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Triphenyl phosphate, isopropylated

MAK Value Documentation – Translation of the German version from 2016

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Keywords

triphenyl phosphate, isopropylated; adrenal glands; ovaries; MAK value; maximum workplace concentration; developmental toxicity; neurotoxicity

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated triphenyl phosphate, isopropylated [68937-41-7] to derive a maximum concentration at the workplace (MAK value), considering all toxicity end points. Available unpublished study reports and publications are described in detail. Isopropylated triphenyl phosphate has no irritant effects on the skin of rats and rabbits, and is not, or at most minimally, irritating to the eyes of rabbits. It belongs to the group of organophosphates and shows the typical delayed organophosphate neurotoxicity (axonal degeneration). The neurotoxicity decreases with increasing isopropylation. However, the most sensitive toxicological end points following repeated exposures are histopathological changes in the adrenal gland and ovary. The LOAEC in 90-day inhalation studies in rats and in hamsters was 10 mg/m^3, the lowest tested concentration. Oral studies according to OECD TG 422 and TG 408 have revealed a LOAEL of 25 mg/kg body weight and day in rats. Neurotoxicity tests in hens have yielded a NOAEL of 20 mg/kg body weight and day. After scaling these NOAELs to a concentration at the workplace, a MAK value of 1 mg/m^3 is derived. As the systemic effect is critical, isopropylated triphenyl phosphate is assigned to Peak Limitation Category II with the default excursion factor of 2, as no specific toxicokinetic data are available. No developmental toxicity was observed at 260 mg isopropylated triphenyl phosphate/kg body weight and day. Therefore, no damage to the embryo or foetus has to be expected and isopropylated triphenyl phosphate is classified in Pregnancy Risk Group C. Isopropylated triphenyl phosphate is not genotoxic in vitro or in vivo nor does it have cell-transforming activity. No data on carcinogenicity are available. Overall, the available data do not indicate that the substance should be classified as a carcinogen or a germ cell mutagen. Sensitizing potential was not investigated with isopropylated triphenyl phosphate, and similar compounds have led to inconclusive results. Absorption through the skin is low and does not relevantly contribute to systemic toxicity.

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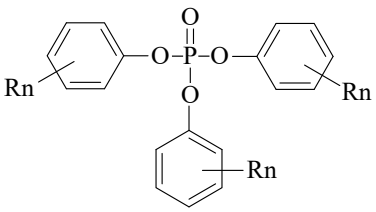
MAK value (2015)	**1 mg/m³ I (inhalable fraction)**
Peak limitation (2015)	**Category II, excursion factor 2**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2016)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–
Synonyms	isopropylated triphenyl phosphate triaryl phosphate, isopropylated
Chemical name	isopropylated phenyl phosphate (3 : 1)
CAS number	68937-41-7
Structural formula	 R = $CH(CH_3)_2$ n = 0–3
Molecular formula	$C_{27}H_{33}O_4P$ (for 3 R)
Molar mass	452.52 g/mol (for 3 R)
Melting point	< –20 °C (ECHA 2013) < 25 °C (US EPA 2010)
Boiling point at 980 hPa	> 400 °C (ECHA 2013)
Density at 20 °C	1.168 g/cm³ (ECHA 2013)
Vapour pressure at 25 °C	1.46×10^{-6}–1.33×10^{-7} hPa (calculated) (US EPA 2010)
log K_{OW}	4.92–5.17 (ECHA 2013) 5.44 (US EPA 2010)
Solubility at 20 °C	0.33–0.367 mg/l water (ECHA 2013)
pKa value	cannot be determined because of low solubility in water (ECHA 2013)
Stability	isopropylated triphenyl phosphate probably does not undergo oxidation (ECHA 2013)
Production	reaction of isopropylated phenol with phosphorus oxychloride (US EPA 1992)

Purity	The commercial products contain triphenyl phosphate in varying amounts (Table 1). The substance is a mixture of more than 50 different components, many of which are positional isomers. The phenol group may be monoisopropylated, diisopropylated or triisopropylated (US EPA 2010).
Impurities	no data
Uses	in metal-working fluids, lubricants, lubricant additives, hydraulic fluids, lubricating greases, cutting oils for metal-working and in coatings, paints, diluents, paint removers, adhesives, sealing agents, photo chemicals, polymer preparations and components and as a laboratory chemical (ECHA 2013)

This documentation is based primarily on the dataset publicly available through REACH (ECHA 2013) and compilations of data by the Environment Agency UK (2009) and the US EPA (2010).

The CAS number 68937-41-7 applies to only one of the components, namely tris(4-isopropylphenyl) phosphate. In the REACH dossier, however, the mixture is registered under this CAS number (ECHA 2013) as a UVCB substance (substance of unknown or variable composition, complex reaction products or biological materials). The mixture is triphenyl phosphate, a substance which is monoisopropylated, diisopropylated or triisopropylated at the second or fourth position. The commercial products have undergone different degrees of isopropylation and contain also non-isopropylated triphenyl phosphate in varying amounts (Table 1).

Tab. 1 Example compositions of commercial products of isopropylated triphenyl phosphate (Environment Agency UK 2009)

Component	Kronitex 50 (Durad 110)	Kronitex 100	Kronitex 200	Phosflex 31P	Reolube HYD 46	Reofos 35	Reofos 50	Reofos 65	Reofos 95	Reofos 120	Durad 300	Durad 310M
triphenyl phosphate	33%	18%	4%–6%	28%–30%	7%	35%	28%–32%	20%	9%	7.5%	5%	4%
2-isopropyl-phenyl diphenyl phosphate	21%	27%	7%–10%	present	35%	no data	no data	no data	no data	no data	no data	no data
4-isopropyl-phenyl diphenyl phosphate	12%	11%	20%–25%	present	no data	no data	no data	no data	no data	no data	no data	no data
bis(2-isopropyl-phenyl) phenyl phosphate	6%	7%	present	–	25%	no data	no data	no data	no data	no data	no data	no data
bis(4-isopropyl-phenyl) phenyl phosphate	2%	5%	–	–	no data	no data	no data	no data	no data	no data	no data	no data
tris(isopropyl-phenyl) phosphate	8%	11%	–	–	10%	no data	no data	no data	no data	no data	no data	no data
isopropylated triphenyl phosphate	–	–	–	–	–	65%	70%	80%	91%	92.5%	95%	91%
others	18%	21%	minor components: di-, tri- and tetraisopropyl-substituted triphenyl phosphates	3-isopropyl-phenyl diphenyl phosphate, diisopropyl-phenyl diphenyl phosphate isomers (2,6-, 2,4-, 2,5-, 3,5-) and trisubstituted phenol isomers	no data	–	–	–	–	–	–	5%

1 Toxic Effects and Mode of Action

Isopropylated triphenyl phosphate is an organophosphate that, depending upon its composition, may cause organophosphate-induced delayed neuropathy. A decisive factor for the induction of neurotoxicity seems to be the amount of 2-isopropylphenyl diphenyl phosphate the substance contains. However, the most sensitive toxicological end point is not neurotoxicity, but effects on the liver, adrenal glands and ovaries.

Isopropylated triphenyl phosphate has low acute toxicity. In a 90-day study with continuous inhalation exposure of rats to Durad MP280 (exact composition not specified), performance in a reflex test was impaired, liver weights were increased and fatty deposits in the adrenal cortex were observed after exposure to concentrations of 10 mg/m^3 and above. In male (29 days of exposure) and female (54 days of exposure) Sprague Dawley rats given daily gavage doses of Reofos 65, a dose-dependent increase in adrenal gland weights, vacuolation in the cells of the adrenal cortex and interstitial cell hyperplasia and hypertrophy in the ovaries were observed at the low dose of 25 mg/kg body weight and day and above. After 90-day administration of oral doses of Reofos 35, similar effects were induced at the low dose of 25 mg/kg body weight and day and above. In a study with oral exposure of rats to Kronitex K-100 for 28 days, mortality was increased at the low dose of about 100 mg/kg body weight and day and above. Neurotoxicity in the form of ataxia and nerve degeneration was observed in hens given oral Kronitex 50 doses of 90 mg/kg body weight and day and above for 91 days; erythrocyte cholinesterase activity was inhibited in female rats after the application of Kronitex 50 to the skin for 28 days at doses of 500 mg/kg body weight and day and above.

Isopropylated triphenyl phosphate does not cause skin irritation in rats and rabbits and no or only minimal irritation of the eyes.

A skin sensitization potential could not be derived for isopropylated phenyl phosphate, triphenyl phosphate or the structurally closely related tri-*o*-cresyl phosphate on the basis of the in some cases contradictory data available for these substances. No data are available for sensitizing effects on the airways.

Male and female fertility was reduced in rats given Reofos 65 by gavage at doses of 100 mg/kg body weight and day and above, and mortality was increased during early postnatal development up to lactation day 4. In another study, foetal body weights were reduced on lactation day 4 after exposure to 400 mg/kg body weight and day. At this dose, which was the only dose tested, offspring mortality was increased also after exposure to Reofos 35 and Reofos 120. In a study carried out according to OECD Test Guideline 414 with oral doses of Reofos 35 given to rats from the beginning of gestation up to gestation day 19, developmental toxicity was not observed up to a dose of 400 mg/kg body weight and day. Maternal toxicity was noted at 200 mg/kg body weight and day.

Isopropylated triphenyl phosphate did not cause genotoxic or cell transforming effects in vitro or in vivo. There are no studies available of the carcinogenicity of the substance.

2 Mechanism of Action

Isopropylated triphenyl phosphate belongs to the group of organophosphates; they are known to lead to delayed neurotoxic effects. Isopropylated triphenyl phosphate contains positional isomers of isopropylated phenyl phosphates in varying amounts.

In analogy to other alkylated aryl phosphates, only 2-substituted isomers appear to induce neurotoxic effects, if a hydrogen atom is present at the alpha-C atom. Phenyl saligenin phosphate is formed only by these isomers; this metabolite is considered to be responsible for the neurotoxic effects (Johnson 1975). By contrast, branching of the alkyl residue reduces the neurotoxic potential (Bondy et al. 1960; Johannsen et al. 1977). Neurotoxicity is caused by the inactivation of the enzyme NTE (neuropathy target esterase, formerly also known as neurotoxic esterase). In the first step, NTE is phosphorylated by phenyl saligenin phosphate. In the second step, the enzyme-substrate complex is ionized by hydrolysis of the ester group (Johnson 1975; see also Hartwig 2016).

In studies with hens, axon degeneration in the spinal nerves and the peripheral nerves (see also Section 5.1.2 and 5.2.2) was observed. Degeneration and demyelination were preceded by swelling of the axon leading to compression and ellipsoidal deformation of the myelin, followed by fragmentation and lysis up to complete myelin loss. The same changes were observed also after exposure to tri-*o*-cresyl phosphate, although they were more marked in this case (US Air Force 1983).

The degeneration of the nerves is likewise preceded by marked inhibition of the activity of NTE (see Section 5.1.2). However, 90% inhibition of the activity of NTE by triaryl phosphate is required for neurotoxic effects to become noticeable (Johnson 1975).

The mechanism underlying the effects on the adrenal glands and the ovaries is unknown.

Structure–effect relationships of the neurotoxic effect

Of the isomers of isopropylated triphenyl phosphate, mono-2-isopropylphenyl diphenyl phosphate induces the strongest neurotoxic effects, followed by bis(2-isopropylphenyl) phenyl phosphate. The isomer tris(2-isopropylphenyl) phosphate causes the weakest neurotoxic effects. Tris(3-isopropylphenyl) phosphate, tris(4-isopropylphenyl) phosphate, bis(4-isopropylphenyl) phenyl phosphate and 4-isopropylphenyl diphenyl phosphate are not neurotoxic (Johnson 1975; see also Section 5.1.2). When toxicity is assessed based on the NOAEL (no observed adverse effect level) for ataxia, it decreases in severity with increasing isopropylation, as is demonstrated by the studies of neurotoxicity in hens (see Section 5.1.2). In these studies, the NOAEL for Kronitex 50 was below 2000 mg/kg body weight and that for Kronitex 100 was below 3000 mg/kg body weight. The NOAELs for Kronitex 200, Reofos 95 and Durad 300 were 10 000 mg/kg body weight or higher.

A comparative study of reproductive toxicity induced in rats by Reofos 35, Reofos 65 and Reofos 120 confirmed that neurotoxicity decreases with increasing isopropylation (ECHA 2013; see also Section 5.5.1). Reofos 35 induces more severe toxic effects in parent animals than Reofos 65, which is more potent than Reofos 120. The opposite is true for the reduction of the fertility and fecundity indices.

In a comparative study of acute toxicity (see Section 5.1.2) with groups of 3 male and 3 female rats given oral doses of Reofos 50 or Durad 300 of 5000 mg/kg body weight, neurotoxicity was observed only after exposure to Reofos 50, but not after exposure to Durad 300, which has a higher degree of isopropylation (95%).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Toxicokinetic studies investigating exposure by inhalation are not available. The systemic toxic effects induced after repeated inhalation exposure of rats (see Section 5.2.1) are regarded as evidence that absorption occurs after inhalation.

A number of studies of rats given oral doses of tricresyl phosphate esters demonstrated that the substances are absorbed after oral administration and the substances and their metabolites are excreted completely via the urine and faeces (ATSDR 1997). It is to be assumed that isopropylated triphenyl phosphate is absorbed similarly well.

Two in vitro studies using identical methods (unpublished company studies) investigated the absorption of Reolube HYD 46 and Reofos 50 through the skin. Human epidermis was drawn over a receptor chamber containing 70% ethanol; the test substances Reolube HYD 46 or Reofos 50 (concentrations not specified) were placed in the donor chamber (no other details). After exposure for 57 hours, the ethanol fraction was analysed for the presence of the test substances. In one study, the absorption rates for "TPP" (probably triphenyl phosphate) and "2-IDPP" (probably 2-isopropylphenyl diphenyl phosphate) were calculated to be 0.67 ± 0.3 and 3.32 ± 0.12 µg/cm^2 and hour, respectively, and in the other, 0.9 ± 0.13 and 0.54 ± 0.12 µg/cm^2 and hour, respectively. It is unclear to which test substance the results refer (Environment Agency UK 2009). Firstly, these studies used an unphysiological receptor solution (70% ethanol), which

markedly accelerated absorption, and secondly, the exposure period was very long (57 hours). This may have impaired the integrity of the skin. Both factors would lead to an overestimation of absorption.

