year study that investigated a formulation of a mixture of isomers of tricresyl phosphate containing less than 0.1% tri-*o*-cresyl phosphate, the NOAEL (no observed adverse effect level) for neurotoxic effects in B6C3F1 mice was the high dose of 37 mg/kg body weight and day and in F344 rats, the highest dose tested of 15 mg/kg body weight and day. This study investigated only the inhibition of serum cholinesterase activity and not that of acetylcholinesterase, which is a marker for acute neurotoxicity, or that of NTE, which is regarded as a marker for the development of OPIDN. Also the levels of NTE activity were not determined by these studies (NTP 1994; see Section 5.2.2).

When White Leghorn hens were treated with a single oral dose of tricresyl phosphate (Durad 125L®) of 2000 mg/kg body weight, the NTE activity levels were reduced by 45% and 83% in the brain and spinal cord, respectively, after 48 hours, in comparison with the levels determined in the control animals. The latter was regarded as toxicologically relevant. However, the acetylcholinesterase activity was not impaired (see Section 5.1.2; FMC Corp 1995). Durad 125® contains 0.3% tri-*o*-cresyl phosphate. There are no data available for the fractions of other *o*-isomers (Duarte et al. 2017).

The neurotoxic potential was examined **in vitro** with different tricresyl phosphates, "free of o-isomers".

Primary cortical neurons isolated from mouse embryos were cultured in vitro for 6 days and then incubated with tri-*m*-cresyl phosphate or tri-*p*-cresyl phosphate. After incubation for 24 hours, an IC_{50} of 83 µM for tri-*m*-cresyl phosphate and 122 µM for tri-*p*-cresyl phosphate was determined as a measure of the cytotoxicity of neurite outgrowth. Concentrations of up to 1 µM had no effect on neurite outgrowth. An IC_{50} of 15 µM was determined following incubation with the neurotoxic metabolite of tri-*o*-cresyl phosphate, *o*-cresyl-saligenin phosphate (CBDP). The complexity and integrity of the developing neurite network was not influenced by the presence of tri-*m*-cresyl phosphate and tri-*p*-cresyl phosphate. The reaction to glutamatergic signals was reduced at the highest concentration tested of 10 µM tri-*m*-cresyl phosphate or tri-*p*-cresyl phosphate, but not at 1 µM or below. Additionally, the Ca^{2+} influx into the cell in response to glutamate or KCI stimulation was increased only at a concentration of 10 µM; in the case of tri-*m*-cresyl phosphate by 34% and in the case of tri-*p*-cresyl phosphate by 31%. This was regarded as a very slight non-specific neurotoxic effect (Hausherr et al. 2017).

Primary cortical neurons from the rat treated for 24 or 28 hours with mixtures of tricresyl phosphates (containing a maximum of 2% tri-*o*-cresyl phosphate) or with tri-*m*-cresyl phosphate and tri-*p*-cresyl phosphate at concentrations up to 100 µM exhibited increased mitochondrial activity without affecting neuron viability at concentrations of 10 µM and above. Exposure for 30 minutes had a very limited effect on neuronal electrical activity; however, activity levels were decreased after exposure to 10 µM for 48 hours. The number of axons per cell or their length remained unchanged (Duarte et al. 2017). One conclusion that may be drawn from these findings is that increased mitochondrial activity has no effect on neuronal viability.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

None of the available studies carried out an in-depth assessment of quantitative inhalation exposure. According to NTP (1994), tricresyl phosphate is readily absorbed via inhalation.

When chickens were given a single oral dose of ^{32}P-tricresyl phosphate (no other details) of 770 mg/kg body weight, the amount of radioactivity determined in the liver increased steadily over a period of 72 hours. The amount of radioactivity in the plasma was attributed to unmetabolized tricresyl phosphate and was always lower than that in the liver. Within 72 hours, 26.5% of the radioactivity had been eliminated (NICNAS 2017).

According to NTP (1994), the toxicokinetic studies were carried out with tri-*o*-cresyl phosphate, tri-*m*-cresyl phosphate or tri-*p*-cresyl phosphate and not with formulations of a mixture of isomers. Tri-*o*-cresyl phosphate was examined most extensively, which is why this section includes data for tri-*o*-cresyl phosphate. To investigate distribution and elimination, male F344/N rats were given single doses of ^{14}C-labelled tri-*o*-cresyl phosphate, tri-*m*-cresyl phosphate or tri-*p*-cresyl phosphate of 0.5, 2, 20 or 200 mg/kg body weight in corn oil by gavage or 20 mg/kg body weight intravenously. The substances were distributed in the entire body. All isomers were readily absorbed after oral administration; however, the pattern of elimination varied. Within 24 hours, 70% of the administered tri-*o*-cresyl phosphate had been excreted with the urine and 20% with the faeces at all doses. Tri-*m*-cresyl phosphate was excreted mainly with the faeces and only a small fraction was excreted with the urine (no other details); the urinary fraction decreased as the dose increased. Tri-*p*-cresyl phosphate was excreted mainly with the urine up to a dose of 2 mg/kg body weight and mainly with the faeces at higher doses (no other details). The *o*-hydroxybenzoic acid or *p*-hydroxybenzoic acid formed during the metabolism of tri-*o*-cresyl phosphate and tri-*p*-cresyl phosphate was excreted with the urine either in free or in conjugated form (NTP 1994).

Within the first 6 hours after the administration of a single intravenous dose of 2 or 20 mg tri-*o*-cresyl phosphate or tri-*m*-cresyl phosphate, 40% to 60% of the radioactivity was excreted with the bile. After exposure to tri-*p*-cresyl phosphate, this fraction increased with the dose to about double the amount. As the amount of radioactivity recovered in the faeces was lower than that recovered in the urine for all 3 isomers, enterohepatic circulation is assumed. However, for all 3 isomers, the total amount of administered radioactivity was excreted within 3 days. All 3 isomers were rapidly distributed to muscles and the liver and then redistributed to adipose tissue and skin. The parent substances were rapidly metabolized and were not found to accumulate in the organs (NTP 1994).

Only few studies are available that investigated absorption through the skin and these vary greatly in the exposure parameters applied.

A single dose of ^{32}P-tricresyl phosphate (no other details) of 200 mg/kg body weight applied to the dorsal skin of dogs led to a concentration in the blood of 80 µg/l within 24 hours; this was determined as radioactivity. Tricresyl phosphate was found in decreasing amounts in the liver, blood, kidneys, lungs, muscles and brain (Hodge and Sterner 1943).

After a single application of ^{14}C-tri-*o*-cresyl phosphate to the skin between the shoulder blades of cats at a dose level of 50 mg/kg body weight, more than 73% of the dose had disappeared from the surface of the skin within 12 hours. The maximum levels of radioactivity were determined in the organs and tissues 24 hours after application. Within 10 days, 28% of the radioactivity had been excreted with the urine and 20% with the faeces (Nomeir and Abou-Donia 1986).

In 2 test persons, a rapid increase in radioactivity in the blood and urine was determined after the application of radioactively labelled tri-*o*-cresyl phosphate to the palm of the hands (220 mg and 110 mg, respectively) (Hodge and Sterner 1943). The total amount of radioactivity excreted with the urine was equivalent to the excretion of 796 µg and 143 µg of tri-*o*-cresyl phosphate.

Assuming that the findings observed in cats (Nomeir and Abou-Donia 1986) are suitable for extrapolation to humans, tri-o-cresyl phosphate was excreted with the urine and faeces in almost the same amounts. Therefore, it is assumed that total amounts of about 1592 µg and 286 µg, respectively, would be absorbed from a surface area of 200 cm^2

(according to Hodge and Sterner (1943): 2/3 of the surface area used in the experiment with dogs, which was given as 300 cm^2) within a period of 3.5 hours. Dermal fluxes of 1592 µg / 200 cm^2 / 3.5 hours = 2.3 µg/cm^2 and hour and 0.4 µg/cm^2 and hour, respectively, are calculated from these values. Assuming a skin surface area of 2000 cm^2 (surface of hands and forearms), it is estimated that a total of 4.6 mg and 0.8 mg tri-*o*-cresyl phosphate, respectively, is absorbed through the skin under standard conditions.

An in vitro study was carried out to investigate the dermal penetration of a test substance that was representative of commercially available tricresyl phosphates, "free of o-isomers", in 8 dermatomed human skin samples (0.64 cm^2) taken from 4 persons. The integrity of the skin samples was confirmed on the basis of the permeability of distilled water. Then, 500 µl each of 100%, 40% or 5% ^{14}C ring-labelled tricresyl phosphate in mineral oil was left on the skin for 8 hours before being rinsed off. The radioactivity in the skin and in the solutions was determined 24 hours after beginning exposure. The receptor solution contained 40% ethanol, as tricresyl phosphate did not dissolve sufficiently in the standard receptor solutions. From the test solutions containing 100%, 40% and 5% tricresyl phosphate, 275, 61.8 and 36.6 µg/cm^2, respectively, were directly absorbed and 605, 139 and 55.4 µg/cm^2, respectively, were potentially absorbed. Up to 75% of the amount in the receptor solution was absorbed during the first half of the test period (Pharmaron UK Limited 2018). The findings were not dependent on the dose and the receptor solution should be similar in composition to the interstitial fluid, which was not the case here because of the addition of 40% ethanol. Ethanol was added to increase the solubility of the lipophilic tricresyl phosphate. Fluxes of 76, 17 and 6.9 µg/cm^2 and hour are calculated from the potentially absorbed amounts. On the basis of these data, it can be assumed that under standard conditions (1 hour, area exposed 2000 cm^2) 152 mg would be absorbed after application of the undiluted substance. However, the level of dermal penetration was artificially increased because of the unphysiological receptor solution and the data cannot be used to evaluate the level of penetration through the skin.

