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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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Diphenyl cresyl phosphate

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CAS No. 26444-49-5

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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Diphenyl cresyl phosphate

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The term, diphenyl cresyl phosphate, comprises the three position-isomeric cresyl derivatives, diphenyl o-cresyl, diphenyl m-cresyl and diphenyl p-cresyl phosphate. As a rule, no details of the composition of the diphenyl cresyl phosphates used are given in the publications available. A decisive factor in the toxicological activity profile of aryl phosphates and alkylaryl phosphates is their content of o-cresol isomers. The diphenyl cresyl phosphate manufactured in the Federal Republic of Germany no longer contains o-cresol so that the toxicological findings reported in older publications do not apply to the present product and in that respect are only of historical interest. Synthetically produced mixtures of m-cresol and p-cresol do not contain any o-cresol, whereas diphenyl cresyl phosphate which is manufactured on the basis of cresylic acid, or tar acid, may contain from < 1 up to > 3 percent by weight of esterified o-cresol.

1 Summary and assessment

Experimental data on the metabolism of diphenyl cresyl phosphate are lacking. Based on the metabolisation of tri-o-cresyl phosphate in the rat it is assumed, however, that in this animal the neurotoxic o-cresyl isomer is likely to be metabolised to phenyl saligenin phosphate, whereas the m-cresyl and p-cresyl isomers probably undergo degradation to the respective diphenyl formylphenyl phosphates.

According to the majority of the available acute toxicity studies in the rat, technical-grade diphenyl cresyl phosphate is practically devoid of toxicity on oral and dermal administration. The inhalation hazard test in the rat reveals no toxic effects in 6-hour and 7-hour exposures to diphenyl cresyl phosphate, apart from slight irritation of the mucous membranes. A 28-day subacute oral toxicity study of o-cresyl isomer-free technical diphenyl cresyl phosphate (total content of diphenyl cresyl phosphate 44.4%) was conducted in rats at dose levels of 0 (controls), 62.5, 250 and 1000 mg/kg bo-

dy weight. The clinical signs of toxicity included salivation, increased water consumption, slight anaemia with leukocytosis, elevated aminotransferase activity as well as changes of the liver, the renal tubules and the adrenal cortex. The *no observed adverse effect level* is reported as being 62.5 mg/kg body weight.

Undiluted technical-grade diphenyl cresyl phosphate has no irritant effect on the skin of the rabbit but it is slightly irritating to the rabbit eye.

In the rabbit, there is no evidence of a skin sensitisation potential.

In an exploratory study in 4 guinea pigs/dose group, subchronic daily dermal application of technical-grade diphenyl cresyl phosphate for 73 days led to dose-dependent alopecia at and above 0.2 ml/kg body weight. A dose of 0.4 ml/kg body weight caused paralysis of the hind limbs, and higher doses also caused paralysis of the lower back muscles. From 0.4 ml/kg body weight, dose-dependent liver and kidney changes were observed and at 0.6 ml/kg body weight and above retarded body weight gain and deaths occurred.

In the Salmonella/microsome assay and in *Escherichia coli*, diphenyl cresyl phosphate shows no mutagenic effects. In vitro, an increase in chromosome aberrations in Chinese hamster cells is seen only in the cytotoxic dose range in the presence of metabolic activation, whereas there is no evidence of a chromosome-damaging effect in the absence of activation. In vivo, the mouse micronucleus test has not produced any evidence of a chromosome damaging potential. Structurally related aryl phosphates, e. g. tricresyl phosphate, triphenyl phosphate and 2-ethylhexyl diphenyl phosphate, have not exhibited any genotoxic potential in in-vitro and in-vivo genotoxicity studies. Based on this information, diphenyl cresyl phosphate may therefore be assumed also to be devoid of genotoxic potential.

In an embryotoxicity/teratogenicity study in rats, which was conducted in accordance with the relevant guidelines with oral doses of 0 (controls), 100, 300 and 900 mg o-cresyl isomer-free technical diphenyl cresyl phosphate (total content of diphenyl cresyl phosphate 44.4%) per kilogram body weight, doses of 900 and 300 mg/kg body weight showed maternal toxicity, but no embryotoxic or teratogenic effects on the offspring were observed even at 900 mg/kg body weight. On daily administration by oral gavage of diphenyl cresyl phosphate (containing no tri-o-cresol) at 300 mg/kg body weight for approximately 6 weeks, the rats exhibited reduced fertility and

nidation rates, which are the result of the inhibition of spermatogenesis in the male parental animals at this systemically toxic dose, whereas in the 28-day study in rats described above no such sperm changes were observed up to the highest test dose of 1000 mg/kg body weight. The reproductive toxicity parameters in the young, however, showed no substance-related changes. No malformations were observed. For this endpoint, the *no effect level* for the offspring is 300 mg/kg body weight, i. e. the highest test dose.