Fluxes of 0.26, 0.004 and 0.0027 µg/cm^2 and hour, respectively, were calculated for a saturated aqueous solution using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995). Assuming the exposure of 2000 cm^2 of skin for 1 hour, the amount absorbed would be 0.52, 0.008 and 0.0054 mg, respectively.

As absorption was clearly overestimated in the in vitro study, a flux of 1 µg/cm^2 and hour is used to calculate the amount absorbed through the skin. This flux is the mean of the flux determined in vitro (4 µg/cm^2 and hour) and the highest flux calculated by applying the models (0.26 µg/cm^2 and hour). Assuming the exposure of 2000 cm^2 of skin for 1 hour, this would be equivalent to the absorption of 2 mg.

3.2 Metabolism

The bile extracts from rabbits given a single oral dose of Reolube HYD46 of 2000 mg/kg body weight were analysed by mass spectrometry to identify the metabolites. Following treatment with β-glucuronidase, isopropylated triphenyl phosphate derivatives were determined in the bile extract that were hydroxylated at the phenyl or the isopropyl group. This suggests phase I oxidation by microsomal cytochrome P-450 oxidases followed by phase II glucuronidation. If the bile extracts were not treated with β-glucuronidase, 2 cyclic metabolites with only 2 of what were originally 3 phenyl groups were identified (ATSDR 1997).

No other studies are available that investigated the metabolism of isopropylated triphenyl phosphate.

4 Effects in Humans

Repeated exposure

At a plant producing aryl phosphates (no other details), 60 exposed persons (52 men, 8 women) and 53 control persons without exposure (39 men, 14 women) were subject to clinical examination including nerve conduction velocity tests on 4 nerves (no other details) in the period from July 1980 to December 1981. One group of workers (no other details) had worked in the production plant prior to 1974. After 1974, the aryl phosphate production system was "enclosed", which reduced the contact the workers had with the substance and the intensity of the exposure (no other details). Surface samples yielded evidence of "small quantities" of aryl phosphates, the concentration in air was 1 µl/m^3 or less. Nerve conduction velocity was similar in exposed persons and control persons. Given the limited study reporting and lack of data for exposure and other results, the findings are considered of limited value (Environment Agency UK 2009). For this reason, the study is not included in the evaluation.

A case report about a 48-year-old worker who had been exposed to hydraulic fluids containing isopropylated triphenyl phosphate (exact composition not specified), particularly on his hands and arms, described the development of weakness and paraesthesia in the hands and a reduction (no other details) in nerve conduction velocities. In the months preceding the development of the symptoms, the worker had used hydraulic fluid containing 0.5% isopropylated triphenyl phosphate, which in turn contained less than 50 mg/kg of tri-*o*-cresyl phosphate. In a work-free period, the man noticed muscle weakness in his hands and forearms, which developed 2 weeks after the last exposure. Electromyographs showed a reduced number of motor axon potentials. After 3 years, his symptoms had improved only slightly (no data for exposure) (Environment Agency UK 2009; Sjögren et al. 2010).

In an investigation of 8 other workers with a history of exposure to hydraulic fluids, electromyographs of 4 nerves (no other details) in half of the men, in comparison with those from 8 control persons, revealed a reduced number of motor unit potentials and several single potentials of increased duration and amplitude. No unusual findings were reported for nerve conduction velocities and clinical observations (Environment Agency UK 2009; Sjögren et al. 2010). The study is not included in the evaluation because of a lack of exposure data.

In a Danish case study, a 27-year-old mechanic who was exposed to hydraulic oil (23% triphenyl phosphate, 24% mono-2-isopropylphenyl diphenyl phosphate, 8% bis(2-isopropylphenyl) phenyl phosphate and 1% tris(2-isopropylphenyl) phosphate) developed paresis of both legs and of the thumb and index finger of both hands. The study compared men working in epoxide resin processing who were exposed to a mixture of 30% triphenyl phosphate, 40% monoisopropyl triphenyl phosphate and 30% diisopropyl triphenyl phosphate, triisopropyl triphenyl phosphate and higher congeners with 33 men without exposure. The erythrocyte cholinesterase activity was significantly lower in the exposed men and correlated significantly with the monocyte esterase activity. The plasma cholinesterase activity was not impaired (Sjögren et al. 2010).

In summary, the case studies yielded evidence of neurotoxic effects.

An epidemiological study investigating the cancer risk of workers employed at factories in the USA did not determine an increase in cancer mortality among the exposed persons (no other details) compared with that of the US population (Environment Agency UK 2009). Because of the unspecific nature of the chemical exposure and thus its limited meaningfulness, the study is not included in the evaluation.

Allergenic effects

No clinical data are available for isopropylated triphenyl phosphate. At a production plant, no cases of allergic skin disorders induced by isopropylated triphenyl phosphate were reported (ECHA 2013).

Likewise, there are few data for sensitization caused by contact with triphenyl phosphate or substances containing triphenyl phosphate. In an isolated case, contact eczema developed on the bridge of the nose and the temples which was attributed to spectacle frames made of a polymerization product containing triphenyl phosphate. Patch tests with 5% and 0.5% triphenyl phosphate yielded 2+ reactions, and a 1+ reaction was obtained with 0.05% tri-*o*-cresyl phosphate. Co-reactivity to 0.5% tri-*m*-cresyl phosphate was determined (Carlsen et al. 1986; see also Henschler 1991).

Several additional cases were reported of allergic contact eczema induced by triphenyl phosphate and of positive reactions in the patch test (Berkoff 1938; Camarasa and Serra-Baldrich 1992; Pegum 1966; Spirig and Elsner 1995).

Of a total of 23 192 patients who were patch tested between 1950 and 1962, 15 produced reactions to the cellulose acetate film containing 7% to 10% triphenyl phosphate (and 3% to 4% esters of phthalic acid) used for patch testing. A closer examination was carried out only in 2 cases; both patients produced reactions in patch tests with triphenyl phosphate (and tri-*o*-cresyl phosphate). According to the authors, positive reactions to the 2 substances were obtained in a total of 4 cases (Hjorth 1964).

Positive reactions to triphenyl phosphate were not produced in patch tests performed in 343 and 174 test persons with the constituents of a series of plastics and glues (Kanerva et al. 1997, 1999; Tarvainen 1995). In the clinics of the Information Network of Departments of Dermatology (IVDK), a total of 2831 patients were tested with 5% triphenyl phosphate between 1990 and 1994; 1 positive reaction with unclear relevance, 1 irritant reaction and 6 questionable reactions were obtained (Kayser and Schlede 2001).

In addition to a few isolated, earlier reports of positive reactions produced in patch tests with tri-*o*-cresyl phosphate (Carlsen et al. 1986; Grimalt et al. 2009; Hjorth 1964; Norris and Storrs 1990), a report of a contact allergic reaction and a positive patch test result with 5% tri-*o*-cresyl phosphate in petrolatum has recently become available. The PVC gloves that were used were found to contain this substance in an amount of about 21 µg/g in addition to triphenyl phosphate (about 55 µg/g) and triphenyl phosphite (116 µg/g). Patch tests were not carried out with the latter 2 substances (Crépy et al. 2014).

In tests carried out in the clinics of the IVDK, no reactions to 5% tri-*o*-cresyl phosphate in petrolatum were produced in 199 persons with exposure to metal-working fluids (Geier et al. 2004).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

The findings of the studies are shown in Table 2.

The 4-hour LC_{50} was determined for Durad MP280 aerosol (exact composition not specified) in male and female Sprague Dawley rats. Groups of 5 animals per sex were exposed to analysed concentrations of 6190 to 6350 mg/m³. As mortality was not observed during the 14 days of the observation period, no other concentrations were tested. In the first 3 hours after exposure, the animals exhibited slight lethargy, their fur was unkempt and soaked with the hydraulic fluid. No unusual findings were determined in the gross-pathological examination (US Air Force 1982).

In a limit test conducted in 1975, 5 male and 5 female Wistar rats were exposed whole-body to Kronitex 50 aerosol for 1 hour at a concentration of 200 000 mg/m³. The LC_{50} was above 200 000 mg/m³. One female died after 7 days without acute clinical symptoms. The observation period lasted 14 days. No unusual findings were determined in the gross-pathological examination (ECHA 2013).

In another limit test conducted in 1975, which is considered to be of only limited validity, 5 male and 5 female Wistar rats were exposed whole-body to Kronitex 200 vapour for 1 hour at a concentration of 2000 mg/m³. Exposure was not lethal for the animals; the examination period was 48 hours (ECHA 2013).

An acute limit test was carried out with inhalation exposure of groups of 10 chickens. The animals were exposed to Reofos 50 aerosol at concentrations of 620, 2400, 2540 or 3090 mg/m³ for 8 hours and then observed for 21 days to determine whether neurotoxic effects had been induced. Mild to moderate ataxia was observed in all animals of the group exposed to 2400 mg/m³ and in 4 of 10 animals at 3090 mg/m³. The histopathological examination of the nerves confirmed that degenerative changes were induced at these concentrations. Therefore, the NOAEC (no observed adverse effect concentration) for neurotoxicity was 620 mg/m³ (ECHA 2013; Environment Agency UK 2009).

Tab. 2 LC_{50} values after inhalation exposure to isopropylated triphenyl phosphate

Species, strain, number per group	Substance	LC_{50}	References
rat, Sprague Dawley, 5 ♀, 5 ♂	Durad MP280 aerosol exact composition not specified	4-hour LC_{50} > 6190 to > 6350 mg/m³	US Air Force 1982
rat, Wistar, 5 ♀, 5 ♂	Kronitex 50 aerosol 33% triphenyl phosphate, 41% different monoisopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate	1-hour LC_{50} > 200 000 mg/m³	ECHA 2013
rat, Wistar, 5 ♀, 5 ♂	Kronitex 200 vapour 4%–6% triphenyl phosphate, 27%–35% different monoisopropylated and diisopropylated triphenyl phosphates	1-hour LC_{50} > 2000 mg/m³	ECHA 2013
chicken, 10 ♀, 10 ♂	Reofos 50 aerosol 30% triphenyl phosphate, 70% isopropylated triphenyl phosphate	8-hour LC_{50} > 2400 mg/m³	ECHA 2013; Environment Agency UK 2009

5.1.2 Oral administration

5.1.2.1 Rat

The findings of the studies are shown in Table 3.

Groups of 5 male and 5 female Sprague Dawley rats were given a Durad MP280 dose of 5 ml/kg body weight to determine the oral LD_{50}. As mortality did not occur during the observation period of 14 days, no other doses were tested. Diarrhoea developed in the first 6 hours after administration of the substance, which lasted for 1 to 2 days and led to a decrease in body weight for most of the animals; all of the animals subsequently recovered. No unusual findings were determined in the gross-pathological examination (US Air Force 1982). Assuming a density of 1.2 g/ml, 5 ml/kg body weight is equivalent to about 6000 mg/kg body weight.

Groups of 5 male and 5 female Wistar rats were given gavage doses of Kronitex 50 of 15, 20 or 25 ml/kg body weight and were observed for 14 days after the end of exposure. Four animals of the low dose group died between days 2 and 4, 6 animals of the medium dose group died between days 3 and 9, and 5 animals of the high dose group died between days 2 and 7. The gross-pathological examination found visceral haemorrhage and haematuria. Clinical observations were not reported. The LD_{50} was 21.0 ml/kg body weight (ECHA 2013). Assuming a density of about 1.2 g/ml, this is equivalent to about 25 000 mg/kg body weight.

Another limit test, carried out in 1978 and reported only in abridged form, was performed with 5 male and 5 female rats (strain not specified). Following exposure to a single oral dose of Kronitex 50 of 5000 mg/kg body weight, 3 of the 10 animals died (1 male on day 1, 2 females on day 2) during the 14-day observation period. Clinical observations were not reported. The LD_{50} determined in this study was above 5000 mg/kg body weight (ECHA 2013).

In a third limit test, carried out in 1976 and likewise available only in abridged form, 5 male and 5 female Wistar rats were given a single gavage dose of Kronitex 50 of 20 000 mg/kg body weight. Three animals died on day 1 and 1 animal on day 2. The animals were observed for 14 days after the end of exposure. Chromodacryorrhea ("red tears", deposits of the discharge secreted by the Harderian gland) and visceral haemorrhages were determined by gross-pathological examination. Clinical observations were not reported. In this study, the LD_{50} was above 20 000 mg/kg body weight (ECHA 2013; Environment Agency UK 2009).

In 2 other studies, oral doses of Reofos 50 or Durad 300 of 5000 mg/kg body weight given to 3 male and 3 female rats were not lethal. The clinical signs of toxicity observed after exposure to Reofos 50 were tremor, salivation, ataxia, decreased locomotion, chromorhinorrhea (reddish discharge from the nasal mucosa), chromodacryorrhea and abdominal staining. After 11 days, the symptoms were no longer noticeable. Abdominal staining and chromorhinorrhea were observed during the first 2 days after treatment with Durad 300 (Environment Agency UK 2009). The findings of this comparative study showed that, unlike Reofos 50, Durad 300 did not induce neurotoxic effects.

In an acute limit test, 5 male Long-Evans rats were given a single oral dose of Reofos 65 of 0 or 2000 mg/kg body weight (no other details). Blood samples were taken prior to and 24 hours after treatment and analysed for serum cholinesterase activity (serum ChE). The animals were sacrificed 44 hours after dosing and samples of brain tissue were examined for ChE and NTE activity. The test included a group of positive control animals (treated with tri-*o*-cresyl phosphate). In comparison with the levels determined in the untreated animals, the serum ChE activity was reduced in the treated animals by 87%, which was almost equivalent to the 94% decrease observed in the positive controls. The ChE and NTE activities in the brain were significantly inhibited (–35% and –50%, respectively; tri-*o*-cresyl phosphate: –69% and –91%, respectively). Clinical symptoms were not observed in the animals treated with Reofos 65, while lacrimation, tremor, staining and reduced body temperatures were noted in the animals of the positive control group (ECHA 2013; Environment Agency UK 2009).

5.1.2.2 Chinese hamster

In a study with 5 male and 5 female Chinese hamsters, none of the animals exposed to a Reofos 50 dose of 5000 mg/kg body weight died during the observation period of 14 days (Environment Agency UK 2009).