As the isomers all have similar physico-chemical properties, they are probably absorbed through the skin to a similar degree (no other details; NICNAS 2017; NTP 1994).

By applying the mathematical model of Fiserova-Bergerova et al. (1990) and the algorithm of the IH SkinPerm model (Tibaldi et al. 2014), fluxes of 6.27 and 0.03 µg/cm^2 and hour, respectively, were calculated for a saturated aqueous solution of tri-*o*-cresyl phosphate (solubility 0.102 mg/l, log K_{OW} = 6.34; NCBI 2017 b). Therefore, the maximum amount absorbed under standard conditions (saturated aqueous solution, 2000 cm^2 of skin, 1-hour exposure) would be 12.54 mg (Fiserova-Bergerova et al. 1990).

Dermal fluxes of 1.3 µg/cm^2 and hour (Fiserova-Bergerova et al. 1990) and 0.015 µg/cm^2 and hour (Tibaldi et al. 2014) were calculated for tricresyl phosphate, "free of *o*-isomers". On the basis of these values, the amount of substance absorbed under standard conditions would be 2.6 mg and 0.03 mg, respectively.

3.2 Metabolism

As reported by NTP (1994), studies investigating metabolism were carried out with tri-*o*-cresyl phosphate, tri-*m*-cresyl phosphate or tri-*p*-cresyl phosphate, but not with formulations containing a mixture of isomers. Tri-*o*-cresyl phosphate was studied the most extensively (NTP 1994).

The metabolism follows similar pathways in different species, differing only in the amount or in the rate at which certain metabolites are formed. Tricresyl phosphates are metabolized in the liver by hydroxylation of one or more methyl groups, which leads to the formation of hydroxy benzyl alcohols. In the case of tri-*m*-cresyl phosphate and tri-*p*-cresyl phosphate, in some cases this is followed by further oxidation to aldehydes and carboxylic acids or by dearylation. Possible metabolites are mono-hydroxymethyl tricresyl phosphate and di-hydroxymethyl tricresyl phosphate, hydroxy benzyl alcohol, cresol, dicresyl phosphate, monocresyl phosphate and phosphoric acid, monocresyl-di(or mono)carboxyphenyl phosphate and dicresyl-di(or mono)carboxyphenyl phosphate and hydroxybenzoic acid. The metabolism of cresol does not lead to ring opening and degradation, as has been shown by studies with ^{14}C-ring labelled cresol. The end products recovered in the urine of rats were *o*-hydroxybenzoic acid or *p*-hydroxybenzoic acid. The most probable metabolic pathways of tri-*p*-cresyl phosphate in Wistar rats are shown in Figure 1 (NTP 1994).

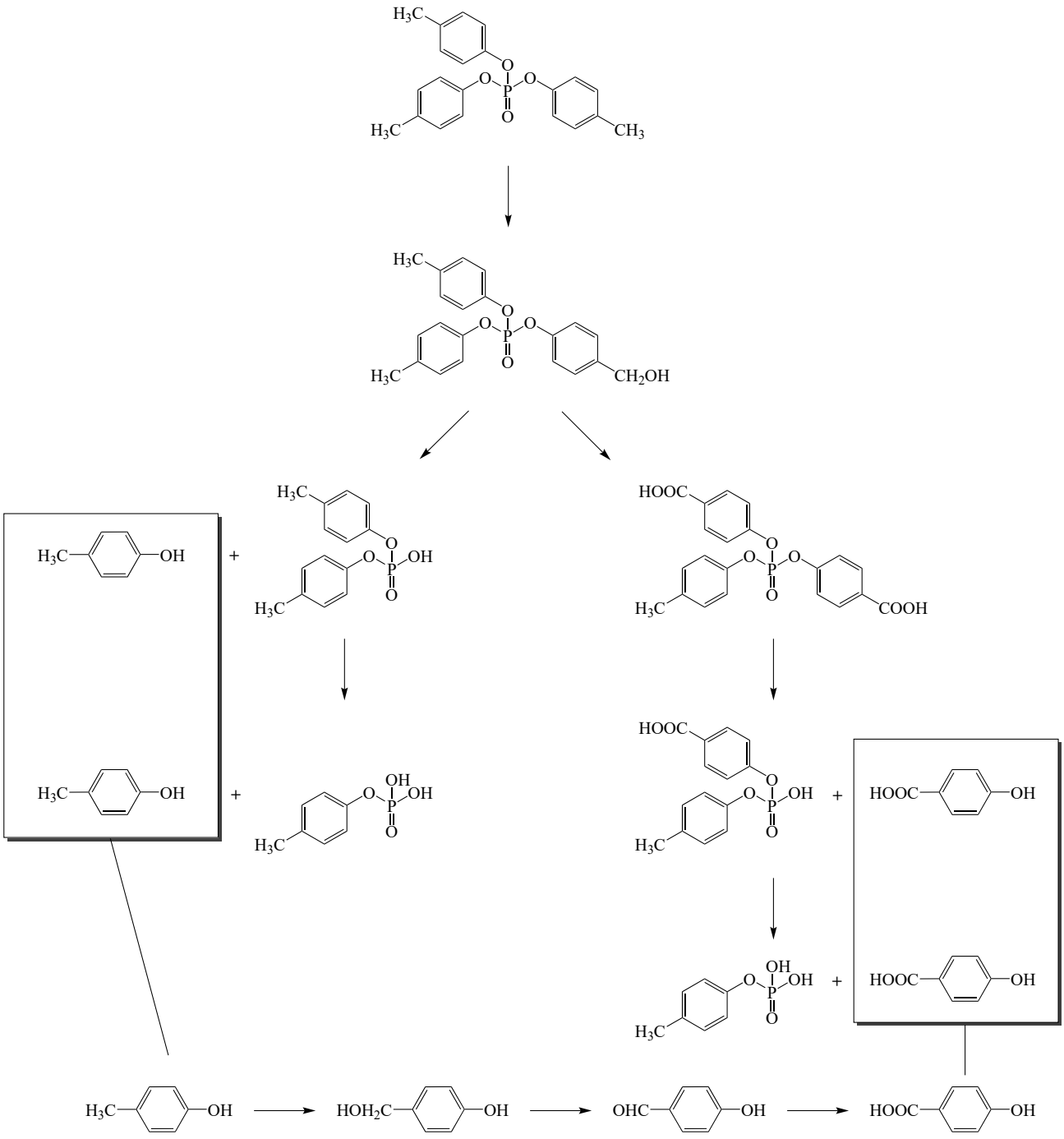


Fig. 1 Postulated metabolic pathways of tri-*p*-cresyl phosphate in rats (according to NTP 1994)

4 Effects in Humans

Case reports of poisonings after the ingestion, either once or repeatedly, of foods contaminated with tricresyl phosphates describe symptoms of vomiting, stomach pains and diarrhoea. Neurological effects such as paralysis and findings associated with damage to the pyramidal tracts occurred as a delayed reaction and were attributed to the presence of *o*-cresyl phosphate isomers (NICNAS 2017; NTP 1994).

The so-called "aerotoxic syndrome": the presence of tricresyl phosphate containing *o*-cresyl phosphate in the cabin air of aeroplanes has been suggested as the cause of the so-called "aerotoxic syndrome". However, there is no supporting evidence for a corresponding causal relationship (documentation "Tricresyl phosphate, sum of all *ortho* isomers" (Hartwig and MAK Commission 2023 a)).

Allergenic effects

Only few clinical findings for contact sensitizing effects induced by tricresyl phosphate are available. Likewise, sensitizing effects induced by contact with triphenyl phosphate have only rarely been reported to date (see also Henschler 1991).

In the period from 1950 to 1962, a reaction to the cellulose acetate film used in patch testing was observed in 15 of a total of 23 192 patients examined at the Finsen Institute in Copenhagen. This film contained 7% to 10% triphenyl phosphate (and 3% to 4% phthalic acid ester). In one case, patch tests were performed after skin reactions occurred upon contact with copy paper containing tricresyl phosphate. The patient produced 2+ reactions to 1% tricresyl phosphate (no other details) and to 1% triphenyl phosphate. The authors reported that 3 other patients who had reacted to the cellulose acetate film also produced positive reactions to 10% triphenyl phosphate and to 2% tricresyl phosphate (no other details, both substances in acetone). No reactions to tricresyl phosphate were produced by another 487 consecutively tested patients (Hjorth 1964).

An isolated case of contact eczema that developed on the bridge of the nose and the temples was attributed to spectacle frames made from a polymerization product containing triphenyl phosphate. A 2+ reaction was obtained in patch tests with 5% and 0.5% triphenyl phosphate. A 2+ reaction was likewise obtained with a 5% tricresyl phosphate mixture (of *m*-isomers and *p*-isomers with 0.08% triphenyl phosphate). Formulations with 5% and 0.5% tri-*m*-cresyl phosphate yielded 2+ and 1+ reactions, respectively, while 5% tri-*p*-cresyl phosphate produced no reaction (Carlsen et al. 1986).

A female patient who reacted in a patch test to the PVC film containing tricresyl phosphate (no other details) used for the test and who had previously developed a reaction on her nose to cellulose acetate spectacle frames containing triphenyl phosphate, was again tested with both substances. The patient produced 2+ reactions to 5% tricresyl phosphate in arachis oil and to 1% triphenyl phosphate in arachis oil and in acetone (Pegum 1966). Cross-reactivity or co-reactivity to tricresyl phosphate were not observed in other patients who produced positive reactions to triphenyl phosphate (no other details) (Camarasa and Serra-Baldrich 1992).

A female patient who developed a vascular erythematous reaction under a synthetic prosthesis containing tricresyl phosphate produced a 2+ reaction in a patch test with 5% tricresyl phosphate (no other details) in petrolatum after 48 and 96 hours (Grimalt et al. 2009).