Technical-grade diphenyl cresyl phosphate may cause delayed polyneuropathy (ataxia, paralysis of the extremities, histopathological changes of the nerve tissue), particularly in chickens. Only the o-cresyl isomer of diphenyl cresyl phosphate is neurotoxic, as are diphenyl cresyl mixtures which contain the o-cresyl isomer. This is the only isomer capable of forming phenyl saligenin phosphate, a metabolite which is considered responsible for the neurotoxic effects. On single and multiple administration of diphenyl o-cresyl phosphate, hens have been observed to develop signs of neurotoxicity 2 to 3 weeks after dosing, including limping, ataxia and paralysis of the extremities as well as demyelinisation in the cerebrum, the cerebellar folia and the spinal cord. In addition, there are reports that the enzyme, NTE (neuropathy target esterase), is inhibited in the brain, the spinal cord and the peripheral nerves. This inhibition occurs within 24 hours. In the rat, single intraperitoneal administration of 300 mg and of 150 mg diphenyl cresyl phosphate leads to a reversible decrease in plasma pseudocholinesterase activity. The findings obtained with o-cresyl-containing diphenyl cresyl phosphate, however, are now only of historical interest. Today, the product is manufactured from synthetic cresol which contains no o-isomers and hence is not neurotoxic.

In humans, a 10-percent solution of technical-grade diphenyl cresyl phosphate (Santicizer 140) is slightly irritating to the skin. However, there is no evidence of a sensitisation potential.

2 Name of substance

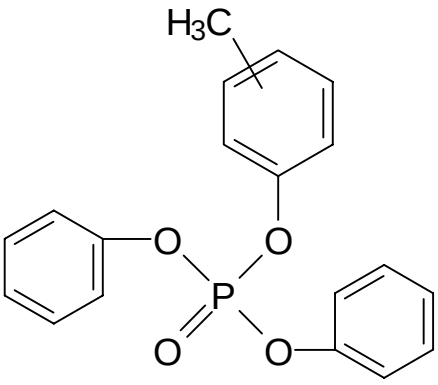
2.1	Usual name	Diphenyl cresyl phosphate
2.2	IUPAC name	Diphenyl cresyl phosphate
2.3	CAS No.	26444-49-5
2.4	EINECS No.	247-693-8

3 Synonyms, common and trade names

Celluflex 112
Cresol diphenyl phosphate
Cresyl diphenyl phosphate
Diphenyl cresyl phosphate
Diphenylcresol phosphate
Diphenylkresylphosphat
Diphenyl tolyl phosphate
Disflamoll DPK
Kronitex CDP
Methylphenyl diphenyl phosphate
Monocresyl diphenyl phosphate
Phosflex 112
Phosphoric acid, cresyl diphenyl ester
Phosphoric acid, diphenyl tolyl ester
Phosphoric acid, methylphenyl diphenyl ester
Santicizer 140
Tolyl diphenyl phosphate

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_{19}H_{17}O_4P$

5 Physical and chemical properties

5.1 Molecular mass, g/mol 340.33

5.2	Melting point, °C	–35 to –45 (solidification point)	(EC, 1996)
5.3	Boiling point, °C	225–235 (at 5 hPa)	(EC, 1996)
5.4	Vapour pressure, hPa	< 0.01 (at 20 °C) 0.000001 (at 41 °C)	(Bayer, 1988 a) (EC, 1996)
5.5	Density, g/cm³	1.2 (at 20 °C)	(EC, 1996)
5.6	Solubility in water	< 0.1 g/l (at 20 °C) 0.0026 g/l (at 25 °C)	(EC, 1996)
5.7	Solubility in organic solvents	Soluble in most solvents	(Sax and Lewis, 1987)
5.8	Solubility in fat	n-Octanol/water partition coefficient log P_{ow} (measured): 4,5 log P_{ow} (measured): 5,1	(EC, 1996)
5.9	pH value	–	
5.10	Conversion factor	For pure diphenyl cresyl phosphate 1 ml/m³ (ppm) ≙ 13.89 mg/m³ 1 mg/m³ ≙ 0.072 ml/m³ (ppm) (at 1013 hPa and 25 °C)	

6 Uses

As a plasticiser and flame retardant in plastics (Bayer, 1988 a).

According to the manufacturers, the o-cresol isomer content of diphenyl cresyl phosphate is given as less than 1% and 0.01%, depending on the source of information (Bayer, 1990; Ciba-Geigy, 1990).

7 Experimental results

The term, diphenyl cresyl phosphate, comprises the three position-isomeric cresyl derivatives, diphenyl o-cresyl, diphenyl m-cresyl and diphenyl p-cresyl phosphate. As a rule, no details of the composition of the diphenyl cresyl phosphates used are given in the publications which are available. Frequently, technical-grade diphenyl cresyl phosphate also contains other organic phosphates. An analysis of Disflamoll DPK/25E (technical diphenyl cresyl phosphate), for instance, revealed the following composition: 45%

diphenyl cresyl phosphate, 35% triphenyl phosphate, 18% dicresyl phenyl phosphate, 2% tricresyl phosphate. The amount of o-cresyl was less than 0.09% of the total amount of all cresyl isomers (Vainiotalo et al., 1987).