Tab. 3 LD_{50} values after oral administration of isopropylated triphenyl phosphate

Species, strain, number per group	Substance	LD_{50}	References
rat, Sprague Dawley, 5 ♀, 5 ♂	Durad MP280 exact composition not specified	> 5 ml/kg body weight (about 6000 mg/kg body weight)	US Air Force 1982
rat, Wistar, 5 ♀, 5 ♂	Kronitex 50 33% triphenyl phosphate, 41% different monoisopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate	21 ml/kg body weight (about 25 000 mg/kg body weight)	ECHA 2013
rat, no other data, 5 ♀, 5 ♂	Kronitex 50 33% triphenyl phosphate, 41% different monoisopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate	> 5000 mg/kg body weight	ECHA 2013
rat, Wistar, 5 ♀, 5 ♂	Kronitex 50 33% triphenyl phosphate, 41% different monoisopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate	> 20 000 mg/kg body weight	ECHA 2013; Environment Agency UK 2009
rat, Long Evans, 5 ♂	Reofos 65 20% triphenyl phosphate, 80% isopropylated triphenyl phosphate	> 2000 mg/kg body weight	ECHA 2013; Environment Agency UK 2009
rat, Wistar, 3 ♀, 3 ♂	Reofos 50 30% triphenyl phosphate, 70% isopropylated triphenyl phosphate	> 5000 mg/kg body weight	Environment Agency UK 2009
rat, Wistar, 3 ♀, 3 ♂	Durad 300 5% triphenyl phosphate, 95% isopropylated triphenyl phosphate	> 5000 mg/kg body weight	Environment Agency UK 2009
Chinese hamster, 5 ♀, 5 ♂	Reofos 50 30% triphenyl phosphate, 70% isopropylated triphenyl phosphate	> 5000 mg/kg body weight	Environment Agency UK 2009

5.1.2.3 Chicken

Two groups consisting of 6 hens each were formed to determine the ED_{50} of Reofos 50. One animal of each group was given an initial oral dose and then observed for the development of neurotoxic symptoms during the following 21 days. Depending upon the findings, the next animal was given a higher or lower dose. The same procedure was used for both groups. The ED_{50} was 3928 mg/kg body weight (95% confidence interval: 2714 to 5265 mg/kg body weight) (no other details; ECHA 2013; Environment Agency UK 2009).

The findings of the studies below are shown in Table 4. The table includes only studies with at least 4 animals per group.

Tab. 4 Studies of acute neurotoxicity after a single oral exposure (gavage) of chickens to isopropylated triphenyl phosphate

Hens per group	Substance	Dose (mg/kg body weight)	NOAEL / LOAEL, animals with ataxia, other findings	References
10	Kronitex 50 33% triphenyl phosphate, 41% different monoisopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate	0, 2000, 4000, 6000, 8000, observed for 21 days, EPA Test Guideline EPA OPP 81-7	LOAEL: 2000 mg/kg body weight 2000 mg/kg body weight and above: 1/10, 4/10, 6/10, 3/8, body weights ↓ 4000 mg/kg body weight and above: degeneration of nerves	ECHA 2013; Environment Agency UK 2009

Tab. 4 *(continued)*

Hens per group	Substance	Dose (mg/kg body weight)	NOAEL / LOAEL, animals with ataxia, other findings	References
10	Kronitex 50 33% triphenyl phosphate, 41% different monoisopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate	0, 4000, observed for 21 days, after 21 days: again 4000	LOAEL: 4000 mg/kg body weight 0/10, 4/10 NTE unchanged, 100% ataxia after second dose	ECHA 2013
10	Kronitex 100 18% triphenyl phosphate, 50% different monoisopropylated and diisopropylated triphenyl phosphates, 11% tris(isopropylphenyl) phosphate	0, 3000, 5000, 7000, 9000, observed for 21 days	LOAEL: 3000 mg/kg body weight 3000 mg/kg body weight and above: transient ataxia (number of affected animals not specified) degeneration of nerves, 9000 mg/kg body weight: body weights ↓	ECHA 2013; Environment Agency UK 2009
10	Reofos 95 9% triphenyl phosphate, 91% isopropylated triphenyl phosphate	0, 2500, 5000, 10 000, 20 000, observed for 21 days, animals of the 20 000 group only: after 21 days: 20 000, observed for 21 days	NOAEL: 10 000 mg/kg body weight 0/10, 0/10, 0/10, 2/10 30% ataxia after second dose	ECHA 2013; Environment Agency UK 2009
10 control: 18	Reofos 95 9% triphenyl phosphate, 91% isopropylated triphenyl phosphate	0, 20 000, 30 000, 40 000, 50 000, observed for 21 days	LOAEL: 20 000 mg/kg body weight 1/10, 2/10, 2/10, 2/10 30 000 and 50 000 mg/kg body weight: histopathological evidence of degeneration of nerves	ECHA 2013
4 high dose: 10	Durad 300 5% triphenyl phosphate, 95% isopropylated triphenyl phosphate	0, 400, 2000, 4000, 8000, 16 000, observed for 21 days	NOAEL: 8000 mg/kg body weight 400 mg/kg body weight: 27%–28% inhibition of NTE in the brain 16 000 mg/kg body weight and above: ataxia	ECHA 2013

LOAEL: lowest observed adverse effect level; NOAEL: no observed adverse effect level; NTE: neuropathy target esterase

The studies in hens (see Table 4) demonstrate that the neurotoxicity decreases with increasing isopropylation when neurotoxicity is determined on the basis of the NOAEL for ataxia. This coincides with the findings of the studies below, which show that mono-2-isopropylphenyl diphenyl phosphate induces the most severe neurotoxic effects.

Tris(2-isopropylphenyl) phosphate, given to hens in oral doses of 600 or 1000 mg/kg body weight and day for 4 days, did not induce clinical symptoms of neurotoxicity. NTE activity was slightly inhibited (by 12%) at the low dose, while no effects on NTE activity were induced at the high dose. A single bis(2-isopropylphenyl) phenyl phosphate dose of 1200 mg/kg body weight yielded unclear findings with respect to clinical neurotoxicity and inhibited NTE activity by 85%, while a dose of 600 mg/kg body weight did not cause ataxia and inhibited NTE activity by 39%. A single 2-isopropylphenyl diphenyl phosphate dose of 1200 mg/kg body weight induced ataxia and inhibited NTE activity by 90%, while a dose of 600 mg/kg body weight did not lead to clinical neurotoxicity and inhibited NTE activity by 84%. No signs of clinical neurotoxicity were observed after oral exposure to tris(3-isopropylphenyl) phosphate, tris(4-isopropylphenyl) phosphate, bis(4-isopropylphenyl) phenyl phosphate or 4-isopropylphenyl diphenyl phosphate at a dose of 1000 mg/kg body weight (Johnson 1975).

Histopathological examinations were carried out in hens (see Table 4), revealing degeneration of the nerves after exposure to Kronitex 100 at doses of 3000 mg/kg body weight and above. After exposure to Durad 300, inhibition of

NTE activity in the brain was observed at doses of 400 mg/kg body weight and above (27% to 28%). In the same study, ataxia was first observed at 16 000 mg/kg body weight (NTE activity was not determined at this dose).

These findings demonstrate that the first signs of neurotoxicity occur only after 90% of the activity of NTE has been inhibited by triaryl phosphate (Johnson 1975).

5.1.2.4 Summary

Isopropylated triphenyl phosphate induces only moderate acute toxicity after oral exposure of rats and hamsters (see Table 3). Neurotoxicity (ataxia) was observed after administration of oral Reofos 50 doses of 5000 mg/kg body weight, but not after exposure to Durad 300 at the same dose. The latter substance has a higher degree of isopropylation (95%). Neurotoxicity thus decreases with increasing isopropylation.

Studies with hens (see Table 4) likewise demonstrated that the toxicity, determined on the basis of the NOAEL for ataxia, decreases with increasing isopropylation. Therefore, the NOAEL for Kronitex 50 was below 2000 mg/kg body weight, the NOAEL for Kronitex 100 was below 3000 mg/kg body weight, and the NOAELs for Kronitex 200, Reofos 95 and Durad 300 were 8000 mg/kg body weight or higher.

5.1.3 Dermal application

The findings of the studies are shown in Table 5.

5.1.3.1 Rabbit

Durad MP280 was applied to the shaved skin of 5 male and 5 female New Zealand White rabbits at a dose of 5 ml/kg body weight and covered with an occlusive dressing for 24 hours. No toxicity was observed during the 14-day observation period. A slight loss in weight was observed in the males after application of the test substance; this led to decreased overall body weight gains during the 14-day period. Skin irritation did not occur. No substance-related findings were determined in the gross-pathological examination (US Air Force 1982). The LD_{50} was thus above 5 ml/kg body weight. Assuming a density of about 1.2 g/ml, this is equivalent to about 6000 mg/kg body weight.

In a limit test carried out in 1976, Kronitex 50 was applied to the intact skin of 5 albino rabbits (no other details) and to the scarified skin of another 5 albino rabbits at a dose of 10 000 mg/kg body weight and the animals were observed for a period of 14 days. The dose was not lethal for any of the animals. The LD_{50} was thus above 10 000 mg/kg body weight (ECHA 2013).

In an invalid limit test carried out in 1975 with an observation period of only 24 hours, Kronitex 200 was applied to the skin of 10 rabbits at a dose of 200 mg/kg body weight. The dose was not lethal for any of the animals (ECHA 2013).

Application of Reofos 50, Reofos 65 or Reofos 95 to the intact or abraded skin of groups of 5 rabbits at a dose of 10 000 mg/kg body weight was not lethal for any of the animals during the 14-day observation period (no other details; Environment Agency UK 2009).

Durad 300 was applied occlusively for 24 hours to the intact skin of 3 rabbits at a dose of 2000 mg/kg body weight (it is unclear whether the substance was rinsed off or left on). The substance was not lethal for any of the animals during the 14-day observation period (no other details; Environment Agency UK 2009).

5.1.3.2 Rat

In 2 studies carried out according to OECD Test Guideline 402, Reofos 50 or Reolube HYD 46 were applied to the intact, shaved skin of groups of 5 male and 5 female rats at a dose of 2000 mg/kg body weight and covered with an occlusive dressing for 24 hours. The test site was then cleaned with lukewarm water and the animals were observed for 14 days. Treatment was not lethal for any of the animals. Clinical signs of toxicity were dyspnoea, ruffled fur, hunched posture, abnormally curved or abdominal position and sedation. Erythema was observed at the treatment site of the animals

treated with Reolube HYD; the study did not report the severity of the erythema or the number of animals affected (Environment Agency UK 2009).

Occlusive application of Reofos 50 to groups of 3 to 5 male and 3 to 5 female Sprague Dawley rats for 24 hours at a dose of 2000 mg/kg body weight was not lethal for any of the animals during the 14-day observation period. The body weights and the gross-pathological examination did not reveal any unusual findings (Environment Agency UK 2009; US EPA 2010).

Tab. 5 Studies of acute toxicity after dermal application of isopropylated triphenyl phosphate

Species, strain, number per group	Substance	LD_{50}	References
rabbit, New Zealand White, 5 ♀, 5 ♂	Durad MP280 exact composition not specified	> 5 ml/kg body weight (about 6000 mg/kg body weight)	US Air Force 1982
rabbit, albino, no other data, 5	Kronitex 50 33% triphenyl phosphate, 41% different mono-isopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate	> 10 000 mg/kg body weight limit test	ECHA 2013
rabbit, no other data, 10	Kronitex 200 4%–6% triphenyl phosphate, 35% different mono-isopropylated and diisopropylated triphenyl phosphates	> 200 mg/kg body weight invalid limit test	ECHA 2013
rabbit, no other data, 5	Reofos 50 30% triphenyl phosphate, 70% isopropylated triphenyl phosphate	> 10 000 mg/kg body weight	Environment Agency UK 2009
rabbit, no other data, 5	Reofos 65 20% triphenyl phosphate, 80% isopropylated triphenyl phosphate	> 10 000 mg/kg body weight	Environment Agency UK 2009
rabbit, no other data, 5	Reofos 95 9% triphenyl phosphate, 91% isopropylated triphenyl phosphate	> 10 000 mg/kg body weight	Environment Agency UK 2009
rabbit, no other data, 3	Durad 300 5% triphenyl phosphate, 95% isopropylated triphenyl phosphate	> 2000 mg/kg body weight	Environment Agency UK 2009
rat, no other data, 5 ♂, 5 ♀	Reolube HYD 46 7% triphenyl phosphate, 35% 2-isopropylphenyl diphenyl phosphate, 25% bis(2-isopropylphenyl) phenyl phosphate, 10% tris(isopropylphenyl) phosphate	> 2000 mg/kg body weight, OECD Test Guideline 402	Environment Agency UK 2009
rat, no other data	Reofos 50 30% triphenyl phosphate, 70% isopropylated triphenyl phosphate	> 2000 mg/kg body weight, OECD Test Guideline 402	Environment Agency UK 2009
rat, Sprague Dawley, 3–5 ♂, 3–5 ♀	Reofos 50 30% triphenyl phosphate, 70% isopropylated triphenyl phosphate	> 2000 mg/kg body weight	Environment Agency UK 2009; US EPA 2010

5.1.3.3 Summary

Isopropylated triphenyl phosphate is hardly toxic in rats and rabbits following acute dermal application (see Table 5). The various products did not differ in toxicity; the absorption through the skin is likely to have played a limiting role in this.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

The findings of the studies are shown in Table 6.

In a 21-day inhalation study, groups of 10 male and 10 female F344 rats, 10 male Syrian hamsters, and 4 male and 4 female New Zealand White rabbits were exposed to Durad MP280 aerosol at concentrations of 0, 25 or 250 mg/m^3 (mass median aerodynamic diameter (MMAD) = 2.3 µm) for 6 hours a day, on 5 days a week. The exact constituents of this substance are not known as the data provided are incomplete. According to ATSDR (1997), its primary components are trixylyl phosphate, CAS number 25155-23-1, and Reofos 95. The studies examined the body weights, organ weights (brain, liver, kidneys, spleen, heart) and haematology (haematocrit, haemoglobin, red and white blood cells, differential blood count, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH)). In the high concentration group, the absolute and relative liver weights of the male rats were significantly increased by 22% and 14%, respectively, in comparison with those of the control group. In the female rats, the liver weights were increased by 14% (absolute) and 13% (relative); compared with control values, the increases were statistically significant. As a histopathological examination was not carried out, it is not possible to determine the extent of the liver damage. In the male rats of the high concentration group, the number of red blood cells (+8%), the haematocrit value (+8%) and the haemoglobin level (+4%) were increased. This trend was evident in the latter 2 values also in the low concentration group; however, the increases were not yet statistically significant. Similar values were observed in the female rats: red blood cells: 7.09, 7.56 and 7.57 at 0, 25 and 250 mg/m^3, respectively; haematocrit: 38.5, 41.4, 40.9; haemoglobin: 14.9, 15.4, 15.1 at 0, 25 and 250 mg/m^3, respectively. However, all values were in the range of the normal biological limits for this species.