One of 2 patients with contact dermatitis caused by pressure-sensitive adhesive bandages produced a positive reaction to 1% tricresyl phosphate (no other details) in petrolatum. The vinyl layer of the bandage contained tricresyl phosphate (Norris and Storrs 1990).

In addition to these earlier reports of positive reactions obtained in patch tests with tricresyl phosphate, a more recent report described a contact allergic reaction and a positive result in the patch test with 5% tricresyl phosphate (no other details) in petrolatum. The PVC gloves used contained about 21 µg/g of tricresyl phosphate in addition to about 55 µg/g of triphenyl phosphate and 116 µg/g of triphenyl phosphite. Patch tests with these 2 substances were evidently not carried out (Crépy et al. 2014).

Of 230 metal workers suspected of having occupational contact dermatitis, 6 produced a reaction in patch tests with a 10% formulation of tricresyl phosphate (no other details) in olive oil. There are no data for possible irritant reactions or control examinations in persons with healthy skin (Alomar et al. 1985). By contrast, in 40 metal workers with dermatitis from a total collective of 286 metal workers from 10 plants, no positive reactions were obtained with 10% tricresyl phosphate (no other details) in olive oil (de Boer et al. 1989).

Three of 505 patients produced a reaction in patch tests with 5% tricresyl phosphate (no other details) in petrolatum. The reaction obtained in 1 patient was assessed as clinically relevant (no other details) (van Ketel 1974). Another study with 52 test persons reported 1 case of an irritant, but not allergic, reaction to 1% tricresyl phosphate (Norris and Storrs 1990).

In the clinics of the Information Network of Departments of Dermatology (IVDK), no reactions to 5% tricresyl phosphate (no other details) in petrolatum were observed in 199 test persons with exposure to metal working fluids (Geier et al. 2004). In the period from 1991 to 1996, no positive reactions were produced in 357 patients tested at the Finnish Institute of Occupational Health with 5% tricresyl phosphate (no other details) as part of a plastics and adhesives series; irritant reactions were observed in 6 cases. Triphenyl phosphate tested at the same concentration yielded 1 allergic and 3 irritant reactions in 358 tested persons (Kanerva et al. 1997, 1999). From 1985 to 1992, a total of 10 280 patients were examined at the Department of Dermatology, University Central Hospital, Helsinki. Of these patients, 839 and 343 were tested with 5% tricresyl phosphate (no other details) and 5% triphenyl phosphate, respectively. Allergic or irritant reactions were not observed in any of the cases (Tarvainen 1995).

A maximization test (induction 100% tricresyl phosphate, challenge 25% tricresyl phosphate, no other details) yielded reactions in 7 of 23 test persons (Kayser and Schlede 2001). As there are no data for potential irritant effects induced by the formulation used for the challenge, an evaluation of these reactions is not possible.

Conclusion: The available data, which are in some cases contradictory, do not provide clear evidence of contact sensitizing effects induced by tricresyl phosphate.

There are no data in humans available for other end points.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

In a study that was not carried out according to the test guidelines, groups of 5 male and 5 female Sprague Dawley rats were exposed whole-body for 1 hour to tricresyl phosphate (no other details) at a concentration of 11 100 mg/m^3 and then observed for 14 days. Symptoms observed in the animals during exposure were excessive salivation and, at the end of exposure, the discharge of nasal mucus and dyspnoea. When the animals were removed from the exposure chamber, rattling breathing sounds were heard in 2 animals and dyspnoea was still evident in 1 animal. The discharge of mucus from the nose lasted about 4 hours. During the observation period of 14 days, rattling breathing sounds were often heard in 8 of 10 animals, which is regarded as a finding typical for inhalation studies carried out with particles, and the discharge of nasal mucus was still noticeable in 2 animals. None of the animals died. At necropsy, 7 of 10 animals were found to have pale lungs. The substance was regarded as a lung irritant (FMC Corp 1979).

In groups of 5 male and 5 female albino rats exposed whole-body to tricresyl phosphate (no other details) for 1 hour at a concentration of 20 000 mg/m^3 and then observed for 14 days, 1 male and 1 female animal died (Mobil Oil Corp 1982). In this study, the LC_{50} in rats for tricresyl phosphate was above 20 000 mg/m^3.

5.1.2 Oral administration

The oral LD_{50} in rats for the isomer mixtures of tricresyl phosphate was above 2000 mg/kg body weight; values of 5190, > 15 800 (NTP 1994) and > 16 100 mg/kg body weight were reported (Mobil Oil Corp 1982). The LD_{50} in Wistar rats for the flame retardant Kronitex® tricresyl phosphate was above 20 000 mg/kg body weight (ECHA 2019). The LD_{50} for tricresyl phosphate in mice was 3900 mg/kg body weight and in chickens above 10 000 mg/kg body weight. The LD_{50} for tri-*p*-cresyl phosphate was > 3000 mg/kg body weight in rabbits and > 1000 mg/kg body weight in chickens. The LD_{50} values for tri-*m*-cresyl phosphate were > 3000 mg/kg body weight in rabbits and > 2000 mg/kg body weight in chickens (NTP 1994). Target organs were the central and peripheral nervous systems; however, the symptoms developed only 1 to 3 weeks after exposure. Effects on the testes and ovaries were likewise observed (see Section 5.5.1).

Table 1 provides an overview of the findings of 2 studies of acute oral toxicity; the original reports of these studies were made available to the Commission.

Groups of 11 White Leghorn hens were given single oral doses of tricresyl phosphate (Durad 125L®) of 2000 mg/kg body weight, a tri-*o*-cresyl phosphate dose of 500 mg/kg body weight as the positive control or a dose of corn oil, which was used as the vehicle. Durad 125L® contains 0.3% tri-*o*-cresyl phosphate. The amounts of the other *o*-isomers were not specified (Duarte et al. 2017). In 3 animals of each group, the acetylcholinesterase activity in the brain and the neurotoxic esterase (NTE) activity in the brain and spinal cord were determined after 48 hours. Following exposure, the animals were observed hourly for signs of clinical toxicity and then once a day on the following 21 days. The motor activity was examined before exposure and then twice a week after substance administration. After 22 days, the brain, spinal cord and the sciatic and tibial nerves were examined for neuropathological damage. After exposure to tricresyl phosphate, the animals displayed no signs of clinical toxicity, and there were no changes in body weights or in body weight gains and no statistically significant differences in the acetylcholinesterase activity in the brain in comparison with the values determined in the control animals. The NTE activity in the brain and spinal cord was reduced by 45% and 83%, respectively, in comparison with the levels determined in the control animals. The latter was regarded as toxicologically relevant. Minimal to slight axonal degeneration in the spinal cord was determined by neuropathological examination of the nervous system; however, this did not impair the motor activity or lead to signs of toxicity. The effects observed in the positive controls were motor changes, OPIDN and a reduction in NTE activity in the brain and spinal cord by 90% and 96%, respectively (FMC Corp 1995). It is unclear why the reduction in NTE activity by 83% that was determined in this study did not lead to motor changes.

Tab. 1 Studies of acute toxicity after oral administration of tricresyl phosphate

Species	Dose (mg/kg body weight)	End point	References
White Leghorn chickens, 11 ♀/group	0, 2000 tricresyl phosphate (Durad 125L®) or corn oil or positive control: 500 tri-*o*-cresyl phosphate	neuropathological examination of the nerves of the hip, shin, spinal cord and brain; **tricresyl phosphate**: no deaths, no signs of clinical toxicity, normal motor activity, 3 animals/group after 48 hours: NTE in the brain decreased by 45% (toxicologically irrelevant) and in the spinal cord by 83%* (toxicologically relevant); after 22 days: minimal to moderate axonal degeneration in the spinal cord; **positive control**: restricted motor skills from day 13 onwards, OPIDN, NTE decreased in the brain by 90% and in the spinal cord by 96%	FMC Corp 1995
Wistar rats, 5 ♂, 5 ♀	6150, 9600, 15 000, 22 500 tricresyl phosphate (no other data)	**6150 mg/kg body weight and above**: diarrhoea, oily body, emaciation, lethargy, discoloured nasal discharge; **15 000 mg/kg body weight and above**: paralysis of the eyelids, ruffled fur, 3 ♂ died, one each on days 3, 4 and 7 after substance administration; **16 100 mg/kg body weight**: LD_{50}; **22 500 mg/kg body weight**: recumbent position, coma, all animals died between days 4 and 6	Mobil Oil Corp 1982

*$p < 0.05$; NTE: neurotoxic esterase; OPIDN: organophosphate-induced delayed neuropathy

5.1.3 Dermal application

The dermal LD_{50} for tricresyl phosphate was above 2000 mg/kg body weight in rabbits. In studies with application of the substance to the abraded skin carried out according to methods that do not comply with current test guidelines, an LD_{50} of 3700 mg/kg body weight was determined in New Zealand White rabbits and an LD_{50} of >10 000 mg/kg body weight in albino rabbits (ECHA 2019). In another study, an LD_{50} of >7900 mg/kg body weight was determined in rabbits and an LD_{50} of 1500 mg/kg body weight in cats (NTP 1994).