A male hamster died after 9 exposures at a concentration of 250 mg/m^3. No other substance-related effects were observed in the hamster.

Two female rabbits in the low concentration group died shortly after the beginning of exposure. The gross-pathological examination revealed purulent exudate in the thorax; this is characteristic for a bacterial infection. The pathogen was identified as Pasteurella multocida. The haematological examination of the rabbits revealed that the number of red blood cells, and the haematocrit and haemoglobin values were increased, but not significantly (male rabbits: erythrocytes: 5.81, 6.55, 6.55 at 0, 25 and 250 mg/m^3, respectively; haematocrit: 37.9, 41.8, 43.6; haemoglobin: 12.8, 14.1, 14.9; female rabbits: erythrocytes: 6.07, 6.2, 6.99; haematocrit: 37.9, 39.2, 44.1; haemoglobin: 12.9, 13.5, 15.0). The authors suggested that the lack of statistical significance may be a result of the small number of animals. Again, all values were within the normal range for rabbits. According to the authors, rabbits were included in the study to identify possible neurotoxic effects. There were no noticeable cholinergic symptoms (US Air Force 1983).

In a 90-day inhalation study, groups of 20 male and 20 female F344 rats, 20 male Syrian hamsters and 4 male and 4 female New Zealand White rabbits were continuously exposed to Durad MP280 aerosol at concentrations of 0, 10 or 100 mg/m^3 (MMAD = 1.9–2.0 µm). Five male and 5 female rats of the high concentration group underwent sensory/motor screening at 2, 4 and 8 weeks of exposure and at the end of the study. The tests performed were the tail tip curl reflex, foot drop (also called "hind foot splay") and the lateral hop. Blood samples were taken from all animals for haematological examination. The haematological examination was performed as described above for the 21-day inhalation study. Clinico-chemical examinations were not carried out. All gross-pathological findings, suspected tumours and regional lymph nodes, larynx, trachea, lungs and bronchi, heart, thyroid gland, liver, spleen, kidneys, bladder, nose, brain, skin, gall bladder, pancreas, adrenal glands, pituitary gland, testes/ovaries, and in addition the sciatic nerve (proximal and distal sections) and the nerves of the spinal marrow in rabbits and rats, were examined histopathologically. Also retained for possible examination were the parathyroid gland, oesophagus, sternebrae, vertebrae and femur (plus bone marrow), lymph tissue (mandibular and mesenteric lymph nodes), mammary gland, stomach, duodenum, ileum, colon, anus, thigh muscles, thymus, seminal vesicles, prostate and uterus.

Several rats in the high concentration group (25% of the females) died at the interim blood sampling. A different procedure was then used and no further animals died. Hunched posture (kyphosis) was observed in the male and female rats of the high concentration group; this remained unchanged until the end of the study. In comparison with control

values, the body weight gains were reduced in the exposed male and female animals at concentrations of 10 mg/m³ and above. The effect was only slight and not statistically significant in the female rats. A decline in performance in the tail tip curl test was noted in male rats exposed to 10 mg/m³ and above. The behaviour of the females in this test was erratic/unpredictable and the loss of test subjects greatly hindered a conclusive interpretation. In the high concentration group, leukocytosis in the male rats, a reduced erythrocyte count in the females and increased relative kidney weights in the males and females were noted. The absolute and relative liver weights were increased in both sexes at 10 mg/m³ (relative weight: +4% and +10%, respectively) and at 100 mg/m³ (relative weight: +40% and 45%, respectively). In the gross-pathological examination, the adrenal glands of the female rats were found to be enlarged at concentrations of 10 mg/m³ and above (0/18, 5/20, 8/15 at 0, 10, 100 mg/m³); however, this finding was not reflected in the organ weights. The same effect was observed in the male rats, but only in the high exposure group (6 of 20 animals in comparison with 0 of 20 animals in the 2 other groups). Another effect that was observed only in the high concentration group was testicular atrophy (5 of 20 animals in comparison with 0 of 20 animals in the 2 other groups). In the histopathological examination, 35% to 40% of the control animals had developed inflammatory signs in the respiratory tract, which the authors interpreted as a mild infection. Slight goblet cell hyperplasia was determined in the noses of male and female rats of the high concentration group. Also in both sexes of the high concentration group, slight hepatocellular swelling was observed. Renal papillary necrosis and fatty deposits in the cells of the renal tubules were found only in the females. Fatty deposits were observed in the adrenal cortex of both sexes at 10 mg/m³ and above (at an assumed respiratory volume of 0.8 l/min/kg body weight, the daily dose was 11.5 mg/kg body weight, or 16 mg/kg body weight and day when extrapolated to 5 days a week); the severity increased with the exposure concentration. Hypertrophy of the interstitial cells was observed in the ovaries of all exposed females. Moderate to severe degeneration of the vas deferens was observed in the testes of all males in the high concentration group and mild interstitial cell hyperplasia in 4 animals; these effects were not observed in the low concentration group or in the controls.

In male hamsters (females were not examined), lethality occurred only in the low concentration group; an explanation for this was not given. One of 20 animals in the low concentration group and 8 of 20 animals in the high concentration group developed minimal to mild inflammation of the pulmonary interstitial cells. These effects were not found in any of the animals of the control group.

After the first 3 days of exposure at a concentration of 100 mg/m³, rabbits exhibited signs of toxic stress (anorexia and lethargy), followed by cachexia and death. Paralysis of the hind legs was not observed. All rabbits of this group died by exposure day 49. Also rabbits in the other groups died, including animals in the control group. These deaths were probably caused by a Pasteurella multocida infection. The histopathological examination revealed chronic inflammation in the nose in 3 males and lymphocytic interstitial inflammation in the lungs in 2 males (test concentration not specified). Centrilobular to panlobular hepatocellular fatty deposits were detected in all 4 females of the high concentration group. Similar effects were not observed in the males (US Air Force 1983, 1990).

Tab. 6 Effects induced after repeated inhalation exposure to isopropylated triphenyl phosphate

Species, strain, number per group	Exposure	Findings	References
rat, F344, 10 ♂, 10 ♀	**21 days**, 0, 25, 250 mg/m³, aerosol, MMAD = 2.3 µm, 6 hours/day, 5 days/week, Durad MP280 (exact composition not specified)	**25 mg/m³: NOAEC;** ♂/♀: effects on the haematological system; however, all values in the normal biological range; **250 mg/m³**: ♂/♀: absolute and relative liver weights ↑; study of limited relevance as histopathological examination not included	US Air Force 1983
hamster, Syrian hamster, 10 ♂	**21 days**, 0, 25, 250 mg/m³, aerosol, MMAD = 2.3 µm, 6 hours/day, 5 days/week, Durad MP280 (exact composition not specified)	**25 mg/m³: NOAEC;** **250 mg/m³**: ♂: lethal for 1 animal after 9 applications; study of limited relevance as histopathological examination not included	US Air Force 1983

Tab. 6 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rabbit, New Zealand White, 4 ♂, 4 ♀	**21 days**, 0, 25, 250 mg/m³, aerosol, MMAD = 2.3 µm, 6 hours/day, 5 days/week, Durad MP280 (exact composition not specified)	**25 mg/m³: NOAEC;** ♂/♀: effects on the haematological system; however, all values in the normal biological range, ♀: lethal for 2 animals; study of limited relevance as histopathological examination not included	US Air Force 1983
rat, F344, 20 ♂, 20 ♀	**90 days**, 0, 10, 100 mg/m³, aerosol, MMAD = 1.9–2.0 µm, continuous, whole body, Durad MP280 (exact composition not specified)	**10 mg/m³ and above**: ♂/♀: body weight gains ↓ (in ♀ only significant at 100 mg/m³ and above), absolute and relative liver weights ↑ (relative weights: +4%/+10%, +40%/45% at 10 and 100 mg/m³, respectively), adrenal cortex: concentration-dependent increase in fatty deposits, ♂: reduced response in the tail tip curl reflex test, ♀: gross-pathological enlargement of adrenal glands (0/18, 5/20, 8/15 at 0, 10, 100 mg/m³), ovaries: hypertrophy of the interstitial cells (6/20, 18/19 at 10, 100 mg/m³, no data for controls); **100 mg/m³**: ♂/♀: hunched posture (kyphosis), relative kidney weights ↑, nose: goblet cell hyperplasia (♂: 1/20, 0/20, 6/20, ♀: 0/20, 0/20, 1/20 at 0, 10, 100 mg/m³), liver: slight cell enlargement (♂: 3/20, ♀: 4/20, no data for controls), ♂: leukocytosis, enlarged adrenal glands (0/20, 0/20, 6/20 at 0, 10, 100 mg/m³), testicular atrophy (0/20, 0/20, 5/20), degeneration of the vas deferens (0/20 0/20, 20/20), interstitial cell hyperplasia (0/20, 0/20, 4/20), ♀: erythrocytes ↓, kidneys: papillary necrosis (16/20) and fatty deposits in the tubular cells (12/20), in each case 0/20 in the control group	US Air Force 1983, 1990
hamster, Syrian hamster, 20 ♂	**90 days**, 0, 10, 100 mg/m³, aerosol, MMAD = 1.9–2.0 µm, continuous, whole body, Durad MP280 (exact composition not specified)	**10 mg/m³: LOAEC;** mortality (5/20), **10 mg/m³ and above**: lungs: mild to minimal interstitial inflammation (0/20,1/20, 8/20 at 0, 10, 100 mg/m³)	US Air Force 1983, 1990
rabbit, New Zealand White, 4 ♂, 4 ♀	**90 days**, 0, 10, 100 mg/m³, aerosol, MMAD = 1.9–2.0 µm, continuous, whole body, Durad MP280 (exact composition not specified)	**10 mg/m³: NOAEC;** **100 mg/m³**: ♂/♀: signs of toxic stress (anorexia and lethargy, followed by cachexia and death, all animals died by day 49), ♀: liver: centrilobular/panlobular hepatocellular fatty deposits; **Pasteurella multocida infection in all concentration groups and the control group;** study of limited relevance due to the occurrence of the infection and as histopathological examination was not performed	US Air Force 1983, 1990

LOAEC: lowest observed adverse effect concentration; NOAEC: no observed adverse effect concentration

In summary, based on the findings of the 21-day and 90-day inhalation studies in rats and hamsters, the NOAEC lies below 10 mg/m³. Some studies are of limited relevance because the reports did not include all of the findings.

5.2.2 Oral administration

The findings of the studies are shown in Table 8.

5.2.2.1 Rat

Groups of 10 male and 10 female Sprague Dawley rats were given 0, 0.1%, 0.5% or 1% Kronitex K-100 (18% triphenyl phosphate, 50% various monoisopropylated and diisopropylated triphenyl phosphates, 11% tris(isopropylphenyl) phosphate) in the feed for 28 days; this is equivalent to doses of about 0, 100, 500, 1000 mg/kg body weight and day. The haematological examination carried out at the end of the study included haemoglobin, haematocrit, erythrocyte count, leukocyte count and differential blood count; the blood chemistry included blood urea nitrogen (BUN), bilirubin, alanine aminotransferase activity (ALT), glucose, cholesterol, lactic acid dehydrogenase activity (LDH), total protein and albumin levels. The urinalysis included pH, glucose, ketones, bilirubin and occult blood. The brain, thyroid gland, heart, liver, spleen, gonads and kidneys were weighed. The report did not specify whether a complete histopathological examination was carried out on all animals; however, the liver and kidneys of the animals in the high dose and control groups were examined. Twelve animals died during the treatment period; 1 in the control group and 4 each in the low and medium dose groups and 3 in the high dose group. The body weights were reduced in the females of the high dose group and feed consumption was reduced in the females and males (no other details) at doses of 500 mg/kg body weight and day and above. Abnormal haematological values were noted in the high dose group and the results of the blood chemistry tests of the middle and high dose groups deviated from those of the control group (no other details). The relative liver weights were increased in all of the treated animals (no other details). A valid NOAEL cannot be derived because of the insufficient documentation (Environment Agency UK 2009).

A study was carried out according to OECD Test Guideline 422 (combined repeated dose toxicity study with a reproductive/developmental toxicity screening test) with male and female Sprague Dawley rats (see also Section 5.5.1). Groups of 12 animals per sex and dose group were given gavage doses of 0, 25, 100 or 400 mg/kg body weight and day (20% triphenyl phosphate, 80% isopropylated triphenyl phosphate) beginning 15 days before mating, continuing during mating and, in the females, up to postnatal day 4. The males were administered a total of 29 doses, the females up to 54 doses. The NOAEL was below 25 mg/kg body weight and day. A dose-dependent increase in adrenal gland weights (males and females) and ovarian interstitial cell hyperplasia and hypertrophy were observed at this dose and above. The liver weights (males) were increased at 100 mg/kg body weight and above and the epididymis weights were reduced at 400 mg/kg body weight and above; these effects were accompanied by corresponding histopathological changes. A study of the neurotoxic effects (functional observation battery) did not yield substance-related findings (Great Lakes Chemical Corp 2004).

In a screening test for reproductive and developmental toxicity, 12 male and 12 female Sprague Dawley rats were given Reofos 35 (35% triphenyl phosphate, 65% isopropylated triphenyl phosphate), Reofos 65 (20% triphenyl phosphate, 80% isopropylated triphenyl phosphate) or Reofos 120 (7.5% triphenyl phosphate, 92.5% isopropylated triphenyl phosphate) in gavage doses of 0 or 400 mg/kg body weight and day (males for 42 days; females for up to 54 days) (see also Section 5.5.1) (Great Lakes Chemical Corp 2005). When analysed on the basis of the organ weight changes (see Table 7), the comparative study (Great Lakes Chemical Corp 2005) and the study with Reofos 65 described above (Great Lakes Chemical Corp 2004) did not find any significant differences in the systemic toxicity induced by the different mixtures of substances.