After occlusive application of tricresyl phosphate to the abraded dorsal skin of 10 New Zealand White rabbits for 24 hours, the dermal LD_{50} was above 5000 mg/kg body weight. The study reported that 85% of the substance was recovered on the dorsal skin, the animals developed diarrhoea and 3 animals showed signs of emaciation from day 4 of substance administration (Mobil Oil Corp 1982).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

For the investigation of neurotoxic effects, an inhalation study with daily nose-only exposure for 90 days was carried out in Sprague Dawley rats using a test method that complied with OECD Test Guideline 424. Ten additional animals from the control group and from the high concentration group were kept for a recovery period of 28 days. The animals were exposed to the aerosol of a tricresyl phosphate mixture at concentrations of 0, 100, 300 or 1000 mg/m³. Behavioural tests (FOB) investigating motor activity, learning and memory, and an adapted open field test did not yield substance-induced results (home cage, handling, open field, sensory, neuromuscular, physiological, motor activity, biel maze swimming trials, adapted open field testing). The organs and tissues were not examined histopathologically with the exception of the regions of the brain and all important nerve tracts and fibres in the body, spinal cord, eyes and skeletal muscles. In addition, the trigeminal nerve, optic nerve, the spinal cord in the area of the cervical spine, the thoracolumbar junction as well as protruding spinal nerves from this area and selected peripheral nerves of the hind legs were examined. In the females of the high concentration group, the acetylcholinesterase activity in the brain was reduced by less than 12% and, at the end of the observation period, by only 8.9%. This finding was not regarded as adverse because effects need to reach a severity of at least 20% to be considered adverse. The effects observed in this study did not cause any changes in behaviour, they were observed in the male animals only in the post-exposure observation group, but not during exposure, and in this group, only with a high level of variation. Thus, the NOAEC (no observed adverse effect concentration) for female rats was found to be the high concentration of 1000 mg/m³ and the NOAEC for male rats was 300 mg/m³ because body weight gains were reduced in this group at 1000 mg/m³ (Table 2; Charles River Laboratories 2019). A MAK value cannot be derived from this study because the nervous system was the primary focus of the histopathological examination. None of the relevant tissues and organs were examined, specifically the adrenal glands and ovaries that had been affected in the oral 2-year study.

Tab. 2 Effects induced by a 1:1 mixture of two commercial tricresyl phosphate products after 90-day inhalation exposure (Charles River Laboratories 2019)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 10 ♂, 10 ♀	**daily for 90 days**, according to OECD Test Guideline 424, tricresyl phosphate mixture of 0, 100, 300, 1000 mg/m³, aerosol, mean MMAD: 2.5, 2.4, 2.0 µm, nose only, 6 hours/day, 7 days/week	**300 mg/m³: NOAEC (♂)**; **1000 mg/m³: NOAEC (♀)**; NOAEC neurotoxicity; ♂: dry red material around the nose 30 minutes after exposure, feed consumption and feed conversion ↓, body weight gains decreased as from days 7 to 14, at end of study: 11.2% ↓, ♀: dirty fur at FOB examination in weeks 7 and 11, brain acetylcholinesterase activity in week 13 ↓ (≤ 12%) – as no abnormal behaviour detected and these effects did not occur in ♂: not evaluated as adverse	Charles River Laboratories 2019

Tab. 2 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 10 ♂, 10 ♀	**daily for 90 days**, tricresyl phosphate mixture of 0, 1000 mg/m³, aerosol, mean MMAD: 2.0 µm, nose only, 6 hours/day, 7 days/week, observation period: 4 weeks	**1000 mg/m³**: ♂: body weight gains normal during the observation period, but body weights still 9.9% lower than the weights in the control animals at the end of the study, mean level of brain acetylcholinesterase activity decreased by 37% in week 17 with large range of fluctuation between individual animals; therefore not relevant; ♀: dirty fur at FOB examination in week 16, brain acetylcholinesterase activity decreased in week 17 (≤ 12%) – as no abnormal behaviour: not evaluated as adverse	Charles River Laboratories 2019

FOB: functional observational battery; MMAD: mass median aerodynamic diameter

5.2.2 Oral administration

In general, rodents are less susceptible to the neurotoxic effects of the *o*-isomers of tricresyl phosphate than chickens. No studies investigating tricresyl phosphate, "free of *o*-isomers", in chickens are available.

Tricresyl phosphate containing less than 0.1% tri-*o*-cresyl phosphate was given with the feed for up to 24 months to male F344 rats at doses of 0, 3, 6 or 13 mg/kg body weight and day, to female F344 rats at doses of 0, 4, 7 or 15 mg/kg body weight and day, to male B6C3F1 mice at doses of 0, 7, 13 or 27 mg/kg body weight and day and to female B6C3F1 mice at doses of 0, 8, 18 or 36 mg/kg body weight and day. In the satellite groups, first grip strength was determined and then the nerves were examined histologically after 3, 9, 15 and 24 months. Survival, body weight gains and feed consumption were similar in all groups. Dose-dependent decreases in serum cholinesterase activity were observed. At doses of up to 10 mg/kg body weight and day, grip strength was not adversely affected in F344 rats or B6C3F1 mice, even though the serum cholinesterase activity had decreased to levels as low as 57% (see Table 3; NTP 1994). However, the serum cholinesterase activity is only a marker of exposure; it has no dose–response relationship for neurotoxic effects. The acetylcholinesterase activity, for example in the erythrocytes, was not determined; this is a more meaningful indicator for acute neurotoxic effects. Clinical symptoms develop when the acetylcholinesterase activity is reduced to a level of 70% or lower (Lewalter 1995). Studies with tricresyl phosphates containing *o*-isomers demonstrated that the inhibition of acetylcholinesterase activity is not correlated with the occurrence of OPIDN (documentation "Tricresyl phosphate, sum of all *ortho* isomers" (Hartwig and MAK Commission 2023 a)). In the study carried out by the NTP (1994), the typical clinical signs of acetylcholinesterase inhibition were not observed despite the inhibition of the serum cholinesterase activity to levels as low as 57%. Effects on grip strength were observed only after 3 months, but not at any other examination time point. On the basis of these findings, it can be concluded that the esterase activity is not inhibited to a level that is clinically relevant.

In female rats, cytoplasmic vacuolation in the cells of the adrenal cortex and ovarian interstitial cell hyperplasia were observed at the highest tricresyl phosphate dose tested of 15 mg/kg body weight and day. The NOAEL was 7 mg/kg body weight and day. Ceroid pigmentation in the adrenal cortex was observed in female mice at the lowest dose tested of 8 mg/kg body weight and day and above and in the control animals (see Section 2.1); the severity increased with the dose. At doses of 13 mg/kg body weight and above, ceroid pigmentation in the liver, foci and changes to the fat cells were observed in male mice. The NOAEL was 7 mg/kg body weight and day. A high incidence of cytoplasmic vacuolation in the cells of the adrenal cortex was observed in 13-week studies in rats and mice at doses of 50 mg/kg body weight and day and above; its severity increased with the dose. The axonal degeneration in the spinal cord typical of *o*-cresyl phosphates that was described in the 13-week gavage study in mice at doses of 100 mg/kg body weight and day and above was attributed to the presence of mono-*o*-isomers and di-*o*-isomers in the tested tricresyl phosphate formulation. However, in which amounts these isomers were present was not determined (NTP 1994).

Studies of recently weaned rats are not considered here as they are not relevant for the evaluation of exposure at the workplace.

Tab. 3 Effects of tricresyl phosphate after repeated oral exposure

Species, strain, number per group	Exposure	Findings	References
rat, F344, 10 ♂, 10 ♀	**16 days**, mixture of isomers[a)] in corn oil, gavage, 0, 360, 730, 1450, 2900, 5800 mg/kg body weight and day, 5 days/week, 13 or 14 doses	**360 mg/kg body weight and above**: relative liver weights ↑, absolute liver weights (♀) ↑; **730 mg/kg body weight and above**: diarrhoea (♂); **1450 mg/kg body weight and above**: mortality (1 ♀), mean body weights ↓, diarrhoea (♀), absolute thymus weights ↓, relative thymus weights (♀) ↓, changes in neurological parameters (correlated with mortality, not directly evaluated as substance-induced); **2900 mg/kg body weight and day and above**: mortality (5 ♂, 8 ♀), relative thymus weights (♂) ↓, necrosis in mandibular lymph nodes and spleen, necrosis and lymphoid depletion in thymus, diffuse aspermatogenesis in testes; **5800 mg/kg body weight**: mortality (10 ♂, 10 ♀)	NTP 1994
rat, Sprague Dawley, no data	**13 weeks**, 0, 30, 100, 300, 1000 mg/kg body weight and day, 6 days/week, no other data	**1000 mg/kg body weight**: "NOAEL"; examination only of body weights, feed and water consumption, urinalysis, haematology, serum chemical parameters, organ weights	NICNAS 2017
rat, F344, 10 ♂, 10 ♀	**13 weeks**, mixture of isomers[a)] in corn oil, gavage, 0, 50, 100, 200, 400, 800 mg/kg body weight and day, 5 days/week	no changes in neurobehavioural parameters; **50 mg/kg body weight and above**: dose-dependent decrease in serum cholinesterase activity, cytoplasmic vacuolation in the cells of the adrenal cortex – dose-dependent increase in severity, ovarian interstitial cell hypertrophy; **200 mg/kg body weight and above**: mean body weight (♂) ↓; **400 mg/kg body weight and above**: atrophy of the seminiferous tubules, absolute and relative liver weights (♀) ↑; **800 mg/kg body weight**: absolute and relative liver weights (♂) ↑	NTP 1994
rat, F344, 10 ♂, 10 ♀	**13 weeks**, mixture of isomers[a)] with the feed, 0, 900, 1700, 3300, 6600, 13 000 mg/kg diet (0, 55/65, 120/120, 220/230, 430/430, 750/770 mg/kg body weight and day for ♂/♀)	no changes in neurobehavioural parameters; **55/65 mg/kg body weight and above**: dose-dependent decrease in serum cholinesterase activity, cytoplasmic vacuolation in the cells of the adrenal cortex (all animals/dose group, severity ♂: 0, 1.6, 2.9, 3.0, 4.0, 4.0; ♀: 0, 1.4, 2.7, 3.0, 4.0, 4.0), ovarian interstitial cell hypertrophy (severity 0, 4.0, 4.0, 3.9, 4.0, 4.0), ovarian interstitial inflammation (severity 0, 2.3, 1.8, 1.5, 1.7, 1.3); **220/230 mg/kg body weight and above**: mean body weights (♀) ↓, relative liver weights ↑; **430 mg/kg body weight and above**: feed consumption ↓, mean body weights (♂) ↓, relative and absolute testis weights ↓, renal papillary oedema and necrosis (♀), atrophy of the seminiferous tubules, basophilic hypertrophy of the pituitary gland pars distalis; **750/770 mg/kg body weight**: renal papillary oedema and necrosis (♂)	NTP 1994
rat, F344, 95 ♂, 95 ♀	**22 weeks**, mixture of isomers[a)] with the feed, then control diet up to month 24, 600 mg/kg feed (26/30 mg/kg body weight and day for ♂/♀)	examination of the grip strength of the hind limbs after 3, 6, 15, 24 months, **26/30 mg/kg body weight**: grip strength of hind limbs (♀) ↓, cytoplasmic vacuolation in the cells of the adrenal cortex after 3 months: ♂ 10/10** (severity 1.0); ♀ 9/10** (1.8) 9 months: ♂ 0/10; ♀ 0/10	NTP 1994
rat, F344, 50 ♂, 50 ♀ an additional 45 ♂, 45 ♀ for interim examination	**24 months**, mixture of isomers[a)] with the feed, 0, 75, 150, 300 mg/kg feed (0, 3/4, 6/7, 13/15 mg/kg body weight and day for ♂/♀) after 3, 6, 15, 24 months, hind limbs: grip strength and histopathological examination	no effects on feed consumption, body weight gains, no clinical symptoms, no changes in haematological parameters; surviving animals: ♂: 32/51, 30/50, 35/50, 28/50; ♀: 34/51, 38/53, 30/50, 26/49; **7 mg/kg body weight**: **NOAEL** (♀); **13/15 mg/kg body weight**: **NOAEL** (♂), cytoplasmic vacuolation in the cells of the adrenal cortex (♀) (controls 14/51 (severity 1.0); dose groups 12/53 (1.2); 16/50 (1.0); 36/50** (1.0)), ovarian interstitial cell hyperplasia (controls 0/51; dose groups 0/53, 0/50, 15/50**); **only after 3 months:** **13 mg/kg body weight**: grip strength of the hind limbs (♂) ↓, serum cholinesterase activity ↓: dose-dependent in all exposed animals	NTP 1994