Tab. 7 Comparison of the percentage increase in organ weights after oral exposure of rats to isopropylated triphenyl phosphate (Great Lakes Chemical Corp 2004, 2005)

	Reofos 65			Reofos 35	Reofos 65	Reofos 120
	Dose (mg/kg body weight and day)					
	25	100	400	400	400	400
males						
adrenal glands						
absolute	9.5	26	36	49	46	39
relative	13	20	40	67	57	47
liver						
absolute	4	16	34	17	19	13
relative	4	16	37	32	30	22
females						
adrenal glands						
absolute	39	60	88	74	73	92
relative	37	59	92	68	65	80
liver						
absolute	no significant increase			30	25	30
relative	(max. 7%)			27	21	23

In a 13-week study carried out according to OECD Test Guideline 408, groups of 10 male and 10 female CD rats were given Reofos 35 doses of 0, 25, 100 or 325 mg/kg body weight and day. Five additional animals per sex in the control group and in the high dose group were observed for 28 days after exposure. During the study period, exposure to the substance did not lead to findings relating to mortality, clinical symptoms, feed consumption, motor activity (functional observational battery), neurological behavioural disorders and ophthalmoscopy. At the end of the study, blood urea nitrogen and cholesterol levels were increased in the males at doses of 100 mg/kg body weight and day and above; cholesterol levels were increased in both sexes in the high dose group. The increases in the fibrinogen and globulin levels determined in the males of the high dose group were probably caused by an inflammatory response. The gross-pathological examination revealed brownish discoloration and enlargement of the adrenal glands in all exposed females and in the males at doses of 100 mg/kg body weight and day and above. There was a corresponding increase in organ weights (see Table 8). The gross-pathological findings and increased organ weights correlated with diffuse vacuolation in the zona fasciculata, characterized by enlarged cells with foamy cytoplasm. In addition, the cells in the zona reticularis had large single vacuoles; this effect was not reversible by the end of the observation period of 28 days. Additionally, substance-related increases in organ weights were found in the livers of both sexes at doses of 100 mg/kg body weight and day and above, in the thyroid glands of the males at 325 mg/kg body weight and day and in the ovaries of all exposed females. Histopathologically, these were accompanied by centrilobular or panlobular hypertrophy in the liver, follicular cell hypertrophy in the thyroid gland and interstitial cell vacuolation in the ovaries. The LOAEL of this study was 25 mg/kg body weight and day; it was not possible to derive a NOAEL (Chemtura Corp 2015).

5.2.2.2 Chicken

Six hens were given oral doses of Reofos 50 of 5000 mg/kg body weight and day on 5 consecutive days. The animals were then observed for 21 days. Five of the 6 hens exhibited signs of ataxia. Treatment was lethal for 1 animal on day 14 and for 1 on day 16. Histopathological examination of the spinal nerves yielded evidence of axonal degeneration, as typical of delayed organophosphate neurotoxicity, in all animals (ECHA 2013; Environment Agency UK 2009).

In a range-finding study carried out in preparation for a 3-month study, groups of 5 hens were given daily oral doses of Kronitex 50 of 1.7, 5, 16, 49, 148, 444, 1333 or 4000 mg/kg body weight and day for 28 days and then observed for the development of clinical neurotoxic symptoms. Signs of ataxia were not observed up to the dose of 49 mg/kg body weight and day. In the groups given doses of 148 and 444 mg/kg body weight and day, ataxia was noted in 20% of the

animals; at 1333 mg/kg body weight and day, 40% of the animals developed ataxia. Signs of ataxia were noted in 2 of 5 animals in the high dose group; this dose was lethal for the remaining 3. After exposure for 28 days, the NOAEL for this study was 49 mg/kg body weight and day (FMC Corp 1984 b, 1986).

In a 3-month neurotoxicity study, groups of 20 White Leghorn hens were given gavage doses of Kronitex 50 of 0, 10, 20, 90 or 270 mg/kg body weight and day. Groups of 20 control animals were given daily tri-*o*-cresyl phosphate doses of 1.5 or 7.5 mg/kg body weight as the positive control. The animals were observed daily for clinical signs of toxicity; body weights and feed consumption were determined weekly. A gross-pathological examination was carried out at the end of the observation period. The brain, spinal cord and peripheral nerves (tibial and sciatic nerves) were examined histopathologically. No signs suggestive of neurotoxicity were determined up to a Reofos 50 dose of 20 mg/kg body weight and day. In the group exposed to 90 mg/kg body weight, 4 hens developed ataxia, 2 of which were sacrificed prior to the end of the study because of the severity of the symptoms, as were 9 animals of the high dose group. The doses of 0, 10, 20, 90 or 270 mg/kg body weight were lethal for 2, 3, 3, 5 and 6 of the 20 animals in each dose group, respectively. Four of 20 animals of the positive control group died. Body weights were decreased at doses of 90 mg/kg body weight and day and above; this effect was observed also in the animals of the positive control group (no other details). Histopathologically, degeneration of the spinal and peripheral nerves was observed at doses of 90 mg/kg body weight and day and above; the magnitude and intensity of the degeneration were dose-related (no other details), which correlated with the clinical findings. Significant degeneration of the spinal nerves was observed also after exposure to tri-*o*-cresyl phosphate and in 2 animals of the negative control group. This study determined a NOAEL for neurotoxicity of 20 mg/kg body weight and day (FMC Corp 1984 b, 1986).

5.2.2.3 Summary

The LOAEL for oral exposure was calculated to be 25 mg/kg body weight and day based on the findings of a study carried out according to OECD Test Guideline 422 with Reofos 65 and of a 90-day study carried out according to OECD Test Guideline 408 with Reofos 35. The target organs in the 2 studies were the adrenal glands and ovaries. In a 28-day study with Kronitex 100, mortality was increased at the lowest dose tested of 100 mg/kg body weight and day and above.

A screening test for reproductive and developmental toxicity in rats did not determine any significant differences with respect to the systemic toxicity (organ weights) induced by Reofos 35, Reofos 65 and Reofos 120 at the only oral dose tested of 400 mg/kg body weight and day.

Neurotoxicity studies in hens given Kronitex 50 for 91 days determined a NOAEL of 20 mg/kg body weight and day; after 28 days, the NOAEL was 49 mg/kg body weight and day. This suggests that the effects increase in severity over time.

Tab. 8 Effects of isopropylated triphenyl phosphate after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 10 ♂, 10 ♀	**28 days**, 0, 0.1%, 0.5%, 1% in the feed (0, about 100, 500, 1000 mg/kg body weight and day), Kronitex 100 18% triphenyl phosphate, 50% monoisopropylated and diisopropylated triphenyl phosphates, 11% tris(isopropylphenyl) phosphate	**0 mg/kg body weight**: lethality: 1/20; **100 mg/kg body weight: LOAEL (questionably valid)**; lethality: 4/20; **100 mg/kg body weight and above**: relative liver weights ↑; **500 mg/kg body weight**: lethality: 4/20; **500 mg/kg body weight and above**: ♂/♀: feed consumption ↓, changes determined by clinico-chemical examination; **1000 mg/kg body weight**: lethality: 3/20, ♀: body weights ↓, haematological changes; **only histopathology of liver and kidneys, adrenal gland weights not determined**	Environment Agency UK 2009

Tab. 8 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 12 ♂, 12 ♀	**29–54 days**, 0, 25, 100, 400 mg/kg body weight and day, gavage, OECD Test Guideline 422, Reofos 65 20% triphenyl phosphate, 80% isopropylated triphenyl phosphate	**25 mg/kg body weight: LOAEL** **25 mg/kg body weight and above**: ♂/♀: dose-dependent increase in absolute and relative adrenal gland weights (relative weights significant only at 100 mg/kg body weight and above; absolute ♂: 9.5%, 26%, 36% at 25, 100, 400 mg/kg body weight; relative ♂: 13%, 20%, 40%; absolute ♀: 39%, 60%, 88%; relative ♀: 37%, 59%, 92%), vacuolation in the cells of the adrenal cortex (in the zona glomerulosa, fasciculata and reticularis), ♀: absolute and relative ovary weights ↑ (not dose-dependent), interstitial cell hyperplasia and hypertrophy in the ovaries (severity increased with the dose at the minimal to mild grade levels; 0/12, 7/12, 12/12, 12/12 at 0, 25, 100, 400 mg/kg body weight), neutrophils ↓; **100 mg/kg body weight and above**: ♂/♀: salivation ↑ 1 hour after dosing, lymphocytes ↑, ♂: neutrophils ↓ (not significant); absolute and relative liver weights ↑, centrilobular hepatocellular hypertrophy, ♀: feed consumption ↑ (no body weight gains, changes in feed conversion probable); **400 mg/kg body weight**: ♂/♀: excessive scratching in the cage 1 hour after dosing ↑, ♂: cholesterol ↑ (47%), globulin ↑, albumin/globulin ↓, epididymis weights ↓, ♀: euthanasia of 5 animals because of complete litter loss up to postnatal day 3, only 1 animal survived until the end of the study (postnatal day 4)	Great Lakes Chemical Corp 2004
rat, Sprague Dawley, 12 ♂, 12 ♀	**42–54 days**, 0, 400 mg/kg body weight and day, gavage, Reofos 35 35% triphenyl phosphate, 65% isopropylated triphenyl phosphate	**400 mg/kg body weight: LOAEL**; **400 mg/kg body weight**: ♂/♀: salivation ↑, absolute and relative adrenal gland weights ↑, relative liver weights ↑, ♂: body weights and body weight gains ↓, fatty deposits and vacuolation in the adrenal glands, ♀: absolute liver weights ↑, centrilobular hypertrophy of the liver; for detailed organ weight data see Table 7	Great Lakes Chemical Corp 2005
rat, Sprague Dawley, 12 ♂, 12 ♀	**42–54 days**, 0, 400 mg/kg body weight and day, gavage, Reofos 65 20% triphenyl phosphate, 80% isopropylated triphenyl phosphate	**400 mg/kg body weight: LOAEL**; **400 mg/kg body weight**: ♂/♀: salivation ↑, absolute and relative adrenal gland weights ↑, absolute and relative liver weights ↑, ♂: body weights and body weight gains ↓, fatty deposits and vacuolation in the adrenal glands, ♀: centrilobular hypertrophy of the liver; for detailed organ weight data see Table 7	Great Lakes Chemical Corp 2005
rat, Sprague Dawley, 12 ♂, 12 ♀	**42–54 days**, 0, 400 mg/kg body weight and day, gavage, Reofos 120 7.5% triphenyl phosphate, 92.5% isopropylated triphenyl phosphate	**400 mg/kg body weight: LOAEL**; **400 mg/kg body weight**: ♂/♀: salivation ↑, absolute and relative adrenal gland weights ↑, absolute and relative liver weights ↑, ♂: fatty deposits and vacuolation in the adrenal glands, ♀: centrilobular hypertrophy of the liver; for detailed organ weight data see Table 7	Great Lakes Chemical Corp 2005

Tab. 8 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, CD (Crl:CD(SD)), 10 ♂, 10 ♀	**91 days**, 0, 25, 100, 325 mg/kg body weight and day, gavage, OECD Test Guideline 408, Reofos 35 35% triphenyl phosphate, 65% isopropylated triphenyl phosphate, 18-day observation period: 5 ♂, 5 ♀	**25 mg/kg body weight: LOAEL**; **25 mg/kg body weight and above**: ♂/♀: brown discoloration and enlargement of the adrenal glands; adrenal glands: diffuse vacuolation in the zona fasciculata (reversible), enlarged cells with foamy cytoplasm (reversible), large single vacuoles expanding outward in the cells close to the zona reticularis (irreversible), ♀: absolute and relative adrenal gland weights ↑, absolute and relative ovary weights ↑ (irreversible), interstitial cell vacuolation in the ovaries; **100 mg/kg body weight and above**: ♂/♀: absolute and relative liver weights ↑ (reversible), centrilobular or panlobular hypertrophy of the liver, ♂: cholesterol ↑ (reversible), blood urea nitrogen ↑ (reversible), absolute and relative adrenal gland weights ↑ (irreversible); **325 mg/kg body weight**: ♂: body weights ↓, relative thyroid gland weights ↑ (reversible), thyroid glands: follicular cell hypertrophy, fibrinogen and globulin ↑ (reversible), ♀: cholesterol ↑ (reversible)	Chemtura Corp 2015
chicken, not specified, 6 ♀	**5 days**, 5000 mg/kg body weight and day, gavage, Reofos 50 30% triphenyl phosphate, 70% isopropylated triphenyl phosphate observation period: 21 days	**5000 mg/kg body weight**: lethality: 2/6; ataxia, axon degeneration of the spinal nerves	ECHA 2013; Environment Agency UK 2009
chicken, not specified, 5 ♀	**28 days**, 1.7, 5, 16, 49, 148, 444, 1333, 4000 mg/kg body weight and day, gavage, Kronitex 50 33% triphenyl phosphate, 41% monoisopropylated and diisopropyated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate	**49 mg/kg body weight: NOAEL for clinical neurotoxicity**; **148 mg/kg body weight**: ataxia 1/5; **444 mg/kg body weight**: ataxia 1/5; **1333 mg/kg body weight**: ataxia 2/5; **4000 mg/kg body weight**: ataxia 2/5, lethality 3/5 **no histopathology**	FMC Corp 1984 b, 1986
chicken, White Leghorn, 20 ♀	**91 days**, 10, 20, 90, 270 mg/kg body weight and day, gavage, Kronitex 50 33% triphenyl phosphate, 41% monoisopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate	**0 mg/kg body weight**: lethality 2/20; **10 mg/kg body weight**: lethality 3/20; **20 mg/kg body weight**: lethality 3/20, **NOAEL** for neurotoxicity; **90 mg/kg body weight**: ataxia 4/20, lethality 5/20, body weights ↓; **90 mg/kg body weight and above**: degeneration of the spinal and peripheral nerves; **270 mg/kg body weight**: ataxia 9/20, lethality 6/20, body weights ↓	FMC Corp 1984 b, 1986

LOAEL: lowest observed adverse effect level; NOAEL: no observed adverse effect level

5.2.3 Dermal application

The findings of the studies are shown in Table 9.

5.2.3.1 Rat

In a study carried out according to OECD Test Guideline 410 in male and female rats (strain: RAIF), Reolube HYD 46 was applied semi-occlusively to the shaved skin of groups of 5 animals per sex and dose for 6 hours a day, on 5 days a week, for 28 days. Doses of 0, 40, 200 and 1000 mg/kg body weight and day were applied. A slight increase (no other details) in the absolute and relative adrenal gland weights was observed in all exposed animals; however, these findings lack a histopathological correlate. Slight inhibition of the plasma cholinesterase activity was noted in the females at 1000 mg/kg body weight and day; however, this does not have toxicological relevance. A decrease in the absolute and relative testis weights was observed in the males (ECHA 2013). As the effects on the adrenal glands were reported also by the study described below and after oral and inhalation exposure of rats, the increase in adrenal gland weights is regarded as adverse. The LOAEL is thus 40 mg/kg body weight and day.

In a subacute limit test carried out according to OECD Test Guideline 410 in male and female rats (F3 hybrid of RII 1/Tif and RII 2/Tif), Kronitex 50 was applied under semi-occlusive conditions to the shaved skin of groups of 5 animals per sex and dose for 6 hours a day, on 5 days a week, for 28 days. Doses of 0, 100, 500 and 2000 mg/kg body weight and day were applied. The weights of the adrenal glands (no other details) were increased in the males at 500 mg/kg body weight and day and above; the histopathological examination revealed fatty deposits in the adrenal cortex in 2 of 5 and 3 of 5 males in the 500 and 2000 mg/kg groups, respectively. Slight inhibition of the plasma cholinesterase activity was observed at 500 mg/kg body weight and day and above in the females, and at 2000 mg/kg body weight and day in both sexes. This finding was not significant in the males. The erythrocyte cholinesterase activity was significantly inhibited in the males of the high dose group (ECHA 2013). The NOAEL was 100 mg/kg body weight and day.

5.2.3.2 Chicken

A subchronic limit test was carried out in 10 hens with exposure to Reofos 65 (no other details) at a dose of 50 mg/kg body weight and day. The test substance was applied to the surface of the combs of the hens by pipette on 5 days a week for 4 months. The animals were observed for neurotoxic symptoms. Blood samples were collected at the end of the treatment period for haematology and clinico-chemistry. All animals were examined gross-pathologically, NTE was analysed in the brain, the spinal and peripheral nerves underwent histopathological examination. Tri-*o*-cresyl phosphate was used as the positive control. No signs of neurotoxicity were noted after exposure to Reofos 65 at a dose of 50 mg/kg body weight and day; therefore, this dose is the NOAEL (ECHA 2013; Environment Agency UK 2009).

Tab. 9 Effects of isopropylated triphenyl phosphate after repeated dermal exposure

Species, strain, number per group	Exposure	Findings	References
rat, RAIF, 5 ♂, 5 ♀	**28 days**, 0, 40, 200, 1000 mg/kg body weight and day, Reolube HYD 46 7% triphenyl phosphate, 35% 2-isopropylphenyl diphenyl phosphate, 25% bis-2-isopropylphenyl phenyl phosphate, 10% tris(isopropylphenyl) phosphate, OECD Test Guideline 410	**40 mg/kg body weight: LOAEL**, a slight increase in the absolute and relative adrenal gland weights was observed in all exposed animals; however, these findings lacked a histopathological correlate; **1000 mg/kg body weight**: ♂: absolute and relative testis weights ↓, ♀: plasma cholinesterase ↓	ECHA 2013

Tab. 9 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, F3 hybrid of RII 1/Tif and RII 2/Tif, 5 ♂, 5 ♀	**28 days**, 0, 100, 500, 2000 mg/kg body weight and day, Kronitex 50 33% triphenyl phosphate, 41% monoisopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate, OECD Test Guideline 410	**100 mg/kg body weight: NOAEL**; **500 mg/kg body weight and above**: ♂: adrenal gland weights (no other data) ↑, fatty deposits in the adrenal cortex, ♀: plasma cholinesterase ↓; **2000 mg/kg body weight and above**: ♂: erythrocyte cholinesterase activity ↓	ECHA 2013
chicken, not specified, 10 ♀	**4 months**, 50 mg/kg body weight and day, Reofos 65 20% triphenyl phosphate, 80% isopropylated triphenyl phosphate	**50 mg/kg body weight: NOAEL**	ECHA 2013; Environment Agency UK 2009

5.2.3.3 Summary

After dermal application for 28 days, a LOAEL of 40 mg/kg body weight and day was obtained in rats. The absolute and relative adrenal gland weights were slightly increased at this dose and above; at higher doses, additional findings were revealed by histopathological examination (fatty deposits in the adrenal cortex).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Reofos 50 (0.1 or 0.5 ml) was applied to the shaved skin of 3 New Zealand White rabbits under semi-occlusive conditions. The substance was left on the skin for 4 hours and then washed off. The test site was scored for irritation using the Draize method after 4.5, 24, 48 and 72 hours. The primary irritation index was 0, indicating that the substance is not an irritant (Environment Agency UK 2009; US EPA 2010).

In another study, 6 albino rats were exposed to Kronitex 50. The test substance (0.5 ml) was applied to the shaved and intact or abraded skin on the backs of the animals. Skin irritation was scored after semi-occlusive exposure for 24 hours and after 72 hours. Neither erythemas nor oedemas were observed. Kronitex 50 was assessed as not irritating (ECHA 2013).

Kronitex 200 (0.5 ml) was applied to the shaved skin on the backs of 6 albino rabbits; the test site was covered with gauze and an occlusive dressing. The gauze was removed after 4 hours and the effects on the skin were scored. Slight erythema was observed in 1 animal, which was found to be reversible when the site was examined again after 72 hours (ECHA 2013).

In another study, 0.5 ml of Reofos 50 was applied under occlusive conditions to the intact, shaved skin on the backs of 3 rabbits for 4 hours. No irritation was observed 30 to 60 minutes and 24, 48 and 72 hours after removal of the gauze (Environment Agency UK 2009).

Durad MP280 (0.5 ml) was applied to the intact or abraded skin of 6 albino rabbits and covered with an occlusive dressing for 24 hours. The gauze was subsequently removed and the effects on the skin scored according to the Draize procedure after another 48 hours. No irritation was observed (US Air Force 1982).

In a skin irritation study, 0.5 ml of Reolube HYD 46 was applied to the intact skin of 2 male and 2 female rabbits and covered with an occlusive dressing for 24 hours. Slight erythema was determined in only 1 animal after 72 hours (Environment Agency UK 2009).

The occlusive application of Reofos 50 for 24 hours at a dose of 2000 mg/kg body weight and day did not induce skin irritation in groups of 3 to 5 male and 3 to 5 female rats (Environment Agency UK 2009).

In summary, commercial isopropylated triphenyl phosphate products were not irritating when applied to the rat and rabbit skin under occlusive conditions for periods of up to 24 hours.

5.3.2 Eyes

The eyes of rabbits were examined for irritation after the instillation of 0.1 ml of Durad MP280 into 1 eye of each of 6 albino rabbits. The eyes of 3 of the animals were rinsed with lukewarm water after 20 seconds. No irritation was observed (US Air Force 1983).

In an irritation study in which 0.1 ml of Reolube HYD 46 was instilled into the eyes of rabbits (2 animals per sex), slight to moderate redness was observed in all animals 1 hour after treatment. Further examinations were carried out after 24, 48 and 72 hours and after 7 and 10 days. The redness had subsided in all animals within 10 days (Environment Agency UK 2009).

Acute eye irritation was investigated in 9 albino rats. Kronitex 50 (0.1 ml) was instilled into 1 eye of each of the animals. The eyes of 6 of the 9 animals were rinsed 4 seconds later. The eyes of all animals were examined after 24, 48 and 72 hours and after 7 days; no reactions were observed either in the rinsed or in the unrinsed eyes. Therefore, the test substance was assessed as not irritating (ECHA 2013; US EPA 2010).

In another study, 0.1 ml of Reofos 50 was instilled into 1 eye of each of 3 New Zealand White rabbits. The eyelids of the rabbits were held closed for about 1 second after instillation. After 24 hours, slight conjunctival redness was observed in the eyes of 2 of 3 rabbits; this was reversible after 48 hours. The effects on the eyes were scored according to the Draize procedure after 1 hour and 24, 48 and 72 hours after instillation. The primary irritation index was 1.3, 0, and 0 at 24, 48 and 72 hours, respectively (Environment Agency UK 2009; US EPA 2010).

In another study, in which 0.1 ml of Reofos 50 was instilled into 1 eye of each of 4 rabbits, signs of conjunctival irritation were observed in 3 of 4 animals. The irritation was reversible on day 7. No additional data were given for the severity, time of appearance and duration of the effect (Environment Agency UK 2009). This study is of only limited use for the evaluation as the data provided were incomplete.

In a study in which Reofos 65 was instilled into the eyes of 3 rabbits with an observation period of 7 days, the test substance was not irritating (no other details; Environment Agency UK 2009).

Eye irritation studies were carried out with 0.1 ml of Reofos 50, Reofos 65, Reofos 95 or Durad 300, instilled into 1 eye of each of 9 rabbits per group. The test substance was rinsed from the eye of 3 of the animals in each group. Readings were taken after 24, 48 and 72 hours. The substance was not irritating (no other details; Environment Agency UK 2009).

In a study which was reported only in abridged form, the instillation of 0.1 ml of Durad 300 was not irritating to the eyes of 3 rabbits (no other details; Environment Agency UK 2009).

In summary, isopropylated triphenyl phosphate caused no or at most minimal irritation in rat and rabbit eyes.

5.4 Allergenic effects

In a local lymph node assay (LLNA) in CBA/J Rj mice, stimulation indices of 7.4, 12.9 and 10.4, respectively, were determined after the application of 25%, 50% or 100% isopropylated phenyl phosphate (technical product with 20% triphenyl phosphate) in acetone/olive oil (4:1) (ECHA 2013).

A maximization test with triphenyl phosphate carried out according to OECD Test Guideline 406 yielded negative results. A reaction was not produced in any of the 10 animals at the challenge treatment. The intradermal induction was carried out with a 5% solution, the topical induction with a 75% solution and the challenge treatment with 75% and 50% solutions of triphenyl phosphate; the vehicle in each case was arachis oil (ECHA 2013).

In an LLNA, stimulation indices of 5.4, 3.4 and 3.7, respectively, were determined after the application of 25%, 50% and 100% tricresyl phosphate (mixture of isomers) in acetone/olive oil (4:1); a clear concentration dependency was not established (ECHA 2013).

In summary, the data available for isopropylated triphenyl phosphate or the structurally closely related tri-*o*-cresyl phosphate are contradictory in some cases; therefore, it is not possible to draw conclusions on skin sensitizing effects.

Data for sensitizing effects on the airways are not available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

The findings of the studies are shown in Table 10.

A study was carried out according to OECD Test Guideline 422 (combined study of the toxic effects of repeated oral doses and a screening test for reproductive and developmental toxicity) in male and female Sprague Dawley rats. Twelve animals per sex and dose were given Reofos 65 by gavage at doses of 0, 25, 100 or 400 mg/kg body weight and day, beginning 15 days before mating, continuing during mating and, in the case of the females, up to postnatal day 4. The males were given a total of 29 doses, the females up to 54 doses. For the parent generation, it was not possible to derive a NOAEL for systemic toxicity and effects on female reproduction; the LOAEL was 25 mg/kg body weight and day (see also Section 5.2.2 and Table 8). At doses of 25 mg/kg and above, ovarian interstitial cell hyperplasia and hypertrophy were observed in addition to an increase in the absolute and relative adrenal gland weights and vacuolation in the cells of the adrenal cortex in the males and females. Decreased male and female fertility, determined on the basis of the copulation index, conception index and the number of implantations, was observed at doses of 100 mg/kg body weight and day and above in addition to reduced absolute and relative epididymis weights at 400 mg/kg body weight and day. The number of live offspring and litter sizes were reduced at 100 mg/kg body weight and day and above. None of the offspring from 5 of the 6 litters of the high dose group with exposure to 400 mg/kg body weight and day survived postnatal day 4. The only abnormal findings in the deceased animals were hypothermia and a lack of mother's milk in the stomach. The NOAEL for fertility and for effects in the offspring was 25 mg/kg body weight and day (Great Lakes Chemical Corp 2004).

In a screening test for reproductive and developmental toxicity, 12 male and 12 female Sprague Dawley rats were given Reofos 35, Reofos 65 or Reofos 120 by gavage at doses of 0 or 400 mg/kg body weight and day (males: 42 days; females: up to 54 days). Following administration of the substance for 2 weeks, the animals were mated for 2 weeks. The females carried their foetuses to term; the offspring were reared until postnatal day 4. The findings of the study are described below.

Increased salivation was observed in the animals treated with Reofos 35. The body weights of the males were significantly lower (6% to 11%) than the body weights of the control animals from weeks 3 to 8. No effects on feed consumption were observed. Increases in the absolute and relative adrenal gland weights and the relative liver weights were noted in the males and females; increased absolute liver weights were determined in the females. Histopathological changes in the adrenal glands (fatty deposits, vacuoles) were determined in the males while histopathological changes in the liver (centrilobular hypertrophy) were observed in the females. The 25% decrease in the fertility and fecundity indices was not statistically significant. The survival index of the offspring for the period from birth to lactation day 4 was 92.4%, which, in comparison with the survival index of the control group (99.4%), represented a statistically significant decrease. Increased mortality was observed in 5 of 9 litters of this group.

Increased salivation was observed in the animals treated with Reofos 65. The body weights of the males were slightly reduced in comparison with those of the control animals; this decrease was statistically significant during the last 2 weeks (–7%). The body weight gains were significantly reduced in weeks 6 and 7. The absolute and relative adrenal gland and liver weights were increased in the males and females. The histopathological changes in the adrenal glands of the males and in the liver of the females were similar to the effects induced by Reofos 35. The fertility and fecundity indices were 50% lower than those of the controls. The survival index of the offspring for the period from birth to lactation day 4 was 86.6% and thus markedly lower than the survival index of 99.4% of the control group. An increase in offspring mortality was observed in 4 of 6 litters of this group. On lactation day 4, the body weights of the offspring were 7% to 8% lower than those of the control animals.