Tab. 3 *(continued)*

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 10 ♂, 10 ♀	**16 days**, mixture of isomers[a)] in corn oil, gavage, 0, 360, 730, 1450, 2900, 5800 mg/kg body weight and day, 5 days/week, 13 or 14 doses	**360 mg/kg body weight and above**: mean body weights (♀) ↓, grip strength of the hind legs (♂) ↓; **730 mg/kg body weight and above**: grip strength of the hind legs (♀) ↓; **1450 mg/kg body weight and above**: mortality (5 ♂, 10 ♀), mean body weights (♂) ↓; **2900 mg/kg body weight and above**: mortality (all animals), necrosis in mandibular lymph nodes, spleen, thymus; **5800 mg/kg body weight**: mortality (4 ♂, 1 ♀)	NTP 1994
mouse, CD1, 20 ♂, 20 ♀	continuous **98-day** mating study (from 1987), not in compliance with a test guideline, see also Section 5.5.1, mixture of tricresyl phosphate isomers[a)] with the feed, 0, 62.5, 124, 250 mg/kg body weight and day	here only the findings of the F0 animals; **62.5 mg/kg body weight and above**: **LOAEL**; hypertrophy of the zona fasciculata and brown-coloured degeneration of the cells in the adrenal juxtamedullary zone: number (♂) ↑ and severity (♂ and ♀) ↑, sperm motility ↓, testis and epididymis weights ↓, atrophy of the seminiferous tubules (ranging from foci of decreased germ cell number to bilateral loss of germ cells); **250 mg/kg body weight**: no strength in the hind limbs (♀), postpartum body weights (♀) ↓, kidney and adrenal gland weights (♀) ↓, testis and epididymis weights ↓, sperm motility and concentration ↓, number of sperm anomalies ↑; **no histopathological changes** in prostate glands, seminal vesicles, ovaries, uterus, vagina, liver, kidneys	Chapin et al. 1988; NTP 1994
mouse, B6C3F1, 10 ♂, 10 ♀	**13 weeks**, mixture of isomers[a)] in corn oil, gavage, 0, 50, 100, 200, 400, 800 mg/kg body weight and day, 5 days/week, GLP study	**50 mg/kg body weight and above**: dose-dependent decrease in serum cholinesterase activity, cytoplasmic vacuolation in the cells of the adrenal cortex – increasing with the dose and in severity (all animals/dose group, severity ♂: 0, 1.5, 1.4, 2.0, 2.0, 3.0; ♀: 0, 1.0, 2.4, 3.0, 3.0, 4.0), ovarian interstitial cell hypertrophy (incidence (severity): 0, 9**(1.2), 10**(1.5), 10**(1.7), 10**(2.3), 10**(2.6)); **100 mg/kg body weight and above**: multifocal neuronal degeneration in the spinal cord and sciatic nerve; **200 mg/kg body weight and above**: mean body weights (♂) ↓, axonal degeneration in the spinal cord and sciatic nerve, grip strength of the hind limbs (♂) ↓, absolute and relative liver weights (♀) ↑; **400 mg/kg body weight and above**: mean body weights (♀) ↓, grip strength of the hind limbs (♀) ↓	NTP 1994
mouse, B6C3F1, 10 ♂, 10 ♀	**13 weeks**, mixture of isomers[a)] with the feed, 0, 250, 500, 1000, 2100, 4200 mg/kg feed (0, 45/65, 110/130, 180/230, 380/530, 900/1050 mg/kg body weight and day for ♂/♀)	**45/64 mg/kg body weight and above**: dose-dependent decrease in serum cholinesterase activity, cytoplasmic vacuolation in the cells of the adrenal cortex; **110 mg/kg body weight and above**: papillary hyperplasia of the gall bladder mucosa (♂); **230 mg/kg body weight and above**: papillary hyperplasia of the gall bladder mucosa (♀), axonal degeneration (♀); **380/530 mg/kg body weight and above**: mean body weights (♀) ↓, axonal degeneration in the spinal cord and sciatic nerve (♂); **900/1050 mg/kg body weight**: tremor (2 ♂, 3 ♀), mean body weights (♂) ↓, degeneration of the renal tubules (♂)	NTP 1994

Tab. 3 *(continued)*

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 50 ♂, 50 ♀ an additional 45 ♂, 45 ♀ for interim examination	**24 months**, mixture of isomers[a] with the feed, 0, 60, 125, 250 mg/kg feed (0, 7/8, 13/18, 27/37 mg/kg body weight and day for ♂/♀) after 3, 6, 15, 24 months, examination of the grip strength of the hind limbs and histopathological examination	no effects on feed consumption, body weight gains, no clinical symptoms, no changes in haematological parameters; surviving animals: ♂: 43/51, 43/49, 44/49, 42/50; ♀: 41/50, 38/50, 42/48, 45/51; **7/8 mg/kg body weight: NOAEL** (♂/♀); **8 mg/kg body weight and above**: ceroid pigmentation in the cells of the adrenal cortex (all animals/dose group, severity ♀: 1.2, 1.6, 2.5, 3.9); **13/18 mg/kg body weight and above**: ceroid pigmentation in the liver cells (♂) (controls 0/52; doses 0/49, 30/49, 28/50), clear cell foci in the liver (♂) (controls 5/52; doses 8/49, 17/49, 12/50), changes in the adipose cells in the liver (♂) (controls 6/52; doses 10/49, 23/49, 22/50); dose-dependent decrease in serum cholinesterase activity in all exposed animals; **only after 3 months:** **37 mg/kg body weight**: grip strength of hind limbs (♀) ↓	NTP 1994

statistically significant differences in comparison with the control values: ** $p < 0.01$

[a] composition: 79% tricresyl phosphate (21% tri-*m*-cresyl phosphate, 4% tri-*p*-cresyl phosphate, < 0.1% tri-*o*-cresyl phosphate, other tricresyl phosphates not determined), 18% dicresyl phosphate

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Occlusive application of 0.5 g of Kronitex® tricresyl phosphate to the intact or abraded skin of 6 New Zealand White rabbits for 4 hours induced very slight irritation after 72 hours, but no irritation after 48 hours. The effects were no longer noticeable after another 24 hours (no other details). Another study carried out according to the same method with occlusive application for 24 hours did not induce irritation (no other details) (ECHA 2019).

Occlusive application of 0.5 ml of tricresyl phosphate to the intact and abraded skin of groups of 3 female and 3 male rabbits for 24 hours followed by rinsing of the application site did not induce irritation. After 24 and 72 hours, a primary irritation index of 0 was determined in all animals (Mobil Oil Corp 1982).

5.3.2 Eyes

In a study that was not carried out according to the test guidelines valid today, 0.1 ml of Kronitex® tricresyl phosphate instilled into 1 eye of New Zealand White rabbits induced slight irritation both in the unrinsed eyes (6 animals) and in the eyes rinsed for 4 seconds (3 animals). The mean maximum irritation scores were 0.7, 0.3 and 0, respectively, after 24, 48 and 72 hours (no other details). Another study carried out with Kronitex® tricresyl phosphate using the same method reported very slight irritation (no other details) (ECHA 2019).

Irritation was scored according to the method of Draize after 0.1 ml of Kronitex® tricresyl phosphate was instilled into 1 eye of each of 6 rabbits without subsequent rinsing: after 1 hour, the irritation score was 7.0 on a scale with a maximum of 110 (in each animal, the weakest effects were observed in the iris and conjunctiva) and after 1 day, the irritation score was 0.7 of 110 (in 2 of 6 animals, the weakest effects were found in the conjunctiva). By day 7 after substance administration, the irritation score was 0 (Mobil Oil Corp 1982). On the basis of these findings, the substance was not irritating in the eyes of rabbits.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

Stimulation indices of 5.4, 3.4 and 3.7, respectively, were determined in the LLNA with 25%, 50% and 100% tricresyl phosphate (isomer mixture) in acetone/olive oil (4:1); this is at best a borderline positive result without clear concentration dependency (ECHA 2019).

In an earlier study in guinea pigs, not carried out according to the test guidelines, with multiple intradermal induction using 0.1% tricresyl phosphate in arachis oil and a single intradermal challenge using the same formulation, no sensitizing effects were detected (Kayser and Schlede 2001).

A maximization test carried out with the structurally similar substance tri**phenyl** phosphate in guinea pigs using a method in compliance with OECD Test Guideline 406 likewise yielded negative results. No reaction was observed in any of the 10 animals at the challenge treatment. The intradermal induction was carried out with 5% triphenyl phosphate, the topical induction with a 75% formulation and the challenge treatment with 75% and 50% formulations. The vehicle in each case was arachis oil (ECHA 2020).

An LLNA in CBA/J Rj mice carried out with 25%, 50% or 100% **isopropylated** triphenyl phosphate (technical product containing 20% triphenyl phosphate) in acetone/olive oil (4:1) yielded stimulation indices of 7.4, 12.9 and 10.4, respectively. Therefore, the results were positive, but questionably valid (Hartwig and MAK Commission 2023 b).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

The fertility studies are shown in Table 4.

In a 1-generation study that was not carried out according to the test guidelines, tricresyl phosphate was administered to male Long Evans rats in gavage doses of 0, 100 or 200 mg/kg body weight and day beginning 56 days before mating and continuing during mating and to female Long Evans rats at doses of 0, 200 or 400 mg/kg body weight and day beginning 14 days before mating and continuing during mating. The tricresyl phosphate used as the test substance contained less than 9% tri-*o*-cresyl phosphate. The animals of the low dose groups were mated with one another, as were the animals of the high dose groups. At both dose levels, tricresyl phosphate led to morphological changes in the testes and ovaries, a reduced fertility index and reduced litter sizes (Carlton et al. 1987). It remains unclear at which dose the effects on fertility were induced in each sex. Therefore, the study cannot be used for evaluation.

In another unpublished mating study with F344 rats (original report not available), the test substance contained a considerable amount of additives (ECHA 2019). For this reason, it is likewise not used for evaluation.

In a continuous mating study with CD1 mice, changes in the sperm parameters and atrophy of the seminiferous tubules were observed at the lowest tricresyl phosphate dose tested of 62.5 mg/kg body weight and day and above. The reduction in the number of litters per mating, the ratio of live-born offspring per litter and the mean weights of the offspring was statistically significant at doses of 124 mg/kg body weight and day and above. A cross-over mating experiment demonstrated that fertility was reduced both in the exposed males and in the exposed females when mated with untreated control animals (Chapin et al. 1988). The NOAEL for effects on male and female fertility and perinatal toxicity was 62.5 mg/kg body weight and day.

Tab. 4 Fertility studies with tricresyl phosphate

Species, strain, number per group	Exposure	Findings	References
rat, Long Evans, 12 ♂, 24 ♀	**1-generation study**, not in compliance with the test guideline, ♂: 0, 100, 200 mg/kg body weight and day, 56 days prior to mating and during the 10-day mating period, ♀: 0, 200, 400 mg/kg body weight and day, 14 days prior to mating, then up to lactation day 21, gavage, vehicle: corn oil, < 9% TOCP, no other data	mating of the ♂ animals of the 100 mg/kg group with the ♀ animals of the 200 mg/kg group and of the ♂ animals of the 200 mg/kg group with the ♀ animals of the 400 mg/kg group; **♂ F0**: **100 mg/kg body weight and above**: number of morphologically abnormal sperm increased 3-fold and 10-fold depending on the dose; **200 mg/kg body weight**: sperm concentration ↓ to 65%, sperm motility ↓ to 4%, progressive linear sperm motility ↓ to 5%, epididymis weights ↓, minimal to slight: degeneration and necrosis in the seminiferous tubules, hypospermia in the epididymis, number of degenerated and immature sperm in the seminiferous tubules and epididymis ↑, early sperm granulomas; **♀ F0**: **0 mg/kg body weight**: number of litters 22/24; **200 mg/kg body weight**: number of litters 9/24; **400 mg/kg body weight**: number of litters 1/24 with 3 offspring that died by postnatal day 5 (no milk in stomachs, unclear whether caused by dams not giving milk or a suckling problem), litter size and survival of the pups ↓, number of follicles ↑, number of corpora lutea ↑, diffuse cytoplasmic vacuolar changes in the ovarian interstitial cells; **F1**: no effects on foetal body weights or offspring developmental parameters; study not included in the evaluation because it is unclear whether the effects on the litters are to be attributed to the treatment of the male or female animals (with different doses)	Carlton et al. 1987
rat, F344, 20/40 ♂, 20/40 ♀	**up to 135 days**, 0, 400 mg/kg body weight and day, additives[a)], but no TOCP, 1st mating cycle: exposure 7 days prior to and during the 63-day mating period in addition to 28 days (20 pairs), 2nd mating cycle: exposure for 8 days in cross-over mating experiment, ♂ necropsy, ♀ exposure until after birth, gavage, vehicle: sesame oil	as the number of litters ↓: after mating period of 63 days with exposed ♂ and ♀: cross-over mating experiment with untreated animals, group (1) 20 ♂ and 20 ♀, untreated, (2) 40 ♂ vehicle controls and 40 exposed ♀, (3) 40 ♀ vehicle controls and 40 exposed ♂, mating period of 8 days with control of oestrus cycle length, 1st mating cycle in 3 phases: days 1–40, 41–61, 62–98, as control animals gave birth on days 40, 61 and 98, **400 mg/kg body weight F0**: end of 2nd mating cycle terminal body weights ↓, 2nd mating cycle no effects on oestrus cycle, fertility index ↓, phase 1: 9/20 litters, phases 2 and 3: 0/20 litters, adrenal gland and liver weights ↑, testis and epididymis weights ↓, ovary weights ↑, **F1**: number of living offspring ↓, **as the test substance contained additives, the study cannot be used for the evaluation of tricresyl phosphate**	ECHA 2019

Tab. 4 *(continued)*

Species, strain, number per group	Exposure	Findings	References
mouse, CD1, 20 ♂, 20 ♀	**continuous mating study**, not in compliance with a test guideline, 3 test methods: (1) 98-day continuous mating, (2) cross-over mating, (3) determination of the fertility of the F1 animals, mixture of tricresyl phosphate isomers[b] with the feed, 0, 62.5, 124, 250 mg/kg body weight and day	**no NOAEL for maternal and paternal toxicity; 62.5 mg/kg body weight: NOAEL for effects on ♂/♀ fertility and perinatal toxicity**; **62.5 mg/kg body weight and above**: **F0**: **LOAEL**; hypertrophy of the zona fasciculata and brown-coloured degeneration of the cells in the adrenal juxtamedullary zone: number (♂) ↑ and severity (♂, ♀) ↑, sperm motility ↓, testis and epididymis weights ↓, atrophy of seminiferous tubules (ranging from foci of decreased germ cell number to bilateral loss of germ cells); **F1**: mating within the dose group with non-siblings, decreasing trend in the mating and fertility indices, decrease in the number of living offspring not statistically significant, mean body weights (♀) decreased by 6%, testis and epididymis weights ↓, sperm motility ↓, number of abnormal sperm ↑, histopathological changes (no other data) only in the adrenal glands (♂, ♀); **124 mg/kg body weight and above**: **F0**: and **F1**: decrease in the number of living offspring statistically significant, mean body weights (♀) decreased by 9%, number of abnormal sperm similar to control values; **250 mg/kg body weight**: **F0**: no strength in the hind limbs (♀), postpartum body weights (♀) ↓, number of living pups/dams ↓, **mating with different untreated partner**: fertility in ♀ and ♂ ↓, same number of matings, but fertility index ↓, offspring/litter and living pups ↓, kidney and adrenal gland weights (♀) ↓, testis and epididymis weights ↓, sperm motility and concentration ↓, number of sperm anomalies ↑, **no histopathological changes** in prostate gland, seminal vesicles, ovaries, uterus, vagina, liver, kidneys, **F0**: with increasing number of matings, increasing number of dead pups/litter, 250 mg/kg body weight: dead pups in the 1st litter, 124 mg/kg body weight: dead pups in the last two litters, fertility indices F0: 97%, 95%, 100%, 89%; **F1**: number of surviving offspring too small, therefore, no F1 group	Chapin et al. 1988

[a] composition: 62% by weight tri-*p*-cresyl phosphate and tri-*m*-cresyl phosphate, 18% by weight cresyl xylyl phosphate and 18% by weight cresyl ethyl phenyl phosphate, no *o*-isomer detected

[b] composition: 20.6% tri-*m*-isomer, 3.9% tri-*p*-isomer, < 0.1% tri-*o*-isomer, in total: 74.9% pure *o*-cresyl isomers, *m*-cresyl isomers and *p*-cresyl isomers or a mixture of these, the rest made up of dicresyl phenyl phosphates, dicresyl xylyl phosphates and tricresyl xylyl phosphates

TOCP: tri-*o*-cresyl phosphate

5.5.1.1 Effects on the male reproductive organs

In a 16-day gavage study, diffuse spermatogenesis in the testes was determined in male F344 rats at doses of 2900 mg/kg body weight and day and above. When F344 rats were given tricresyl phosphate by gavage for 13 weeks, atrophy of the seminiferous tubules was observed at doses of 400 mg/kg body weight and day and above. This effect was seen in the same strain also after the substance was given with the feed for 13 weeks at doses of 430 mg/kg body weight and day and above. In a 2-year feeding study in male F344 rats, no effects on the male reproductive organs were observed up to the highest dose tested of 13 mg/kg body weight and day (Table 3; NTP 1994).