The absolute and relative adrenal gland and liver weights were increased in the males and females treated with Reofos 120. The histopathological changes in the adrenal glands and livers observed in the males and females were similar to those described above. The survival index of the offspring for the period from birth to lactation day 4 was 78.6% and thus markedly lower than the survival index of 99.4% of the control group. An increase in mortality was observed among the offspring in 6 of 12 litters of this group (Great Lakes Chemical Corp 2005).

Tab. 10 Effects of isopropylated triphenyl phosphate on fertility after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 12 ♂, 12 ♀	**29–54 days**, 0, 25, 100, 400 mg/kg body weight and day, gavage, Reofos 65 20% triphenyl phosphate, 80% isopropylated triphenyl phosphate, OECD Test Guideline 422	**25 mg/kg body weight: NOAEL for fertility; LOAEL for female reproductive organs**; **25 mg/kg body weight and above**: parent animals ♂/♀: dose-dependent increase in absolute and relative adrenal gland weights (statistically significant at 100 mg/kg body weight and above), vacuolation in the cells of the adrenal cortex (in the zona glomerulosa, fasciculata and reticularis) ↑, ♀: absolute and relative ovarian weights ↑ (not dose-dependent), interstitial cell hyperplasia and hypertrophy in the ovaries (severity increased with the dose at the minimal and mild grade levels; 0/12, 7/12, 12/12, 12/12 at 0, 25, 100, 400 mg/kg body weight), neutrophils ↓; **100 mg/kg body weight and above**: parent animals ♂/♀: salivation ↑ 1 hour after dosing, lymphocytes ↑ (not significant), fertility index ↓ (100%, 91.7%, 75%, 50% at 0, 25, 100, 400 mg/kg body weight), ♂: neutrophils ↓ (not significant); absolute and relative liver weights ↑, centrilobular hepatocellular hypertrophy, copulation index ↓ (100%, 100%, 81.8%, 50% at 0, 25, 100, 400 mg/kg body weight), ♀: conception index ↓ (100%, 100%, 81.8%, 50% at 0, 25, 100, 400 mg/kg body weight), implantations ↓, feed consumption ↑ (without body weight gains, changes in feed conversion likely), offspring: live offspring ↓; litter sizes ↓; surviving animals on postnatal day 4 ↓; **400 mg/kg body weight**: parent animals ♂/♀: excessive scratching in the cage 1 hour after dosing ↑, ♂: cholesterol ↑ (47%), globulin ↑, albumin/globulin ↓, absolute and relative epididymis weights ↓, ♀: euthanasia of 5 animals because of complete litter loss by postnatal day 3, only 1 animal survived until the end of the study (PND 4), offspring: body weights on postnatal day 0 ↓; renal papillae not fully developed in 2 animals of the only remaining litter (postnatal day 4)	Great Lakes Chemical Corp 2004

Tab. 10 *(continued)*

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 12 ♂, 12 ♀	**42–54 days**, 0, 400 mg/kg body weight and day, gavage, Reofos 35 35% triphenyl phosphate, 65% isopropylated triphenyl phosphate	**400 mg/kg body weight: LOAEL**; **400 mg/kg body weight**: parent animals ♂/♀: salivation ↑, absolute (♂: 49%, ♀: 74%) and relative (♂: 67%, ♀: 68%) adrenal gland weights ↑, absolute (♂: 17% not significant, ♀: 30%) and relative liver weights (♂: 32%, ♀: 27%) ↑, fertility and fecundity indices ↓ (–25%, not significant), ♂: body weights and body weight gains ↓, fatty deposits and vacuolation in the adrenal glands ↑, ♀: absolute liver weights ↑, centrilobular hypertrophy of the liver, offspring: survival index on lactation day 4 ↓ (92.4% in comparison with 99.4% in the control group), mortality ↑ in 5/9 litters	Great Lakes Chemical Corp 2005
rat, Sprague Dawley, 12 ♂, 12 ♀	**42–54 days**, 0, 400 mg/kg body weight and day, gavage, Reofos 65 20% triphenyl phosphate, 80% isopropylated triphenyl phosphate	**400 mg/kg body weight: LOAEL**; **400 mg/kg body weight**: parent animals ♂/♀: salivation ↑, absolute (♂: 46%, ♀: 73%) and relative (♂: 57%, ♀: 65%) adrenal gland weights ↑, absolute (♂: 19%, ♀: 25%) and relative (♂: 30%, ♀: 21%) liver weights ↑, fertility and fecundity indices ↓ (–50%), ♂: body weights and body weight gains ↓, fatty deposits and vacuolation in the adrenal glands ↑, ♀: centrilobular hypertrophy of the liver, offspring: survival index on lactation day 4 ↓ (86.6% in comparison with 99.4% in the control group), mortality ↑ in 4/6 litters, body weights on lactation day 4 ↓ (7%–8%)	Great Lakes Chemical Corp 2005
rat, Sprague Dawley, 12 ♂, 12 ♀	**42–54 days**, 0, 400 mg/kg body weight and day, gavage, Reofos 120 7.5% triphenyl phosphate, 92.5% isopropylated triphenyl phosphate	**400 mg/kg body weight: LOAEL**; **400 mg/kg body weight**: parent animals ♂/♀: salivation ↑, absolute (♂: 39%, ♀: 92%) and relative (♂: 47%, ♀: 80%) adrenal gland weights ↑, absolute (♂: 13%, ♀: 30%) and relative (♂: 22%, ♀: 23%) liver weights ↑, ♂: fatty deposits and vacuolation in the adrenal glands ↑, ♀: centrilobular hypertrophy of the liver, offspring: survival index on lactation day 4 ↓ (78.6% in comparison with 99.4% in the control group), mortality ↑ in 6/12 litters	Great Lakes Chemical Corp 2005

In summary, the NOAEL for fertility was found to be 25 mg/kg body weight and day in a study carried out according to OECD Test Guideline 422 in which rats were exposed to Reofos 65. At this dose, effects on the female reproductive organs in the form of ovarian interstitial cell hyperplasia and hypertrophy were observed; these effects were statistically significant. Effects on fertility in the form of reduced copulation and conception indices and a decreased number of implantations were observed at doses of 100 mg/kg body weight and day and above. In addition, the number of live offspring and litter sizes were reduced at this dose and above. At doses of 25 mg/kg body weight and day and above, parental toxicity was observed in the form of increased absolute and relative adrenal gland weights and vacuolation in the cells of the adrenal cortex in the zona glomerulosa, fasciculata and reticularis.

Differences in the severity of the toxic effects induced by the different substance mixtures:

The survival index on lactation day 4 for the litters was lowest for Reofos 120, followed by Reofos 65 and Reofos 35. The effects thus increased in severity with the increasing fraction of isopropylated triphenyl phosphate. The opposite was determined for the fertility and fecundity indices: Reofos 35 induced the most severe effects, followed by Reofos 65 and Reofos 120 (see also Section 2).

5.5.2 Developmental toxicity

In the study with Reofos 65 described in Sections 5.2.2 and 5.5.1, which was carried out in male and female Sprague Dawley rats according to OECD Test Guideline 422, the number of live offspring on postnatal day 4 and the litter size were reduced at doses of 100 mg/kg body weight and day and above. The NOAEL was 25 mg/kg body weight and day (Great Lakes Chemical Corp 2004). This is equivalent to an isopropylated triphenyl phosphate dose of about 20 mg/kg body weight and day. However, this was only a screening study and did not include an in-depth investigation of the toxic effects on development or teratogenicity.

A screening study, which was likewise described in Sections 5.2.2 and 5.5.1, investigated the reproductive and developmental toxicity induced up to lactation day 4 by exposure to single oral doses of Reofos 35, Reofos 65 or Reofos 120 of 400 mg/kg body weight and day (in the case of Reofos 35, this was equivalent to an isopropylated triphenyl phosphate dose of about 260 mg/kg body weight and day, for Reofos 65 about 320 mg/kg body weight and day, and for Reofos 120 about 370 mg/kg body weight and day). Effects on the offspring were induced in the form of increased mortality or reduced body weights (Great Lakes Chemical Corp 2005).

A developmental toxicity study was carried out with Reofos 35 according to OECD Test Guideline 414. Groups of 25 female rats were given daily gavage doses of 0, 100, 200 or 400 mg/kg body weight from the beginning of gestation (day 0) up to gestation day 19. Salivation was observed in all treated animals, but was attributed to the form of application and not regarded as an adverse effect. At the dose of 400 mg/kg body weight and day, maternal toxicity in the form of reduced activity, red material around the nose and muzzle, squatting position, thinness, brown discoloration of the facial fur and fur on the forelegs, and reduced body weight gains and feed consumption were observed during the first days of treatment (gestation days 0 to 3). In addition, the gross-pathological examination yielded evidence of stomach irritation. No effects on gestation parameters, implantations, foetal sex distribution or foetal body weights were determined. In addition, no external, visceral or skeletal changes were observed in the foetuses. In the range-finding study, the body weights of the foetuses were reduced, and a mortality incidence of 60% and reduced body weights and feed consumption were determined in the dams at 500 mg/kg body weight and day. The NOAEL for maternal toxicity was thus 200 mg/kg body weight and day and the NOAEL for developmental toxicity was 400 mg/kg body weight and day, the highest dose tested (Chemtura Corp 2014).

5.6 Genotoxicity

5.6.1 In vitro

In a mutagenicity test with the Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100, Kronitex 50 yielded negative results at concentrations of 0, 0.1, 1, 5, 10 or 100 µl per plate with and without the addition of metabolic activation (S9 mix). Cytotoxicity was not observed. The functioning of the test system was verified by the positive controls (ECHA 2013).

In a mutagenicity test with the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, Kronitex 200 yielded negative results at concentrations of 0.1, 1, 5, 10 or 100 µl per plate with and without the addition of metabolic activation. Cytotoxicity was not observed (ECHA 2013).

Reofos 50, Reofos 65, Reofos 95, Durad 300 and Reolube HYD 46 were not mutagenic in the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 with and without the addition of metabolic activation (no other details; Environment Agency UK 2009).

In a UDS test (unscheduled DNA synthesis) in rat hepatocytes, Reofos 50 did not induce DNA repair at concentrations of 0.6, 3, 15, 75 nl/ml. Data for cytotoxicity were not given (ATSDR 1997; ECHA 2013; Environment Agency UK 2009).

A UDS test with Reolube HYD 46 in rat hepatocytes yielded negative results. The cells were exposed to concentrations of 0, 0.6, 3, 15, 75 and 150 nl/ml for 5 hours. Data for cytotoxicity were not given (ATSDR 1997; ECHA 2013; Environment Agency UK 2009).

In a chromosomal aberration test carried out according to OECD Test Guideline 473 in the lymphocytes of a healthy, 28-year-old female non-smoker, both with and without the addition of metabolic activation, Reofos 65 was not found to be clastogenic at concentrations of 8.75, 17.5, 35, 65, 85, 115, 150 or 200 µg/ml. The cells were incubated for 4 hours in the presence and absence of a metabolic activation system from the rat liver or for 20 hours without a metabolic activation system. The test substance concentrations were chosen prior to the beginning of the test after the mitotic index was reduced by at least 50% in comparison with that for the solvent control for all 3 exposure conditions at concentrations of ≥150 µg/ml. The functioning of the test system was verified by the positive controls (ECHA 2013).

A $TK^{+/-}$ test was carried out with Reofos 50 in L5178Y mouse lymphoma cells at concentrations of 0.0013 to 0.1 µl/ml both with and without the addition of metabolic activation. No genotoxicity was observed in the absence of a metabolic activation system, the results were questionable in the presence of a metabolic activation system. There was evidence of dose-dependency, but the mutation frequency of the cultures with 10% growth was not greater than twice that for the solvent control in any of the cultures. Cytotoxicity was not discussed (ECHA 2013; Environment Agency UK 2009).

5.6.2 In vivo

An SLRL test (sex-linked recessive lethal test) in Drosophila melanogaster treated for 3 days with Kronitex 50 at concentrations of 7.5, 32.5 or 75 mg/ml yielded negative results. Therefore, Kronitex 50 was not mutagenic in the germ cells of male fruit flies. The functioning of the test system was verified by the positive controls (FMC Corp 1984 a).

Another SLRL test in Drosophila melanogaster treated for 3 days with Reofos 50 at concentrations of 32.5, 75 or 150 mg/ml likewise yielded negative results (ECHA 2013; Environment Agency UK 2009).

In a test for sister chromatid exchange, 4 male and 4 female Chinese hamsters per dose group were given single gavage doses of Reolube HYD 46 of 1250, 2500 or 5000 mg/kg body weight. Bone marrow cells were collected 24 hours after administration of the substance and 2 hours after Colcemid was administered by intraperitoneal injection. No data were given for the control animals or for cytotoxicity. In this study, Reolube HYD 46 did not induce sister chromatid exchange (ATSDR 1997; ECHA 2013; Environment Agency UK 2009).

In another test for sister chromatid exchange, 4 male and 4 female Chinese hamsters (strain: Cricetulus griseus) per dose group were given single oral (no other details) doses of Reofos 50 of 0, 1250, 2500 or 5000 mg/kg body weight. Bone marrow cells were collected 24 hours after administration of the substance and 2 hours after Colcemid was administered by intraperitoneal injection. There were no signs of toxicity (no other details) and no increase in sister chromatid exchange (ECHA 2013; Environment Agency UK 2009).

A nuclear anomaly test was carried out in 1984 in male and female Chinese hamsters with either 6 (experiment 1) or 8 animals (experiment 2) per sex and dose group. The animals were given gavage doses of Reolube HYD 46 of 0, 1250, 2500 or 5000 mg/kg body weight on 2 consecutive days. Bone marrow samples were collected from the animals 24 hours later. No data for cytotoxicity were given. In the first experiment, there was a slight, but significant increase in the incidence of anomalies (no other details; the findings do not correspond with the dosage data) at the 3 high concentrations. For this reason, a second experiment was carried out with lower and higher doses (no other details). In this test, the incidence of anomalies was significantly increased in the high dose group in comparison with the incidence determined in the controls (ECHA 2013). The occurrence of nuclear anomalies (changes in the chromatin structure of the nucleus) is not necessarily evidence of a genotoxic effect as nuclear anomalies are characteristic also of apoptosis and cytotoxicity.