As mentioned above, atrophy of the seminiferous tubules, reduced sperm motility and decreased testis and epididymis weights were determined by a continuous 98-day mating study in CD1 mice at tricresyl phosphate doses of 62.5 mg/kg body weight and day and above (Chapin et al. 1988). None of the other studies carried out with B6C3F1 mice reported effects on the male reproductive organs (Table 3; NTP 1994).

5.5.1.2 Effects on the female reproductive organs

Increased incidences and the increasing severity of ovarian interstitial cell hyperplasia were determined in female F344 rats in a 13-week feeding study at tricresyl phosphate doses of 65 mg/kg body weight and day and above and in a 13-week gavage study at doses of 50 mg/kg body weight and day and above. In a 2-year feeding study in the same animal strain, these effects were observed also at the highest tricresyl phosphate dose tested of 15 mg/kg body weight and day. The NOAEL for this effect was 7 mg/kg body weight and day (Table 3; NTP 1994).

In a 13-week gavage study with female B6C3F1 mice, increased incidences and increasing severity of ovarian interstitial cell hyperplasia were observed at the lowest tricresyl phosphate dose tested of 50 mg/kg body weight and day and above. In a 13-week feeding study, these effects were observed at doses of 230 mg/kg body weight and day and above (NTP 1994). In a continuous 98-day mating study, no effects were determined in the ovaries of female CD1 mice up to the tricresyl phosphate dose of 250 mg/kg body weight and day (Chapin et al. 1988). These effects were likewise not observed in the 2-year feeding study in female B6C3F1 mice at tricresyl phosphate doses of up to 37 mg/kg body weight and day (Table 3; NTP 1994).

5.5.2 Developmental toxicity

In a developmental toxicity study carried out using a method similar to OECD Test Guideline 414, groups of 25 female Sprague Dawley rats were given gavage doses of tricresyl phosphate, "free of *o*-isomers", in corn oil of 0, 20, 100, 400 or 750 mg/kg body weight and day from gestation days 0 to 19 and were mated 1:1 with an untreated male animal. The test substance was Kronitex® tricresyl phosphate. The animals were examined on gestation day 20. In the dams, salivation was observed more frequently after administration of the substance at doses of 100 mg/kg body weight and day and above. Ruffled fur, hair loss and reduced body weight gains were observed at doses of 400 mg/kg body weight and day and above and reduced feed consumption was determined at 750 mg/kg body weight and day. At the high dose, marked maternal toxicity was determined with a decrease in body weight gains by 35%. Excessive spillage of feed was observed in 11 animals (44%) at 400 mg/kg body weight and day and in 10 animals (40%) at 750 mg/kg body weight and day. The authors consider this to be a substance-induced effect, but its toxicological relevance remains unclear. An analysis of covariance was applied to the mean foetal weights to determine whether litter size should be included in the significance analysis as a covariate. The results were negative for male foetal weights and a pairwise comparison of the dose groups with the control group found statistically significant differences in foetal weights at dose levels of 20, 400 and 750 mg/kg body weight and day (Table 5). By contrast, litter size proved to be a covariate for female foetal weights and for the foetal weights of the females and males when considered together. Therefore, these foetal weights were analysed in the model using litter size as a covariate. The differences between the weights determined in all dose groups and those of the control group (Dunnett's test) were statistically significant. An increase in the number of unossified or not completely ossified bones (skull and sternebrae) was observed at 750 mg/kg body weight and day. None of the animals died. The mean numbers of corpora lutea, implantation sites, foetuses and resorptions as well as the sex ratio were similar to the corresponding values determined in the control group. This was also true for the pre-implantation loss and post-implantation loss indices. In this study, tricresyl phosphate was not found to be teratogenic. As the mean foetal weights were reduced at the lowest dose tested of 20 mg/kg body weight and day and above, the authors reported a LOAEL (lowest observed adverse effect level) for developmental toxicity of 20 mg/kg body weight and day (MPI Research Inc 2004). The decrease in mean foetal weights by about 5% in the two low dose groups did not show any dependency on the dose and is regarded as a marginal, not adverse effect in the normal range of biological variability. A marked reduction in foetal weights was observed at doses of 400 mg/kg body weight and day and above. This effect was found concurrently with reduced body weight gains in the dams. For this reason, the NOAEL for developmental toxicity was determined to be 100 mg/kg body weight and day. The NOAEL for maternal toxicity is 20 mg/kg body weight and day.

Tab. 5 Selected parameters of the developmental toxicity study in rats (MPI Research Inc 2004)

	Dose (mg/kg body weight and day)				
	0	**20**	**100**	**400**	**750**
mean foetal weights, ♂ (g)	3.84 ± 0.240	3.62 ± 0.210*	3.67 ± 0.212	3.50 ± 0.315**	3.16 ± 0.280**
difference		−5.7%	−4.4%	−8.9%	−17.7%
mean foetal weights, ♀ (g)	3.68 ± 0.238	3.45 ± 0.207**	3.50 ± 0.192*	3.31 ± 0.338**	2.99 ± 0.254**
difference		−6.3%	−4.9%	−10.1%	−18.8%
mean foetal weights, ♂, ♀ (g)	3.76 ± 0.239	3.54 ± 0.198**	3.58 ± 0.203*	3.41 ± 0.315**	3.07 ± 0.252**
difference		−5.9%	−4.8%	−9.3%	−18.4%
litter size per dam	13.9 ± 2.08	13.8 ± 2.27	14.3 ± 2.01	13.2 ± 2.98	15.3 ± 2.14
mean body weight gains dams (g)	146.6 ± 17.76	141.8 ± 19.07	146.6 ± 24.76	126.5 ± 25.74**	94.9 ± 23.80**
difference		−3.3%	0.0%	−13.7%	−35.3%

*$p < 0.05$; **$p < 0.01$

5.6 Genotoxicity

5.6.1 In vitro

Tricresyl phosphate was not mutagenic in the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of up to 10 000 µg/plate in the presence and absence of a metabolic activation system. The test substance precipitated at concentrations of 3300 µg/plate and above. The test substance was a formulation of a mixture of isomers containing 79% tricresyl phosphate (21% tri-*m*-cresyl phosphate, 4% tri-*p*-cresyl phosphate, < 0.1% tri-*o*-cresyl phosphate, other tricresyl phosphates not determined) and 18% dicresyl phosphate (NTP 1994).

Tricresyl phosphate (no other details) was not mutagenic in the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 and in Saccharomyces cerevisiae D4 at concentrations from 0.01 to 10 µl/plate in the presence and absence of a metabolic activation system (Mobil Oil Corp 1982).

In mouse lymphoma cells, chromosomal aberrations and sister chromatid exchange were not detected at tricresyl phosphate concentrations of up to 0.01 µl/ml with and without the addition of a metabolic activation system. Chromosomal aberrations were not observed in a Chinese hamster V79 lung fibroblast cell line up to a concentration of 1000 µg/ml. The test substance was a formulation of a mixture of isomers containing 79% tricresyl phosphate (21% tri-*m*-cresyl phosphate, 4% tri-*p*-cresyl phosphate, < 0.1% tri-*o*-cresyl phosphate, other tricresyl phosphates not determined) and 18% dicresyl phosphate (ECHA 2019; NTP 1994).

According to NTP (1994), chromosomal aberrations and sister chromatid exchange were not found in cultivated Chinese hamster ovary cells (CHO cells) up to a concentration of 5000 µg/ml with and without the addition of a metabolic activation system. The test substance was a formulation of a mixture of isomers containing 79% tricresyl phosphate (21% tri-*m*-cresyl phosphate, 4% tri-*p*-cresyl phosphate, < 0.1% tri-*o*-cresyl phosphate, other tricresyl phosphates not determined) and 18% dicresyl phosphate.

Conclusion: Tricresyl phosphate, "free of *o*-isomers", was neither mutagenic nor clastogenic in the available in vitro studies.

Tab. 6 In vitro genotoxicity tests with tricresyl phosphate

End point	Test system	Concentration	Effective concentration	Cytotoxicity	Result		References
					–m.A.	+m.A.	
Gene mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, similar to OECD Test Guideline 471	0.00001, 0.0001, 0.001, 0.01, 0.1 mg Kronitex® TCP[a)]/l (no other data)	–	no data	–	–	ECHA 2019
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, OECD Test Guideline 471	0.001, 0.01, 0.05, 0.1 and 1 µl Kronitex® TCP 50/plate	–	–	–	–	ECHA 2019
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, similar to OECD Test Guideline 471	0.06, 0.32, 1.6, 3.2, 6.4 µl Kronitex® TCP/plate	–	–	–	–	ECHA 2019
	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, Saccharomyces cerevisiae D4	0.01–10 µl/plate	–	–	–	–	Mobil Oil Corp 1982
	Salmonella typhimurium TA98, TA100, TA1535, TA1537	100, 333, 1000, 3333, 10 000 µg TCP[b)]/plate	–	–	–	–	NTP 1994
SCE	mouse lymphoma cells	0.00063, 0.00125, 0.005, 0.01 µl TCP/ml	–	–	–	–	ECHA 2019
	CHO cells	–m.A.: 0.05, 0.16, 0.5, 1.6, 5, 16 µg TCP[b)]/ml +m.A.: 16, 50, 160, 500, 1600, 5000 µg TCP[b)]/ml	–	–m.A.: 16 µg/ml	–	–	NTP 1994
CA	V79 cells (lung fibroblasts of Chinese hamsters), OECD Test Guideline 473	1.37, 4.12, 12.35, 37.04, 111.1, 333.3, 1000 µg TCP/ml	–	about 50% at the 3 highest concentrations	–	–	ECHA 2019
	CHO cells	–m.A.: 50, 160, 500, 1600, 5000 µg TCP[b)]/ml +m.A.: 160, 500, 1600, 5000 µg TCP[b)]/ml	–	–	–	–	NTP 1994

[a)] 0.07% *o*-isomers, 53% *m*-isomers, 27% *p*-isomers, 15% others (each given as the corresponding cresol fraction)
[b)] 79% tricresyl phosphate (21% tri-*m*-cresyl phosphate, 4% tri-*p*-cresyl phosphate, < 0.1% tri-*o*-cresyl phosphate, other tricresyl phosphates not determined) and 18% dicresyl phosphate
CA: chromosomal aberrations; SCE: sister chromatid exchange; TCP: tricresyl phosphate

5.6.2 In vivo

No in vivo studies of tricresyl phosphate, "free of *o*-isomers", are available.

5.7 Carcinogenicity

For a period of up to 24 months, tricresyl phosphate containing less than 0.1% tri-*o*-cresyl phosphate was administered via the diet to male F344 rats at doses of 0, 3, 6 or 13 mg/kg body weight, to female F344 rats at doses of 0, 4, 7 or 15 mg/kg body weight, to male B6C3F1 mice at doses of 0, 7, 13 or 27 mg/kg body weight and to female B6C3F1 mice at doses of 0, 8, 18 or 37 mg/kg body weight. Survival, body weight gains and feed consumption were similar in all groups. Tricresyl phosphate did not induce an increased incidence of tumours in rats up to the highest doses tested of 15 mg/kg body weight and day and in mice up to 37 mg/kg body weight and day (NTP 1994).

6 Manifesto (MAK value/classification)

There are no data for humans available for the effects induced by tricresyl phosphate, "free of *o*-isomers". Neurotoxic findings in humans after ingesting foods contaminated with tricresyl phosphate were attributed to isomers containing *o*-tricresyl phosphate (see documentation "Tricresyl phosphate, sum of all *ortho* isomers" (Hartwig and MAK Commission 2023 a)).

In 2-year feeding studies with rats, the critical effects of tricresyl phosphate, "free of *o*-isomers", were a higher incidence of cytoplasmic vacuolation in the adrenal cortex and ovarian interstitial cell hyperplasia. In mice, ceroid pigmentation was observed in the liver and adrenal cortex.

MAK value. There are no data for humans that can be used to derive a MAK value.

In a 90-day inhalation study with daily exposure of rats to the aerosol of a tricresyl phosphate mixture at concentrations of up to 1000 mg/m^3, reduced body weight gains were found at the highest concentration tested of 1000 mg/m^3 which were not observed at the medium concentration of 300 mg/m^3 (Charles River Laboratories 2019). However, as the histopathological examination focused mainly on the nerves and a complete examination of the organs and tissues was not performed, specifically not of the adrenal glands and ovaries in which effects had been found in the oral study, this study cannot be used for the derivation of a MAK value.

However, an oral 2-year study that investigated a formulation of tricresyl phosphate containing less than 0.1% tri-*o*-cresyl phosphate observed ovarian interstitial cell hyperplasia and a higher incidence of cytoplasmic vacuolation in the cells of the adrenal cortex in female F344 rats at the highest dose tested of 15 mg/kg body weight and day. The NOAEL was 13 and 7 mg/kg body weight and day, respectively, in male and female rats.

In mice, a NOAEL of 7 mg/kg body weight and day was determined in the males as ceroid pigmentation, foci and changes in the adipose tissue were determined in the liver at doses of 13 mg/kg body weight and above. In the females, the severity of ceroid pigmentation in the cells of the adrenal cortex increased with the dose at the lowest dose tested of 8 mg/kg body weight and day and above. This is a normal effect of ageing (Section 2.1), which in female mice is accelerated by administration of the substance. As this finding was not observed in rats, its relevance for humans is questionable. Likewise, it is not certain whether this can be regarded as an adverse effect. For this reason, this effect is not taken into consideration for the derivation of the MAK value.

All of the tested isomers were readily absorbed by rats after oral exposure (NTP 1994). Therefore, 100% absorption is assumed after oral exposure of rats and mice.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL in rats and mice of 7 mg/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 values for the rat and mouse (1:4 and 1:7), oral absorption (assumed to be 100%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person and the assumed 100% absorption by inhalation. The concentrations calculated from this are 17 and 9.8 mg/m^3, respectively. The lower value is used for the derivation of the MAK value. As this value was based on the findings from long-term studies, no further intensification of the effects over time is assumed. After extrapolation of the data from animal studies to humans (1:2), a MAK value for tricresyl phosphate, "free of o-isomers", of 5 mg/m^3 is derived for the inhalable fraction. The saturation concentration is 0.01 mg/m^3 at a vapour pressure of 8×10^{-7} hPa. Therefore, at 5 mg/m^3, tricresyl phosphate occurs almost exclusively as an aerosol.

Peak limitation. The MAK value is derived from a systemic effect. For this reason, the substance has been classified in Peak Limitation Category II. As the half-life of tricresyl phosphate, "free of o-isomers", is not known, the default excursion factor of 2 has been set.

Prenatal toxicity. A prenatal developmental toxicity study with gavage administration to Sprague Dawley rats from gestation days 0 to 19 did not find evidence of teratogenicity. Reduced foetal weights were observed at the lowest

dose tested of 20 mg/kg body weight and day and above (20, 100, 400, 750 mg/kg body weight: 5.9%, 4.8%, 9.3%, 18.4%). Ossification was delayed in the foetuses at 750 mg/kg body weight and day. The maternal NOAEL was 20 mg/kg body weight and day. The incidence of salivation was increased at doses of 100 mg/kg body weight and day and above (MPI Research Inc 2004). The decrease in the mean foetal weights by about 5% in the two low dose groups, which was not dependent on the dose in these dose groups, is regarded as a marginal, not adverse effect within the range of biological variability. A marked reduction in foetal weights first occurred at a dose of 400 mg/kg body weight and day. This was accompanied by reduced body weight gains in the dams. For this reason, the NOAEL for developmental toxicity was 100 mg/kg body weight and day.

In a continuous mating study in CD1 mice with administration in the diet, the number of living offspring per litter was reduced in the F0 and F1 generations at doses of 124 mg/kg body weight and day and above. Histopathological effects were found in the adrenal glands and testes in the F0 and F1 generations at the lowest dose tested of 62.5 mg/kg body weight and day and above (Chapin et al. 1988). The NOAEL for perinatal toxicity induced by tricresyl phosphate was 62.5 mg/kg body weight and day.

The same toxicokinetic parameters as above (Section "MAK Value") are taken into consideration for the extrapolation of the NOAELs of 100 and 62.5 mg/kg body weight to a concentration in workplace air. The daily exposure of the animals in comparison with the 5 days per week exposure at the workplace is relevant only for the continuous mating study. The concentrations in the workplace air calculated from these NOAELs are 175 and 88 mg/m^3, respectively. These values are 35 and 18 times as high as the MAK value of 5 mg/m^3. As the margins between the NOAELs for developmental toxicity and perinatal toxicity and the MAK value are sufficiently large, tricresyl phosphate, "free of o-isomers", has been classified in Pregnancy Risk Group C.

Carcinogenicity. In a 2-year feeding study investigating a tricresyl phosphate formulation containing less than 0.1% tri-*o*-cresyl phosphate, the tumour incidence was not increased in F344 rats up to the highest doses tested of 15 mg/kg body weight and day and in B6C3F1 mice up to 37 mg/kg body weight and day. Tricresyl phosphate, "free of o-isomers", has not been classified in any of the carcinogen categories.

Germ cell mutagenicity. In the in vitro studies available, tricresyl phosphate, "free of o-isomers", was not mutagenic in Salmonella typhimurium and did not cause sister chromatid exchange in mouse lymphoma cells or chromosomal aberrations in V79 lung fibroblasts or CHO cells. No in vivo studies are available. Tricresyl phosphate containing less than 0.1% tri-*o*-cresyl phosphate yielded negative results in carcinogenicity studies in rats and mice. Tricresyl phosphate, "free of o-isomers", has not been classified in any of the categories for germ cell mutagens.

Absorption through the skin. The quantitative study investigating the dermal flux of tricresyl phosphate, "free of o-isomers", cannot be used for the evaluation because the receptor solution contained 40% ethanol, which artificially increases the flux. A low dermal flux in the µg/cm^2/hour range was determined both by a study investigating undiluted tri-o-cresyl phosphate and by applying the mathematical models for saturated aqueous solutions. Low fluxes were likewise determined after the models were applied to tricresyl phosphate isomers other than the *o*-isomers; based on these values, the maximum total uptake is estimated to be 2.6 mg under standard conditions. A systemically tolerable amount of 50 mg per working day is derived from the MAK value of 5 mg/m^3 I (inhalable fraction). As the maximum possible amount that can be absorbed through the skin of 2.6 mg is much lower than this value, tricresyl phosphate, "free of o-isomers", has not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Only few clinical findings are available for the contact sensitizing effects induced by tricresyl phosphate. A local lymph node assay yielded a borderline positive result that was not possible to clearly interpret. At most, this can be regarded as evidence of a very slight skin sensitizing potency. Overall, the, in some cases contradictory, data are not sufficient to be regarded as evidence of a contact sensitization potential for tricresyl phosphate. Data for sensitizing effects on the respiratory tract are not available. Therefore, tricresyl phosphate, "free of o-isomers", has 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.

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