In a nuclear anomaly test carried out in 1984 with 6 male and 6 female Chinese hamsters per dose group, the animals were given gavage doses of Reofos 50 of 0, 1250, 2500, 5000 mg/kg body weight on 2 consecutive days. Bone marrow was collected from the animals 24 hours later. The study included a positive control group; no data for toxicity were given. The incidence of bone marrow cells with nuclear anomalies was significantly increased at doses of 2500 mg/kg body weight and above in comparison with the incidence determined in the control group; this is evidence of chromosomal damage (ATSDR 1997; ECHA 2013). The occurrence of nuclear anomalies (changes in the chromatin structure of the

nucleus) is not necessarily evidence of a genotoxic effect as nuclear anomalies are characteristic also of apoptosis and cytotoxicity (ECHA 2013).

In a chromosomal aberration test carried out according to OECD Test Guideline 475, 24 male and 24 female Chinese hamsters (strain: Cricetulus griseus) were given a single gavage dose of Reofos 50 of 5000 mg/kg body weight. Bone marrow samples were collected from the femur of 8 female and 8 male hamsters after 16, 24 and 48 hours and analysed for chromosomal aberrations. The study included negative and positive control groups (number of animals not specified). In this study, Reofos 50 did not induce chromosomal aberrations (ECHA 2013).

In a chromosomal aberration test carried out in male and female Chinese hamsters according to OECD Test Guideline 475, groups of 24 animals per sex were given single gavage doses of Reolube HYD 46 of 0 or 5000 mg/kg body weight. Bone marrow was collected from 8 of the 24 animals in each group after 16, 24 or 48 hours. No data for cytotoxicity were given. In this study, Reolube HYD 46 did not induce chromosomal aberrations (ECHA 2013).

Female NMRI mice (number of animals not specified) were given single gavage doses of Reolube HYD 46 of 0, 100, 500, 1000, 10 000 and 50 000 mg/kg body weight. The positive control group was given cyclophosphamide. The ratio of polychromatic (PCE) and normochromatic (NCE) erythrocytes was determined in the bone marrow of the animals. A marked increase in the PCE to NCE ratio was determined at doses of 10 000 mg/kg body weight and above. Irrespective of the dose, there was a slight increase in the number of micronuclei in the polychromatic erythrocytes; this indicates slight inhibition of erythrocyte maturation. Reolube HYD 46 did not induce genotoxicity (ECHA 2013; Environment Agency UK 2009). The doses tested were very high and do not correspond to present-day standards.

5.6.3 Summary

A number of in vitro and in vivo genotoxicity tests are available. Of these, only few yielded positive or questionably positive results. In vitro, Reofos 50, Reofos 65, Reofos 95, Durad 300 and Reolube HYD 46 yielded negative results in mutagenicity tests in bacteria, Reofos 50 and Reolube HYD 46 did not induce DNA repair, Reofos 65 was not clastogenic in a chromosomal aberration test and Reofos 50 was questionably positive only in a $TK^{+/-}$ test in mouse lymphoma cells.

In vivo, Reofos 50 yielded negative results in a dominant lethal test in Drosophila melanogaster. Neither Reolube HYD 46 nor Reofos 50 induced sister chromatid exchange or chromosomal aberrations in the bone marrow of Chinese hamsters after administration of oral doses of up to 5000 mg/kg body weight. Also a micronucleus test in the bone marrow of mice yielded negative results with Reolube HYD 46; slight inhibition of erythrocyte maturation was observed. A test investigating nuclear anomalies in the bone marrow of Chinese hamsters yielded positive results with Reofos 50 and Reolube HYD 46. However, these nuclear anomalies may have been caused by apoptosis or cytotoxicity and thus cannot be used to evaluate the genotoxic potential.

5.7 Carcinogenicity

5.7.1 Short-term studies

Reolube HYD 46 yielded negative results in a cell transformation test with BALB/c3T3 mouse embryo fibroblasts. The cells were exposed to the test substance at concentrations of 0, 0.5, 1, 2, 4, 8 µg/ml for 72 hours without S9 mix or to concentrations of 0, 2.75, 5.5, 11, 22, 44 µg/ml for 24 hours with S9 mix (ECHA 2013; Environment Agency UK 2009).

In another cell transformation test, BALB/c3T3 mouse embryo fibroblasts were incubated with Reofos 50 at concentrations of 0, 0.04, 0.2, 1.0, 5.0 µg/ml for 3 days without the addition of a metabolic activation system. The cells were examined after 4 weeks. No transformation was induced by the test substance (ECHA 2013).

In a second test investigating Reofos 50 in BALB/c3T3 mouse embryo fibroblasts, the test substance did not induce cell transformation. The fibroblasts were exposed to Reofos 50 for 72 hours without the addition of a metabolic activation system (0, 0.05625, 0.1125, 0.225, 0.45, 0.9 µg/ml) and for 24 hours with a metabolic activation system (0, 1.75, 3.5, 7.0, 14.0, 28.0 µg/ml). The cells were analysed 4 weeks after the last exposure (ECHA 2013; Environment Agency UK 2009).

5.7.2 Long-term studies

There are no data available.

6 Manifesto (MAK value/classification)

The critical effects are the neurotoxic effects typical for organophosphates. Neurotoxicity decreases with increasing isopropylation, but is not the most sensitive end point. After repeated exposure, the most sensitive end points are histopathological changes in the adrenal glands and ovaries and increased adrenal gland weights.

MAK value. Isopropylated triphenyl phosphate causes at most very slight irritation of the eyes; skin irritation did not occur in the 2 species investigated.

In a 90-day study with continuous inhalation exposure of rats to Durad MP280 aerosol (exact composition not specified), unclear neurological findings and effects on the liver and adrenal glands were observed at the lowest concentration tested of 10 mg/m^3 and above. The examination of the effects on the respiratory tract was not carried out according to today's standards. A NOAEC was not determined. In the same study, first signs of inflammation were observed in the lungs of male hamsters at 10 mg/m^3 and above (US Air Force 1983, 1990).

Two studies with daily gavage administration to rats determined a LOAEL of 25 mg/kg body weight and day for Reofos 65 and for Reofos 35. The study investigating Reofos 65 (20% triphenyl phosphate, 80% isopropylated triphenyl phosphate) was carried out according to OECD Test Guideline 422 (Great Lakes Chemical Corp 2004) with exposure periods of 29 or 54 days and the study investigating Reofos 35 (35% triphenyl phosphate, 65% isopropylated triphenyl phosphate) was carried out according to OECD Test Guideline 408 (Chemtura Corp 2015) with an exposure period of 90 days. An increase in adrenal gland and ovarian weights and histopathological changes in the adrenal glands and ovaries were observed at this dose and above. Neurotoxicity tests (functional observational battery) did not yield any unusual findings. A NOAEL was not determined.

A NOAEL of 20 mg/kg body weight and day was determined in neurotoxicity studies with chickens given Kronitex 50 (33% triphenyl phosphate, 41% different monoisopropylated and diisopropylated triphenyl phosphates, 8% tris(isopropylphenyl) phosphate) for 91 days by gavage (FMC Corp 1984 b, 1986).

Assuming that it is possible to extrapolate a NAEC (no adverse effect concentration, 1/3 LOAEC) from the LOAEC of 10 mg/m^3 determined in the 90-day study with continuous inhalation exposure of rats and hamsters, a concentration in air of 14 mg/m^3 was calculated after extrapolating the concentration to an exposure scenario of 8 hours a day (24:8) on 5 days a week (7:5). By extrapolating the results from an animal study (1:2) and applying the preferred value approach, a MAK value of 5 mg/m^3 is calculated from this concentration in air. As there is evidence of a possible intensification of the effects over time (1:2) and taking into consideration the increased respiratory volume at the workplace in comparison with exposure of animals at rest (1:2), this would result in a MAK value of 1 mg/m^3.

Assuming that it is possible to extrapolate a NAEL (no adverse effect level) from the oral LOAEL of 25 mg/kg body weight and day established for Reofos 65 and Reofos 35 (1/3 LOAEL), this would result in a NAEL of about 8 mg/kg body weight and day. The following toxicokinetic data are taken into consideration for the extrapolation of this NAEL to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding toxicokinetic species-specific correction value for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person and the assumed 100% absorption by inhalation. The concentration calculated from this is about 20 mg/m^3. Extrapolating the results from an animal study (1:2), taking into consideration the intensification of the effects over time (1:6) and applying the preferred value approach, this would likewise result in a MAK value of 1 mg/m^3.

With respect to neurotoxicity, a NOAEL of 20 mg/kg body weight was determined for chickens after exposure for 91 days. The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days a week exposure at the

workplace (7:5), the corresponding toxicokinetic species-specific correction value for the chicken (1:3 as the mean of the values for rats and rabbits), the oral absorption (100%, assumed in analogy to tri-*o*-cresyl phosphate), the body weight (70 kg) and respiratory volume (10 m^3) of the person and the assumed 100% absorption by inhalation. The concentration calculated from this is about 66 mg/m^3. As the effects were more severe than those induced by exposure for 28 days, the NOAEL is expected to be lower after chronic exposure (1:2). Extrapolating the results from an animal study (1:2) and after applying the preferred value approach, this would result in a MAK value of 10 mg/m^3. Neurotoxicity is therefore a less sensitive end point. The MAK value of 1 mg/m^3 offers sufficient protection also for this end point, particularly as chickens are more sensitive to neurotoxic effects than rats.

Additionally, a reproductive and developmental toxicity screening test (Great Lakes Chemical Corp 2005) with exposure of rats to a single oral dose of Reofos 35, Reofos 65 or Reofos 120 of 400 mg/kg body weight and day did not determine any differences in the systemic toxicity induced by the different substance mixtures after comparing the organ weights of the rats at the end of the exposure period. Therefore, after reviewing the findings from all of the available studies, a MAK value of 1 mg/m^3 I has been established for isopropylated triphenyl phosphate.

Peak limitation. As the MAK value was derived from systemic effects, the substance is assigned to Peak Limitation Category II. The half-life of the substance in humans is not known and it is not possible to determine the half-life on the basis of the data available from animal studies. For this reason, the default excursion factor of 2 has been set.

Prenatal toxicity. It is not possible to derive a NOAEL from the reproductive and developmental toxicity screening test (Great Lakes Chemical Corp 2005) with oral administration of Reofos 35, Reofos 65 or Reofos 120 because at the only dose tested of 400 mg/kg body weight and day increased mortality and reduced body weights were observed in the offspring up to lactation day 4. The greatest decrease in the survival index on lactation day 4 was noted after exposure to Reofos 120 (7.5% triphenyl phosphate, 92.5% isopropylated triphenyl phosphate), followed by Reofos 65 (20% triphenyl phosphate, 80% isopropylated triphenyl phosphate) and Reofos 35 (35% triphenyl phosphate, 65% isopropylated triphenyl phosphate). Therefore, the effects increased in severity with the increasing fraction of isopropylated triphenyl phosphate.

In a study carried out according to OECD Test Guideline 422 (combined study of the toxic effects of repeated oral doses and a reproductive and developmental toxicity screening test) (Great Lakes Chemical Corp 2004) in male and female Sprague Dawley rats, the number of live offspring and the litter sizes were reduced at Reofos 65 (20% triphenyl phosphate, 80% isopropylated triphenyl phosphate) doses of 100 mg/kg body weight and day and above. The NOAEL for foetotoxicity was 25 mg/kg body weight and day for Reofos 65; this is equivalent to an isopropylated triphenyl phosphate dose of about 20 mg/kg body weight and day. Again, this was only a screening test and did not include an in-depth investigation of the toxic effects on development and teratogenic effects.

In a study carried out according to OECD Test Guideline 414 (Chemtura Corp 2014) with oral doses of Reofos 35 given to rats from the beginning of gestation up to gestation day 19, adverse effects on development were not induced up to a dose of 400 mg/kg body weight and day. Maternal toxicity was observed after exposure to Reofos 35 at 200 mg/kg body weight and day. The NOAEL for the developmental toxicity of Reofos 35 was therefore 400 mg/kg body weight and day, the highest dose tested, which is equivalent to an isopropylated triphenyl phosphate dose of about 260 mg/kg body weight and day.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAELs for isopropylated triphenyl phosphate of 20 and 260 mg/kg body weight to a concentration in workplace air: the corresponding toxicokinetic species-specific correction value for the rat (1:4), the oral absorption (100%, assumed in analogy to tri-*o*-cresyl phosphate), 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 about 35 and 455 mg/m^3 and thus a 35-fold and 455-fold margin lies between these values and the MAK value of 1 mg/m^3 I. As the margins between these values and the MAK value are sufficiently large, isopropylated triphenyl phosphate has been classified in Pregnancy Risk Group C.

Carcinogenicity. As no carcinogenicity studies of isopropylated triphenyl phosphate are available, and no evidence of carcinogenic effects was found in studies of repeated toxicity and genotoxicity, the substance has not been classified in a category for carcinogenic substances.

Germ cell mutagenicity. The large number of studies of genotoxicity in vitro and in vivo yielded mostly negative results. The small number of positive reactions in vitro and the nuclear anomalies determined in vivo, which may have been caused by apoptosis or cytotoxicity, are not regarded as evidence of genotoxic effects because of the negative results obtained in the tests for chromosomal aberrations and micronuclei. The substance has not been classified in a category for germ cell mutagens.

Absorption through the skin. On the basis of the findings of an in vitro study (Environment Agency UK 2009), the results of model calculations and assuming standard conditions, it is estimated that humans absorb 2 mg through the skin after exposure to a saturated aqueous solution. Exposure at the level of the MAK value of 1 mg/m^3 leads to the absorption of 10 mg. Therefore, absorption through the skin makes up less than 25% of the systemically tolerable amount and isopropylated triphenyl phosphate has not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. No clinical findings are available for the contact sensitizing effects of isopropylated triphenyl phosphate. An LLNA yielded a positive, but questionably valid, reaction. Isolated clinical findings are available for one of the possible constituents, triphenyl phosphate, but the quality of the documentation varies. However, a valid maximization test in guinea pigs yielded clearly negative results. Only few case reports are available for its structural analogue tri-*o*-cresyl phosphate. The findings of an LLNA in mice demonstrate that its skin sensitization potential is minimal at most. Overall, the data available for isopropylated triphenyl phosphate are in some cases contradictory and cannot be regarded as sufficient evidence for contact sensitizing effects. There are no data available for sensitizing effects on the respiratory tract. Therefore, the substance 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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