Any information which was available on the nature and/or the purity of the isomers investigated, the details have been included in the present evaluation. Where possible, subheadings have been introduced to differentiate between studies using diphenyl cresyl phosphate which contained o-cresyl isomers and studies employing o-cresyl-free substance.

7.1 Toxicokinetics and metabolism

Four hours after a single intraperitoneal administration to 5 rats of technical diphenyl cresyl phosphate (Disflamoll DPK/25E) – containing 45% diphenyl cresyl phosphate – in olive oil at 300 mg/kg body weight, diphenyl cresyl phosphate blood levels of 0.3 ± 0.2 µg/g were observed. After 24 hours, the levels had fallen below the limit of detection (0.2 µg/g). The concentration levels found in the liver after 4 and 24 hours were 45.8 ± 28.1 and 1.7 ± 2.5 µg/g tissue, respectively (Vainiotalo et al., 1987).

There are no studies available on the metabolism of diphenyl cresyl phosphate. It is presumed, however, that the diphenyl o-cresyl phosphate isomer can undergo cyclisation to neurotoxic phenyl saligenin phosphate, whereas this type of metabolisation can not take place with the diphenyl m-cresyl and diphenyl p-cresyl phosphate isomers because the position of the alkyl group causes steric hindrance (Johnson, 1975; Lotti and Johnson, 1980). This metabolisation was deduced from toxicological studies on the neurotoxicity of organophosphates as well as from the biotransformation of tri-o-cresyl phosphate, which can be metabolised by rats to cresyl saligenin phosphate (Eto et al., 1962; Johnson, 1975).

7.2 Acute and subacute toxicity

Studies with diphenyl cresyl phosphate (probably) containing o-cresyl isomers

Following single oral, dermal or intraperitoneal administration of technical-grade *diphenyl cresyl phosphate*, the following LD_{50} values were determi-

ned (cf. Table 1). The data indicate that diphenyl cresyl phosphate is practically not toxic when given acutely via different routes of administration.

Beginning of Table 1

Table 1. Acute toxicity of diphenyl cresyl phosphate						
Species	No. of animals/ dose	Sex	Route of administration	Observation period (days)	LD_{50} (mg/kg b. w., 95% confidence interval)	Reference
Rat (Sprague-Dawley)	5–6	male female	oral	n. d.	18500 (17850–19795)	Younger Laboratories, 1958
Rat	5	male female	oral	7	1420 (1300–1550)	Younger Laboratories, 1972 c
Rat (BOR:WISW)	5	male female	oral	14	> 6000	Bayer, 1982
Rat	n. d.	n. d.	oral	n. d.	6400–12800	Sandmeyer and Kirwin, 1981
Rat	5	male female	oral	7	6700 (6030–7440)	Younger Laboratories, 1973
Rat	5	male female	oral	7	8250 (7340–9280)	Younger Laboratories, 1972 b
Rat	6	male	oral	14	> 40000	AMR, 1974
Rat	5	male female	oral	14	> 20000	FDRL, 1976 a
Rat	5	male female	oral	14	< 20000 (LD_{90})	FDRL, 1976 b
Rat	5	male female	oral	7	10400 (9260–11650)	Younger Laboratories, 1972 a
Rat (Sprague-Dawley)	n. d.	male female	oral	14	10400	Johannsen et al., 1977
Rat	n. d.	n. d.	oral	n. d.	> 4000	Mallette and von Haam, 1952
Rat	n. d.	male female	oral	n. d.	> 4311	Weeks and Pope, 1974
Rat	5	male female	oral	7	> 10000 < 12600	Younger Laboratories, 1971
Mouse	n. d.	n. d.	oral	n. d.	6400–12800	Sandmeyer and Kirwin, 1981
Rabbit	5	female	oral	14	1028 (893–1183)	Bayer, 1977
Rabbit	1–2	male female	oral	10	1500–2500 (minimum lethal dose)	Younger Laboratories, 1956
Guinea pig	n. d.	n. d.	oral	n. d.	1600–3200	Sandmeyer and Kirwin, 1981
Hen	n. d.	female	oral	14	> 10000	Johannsen et al., 1977; Monsanto, 1977

Table 1. Acute toxicity of diphenyl cresyl phosphate						
Species	No. of animals/ dose	Sex	Route of administration	Observation period (days)	LD_{50} (mg/kg b. w., 95% confidence interval)	Reference
Hen	5	n. d.	oral	42	> 12000	Bayer, 1976
Hen	2	female	oral	14	> 10000	IBT, 1972 a, b
Rabbit	n. d.	n. d.	dermal	n. d.	> 5000	Monsanto, 1977
Rabbit	n. d.	male female	dermal (24 hours, occlusive)	14	> 5000	Johannsen et al., 1977
Rabbit	10	n. d.	dermal	14	> 10000	FDRL, 1976 a
Rabbit	10	male female	dermal	14	> 10000	FDRL, 1976 b
Rabbit	1–2	male female	dermal	n. d.	ca. 5000 (minimum lethal dose)	Younger Laboratories, 1958
Rabbit	1	male female	dermal (24 hours, occlusive)	14	> 1260 < 2000 (minimum lethal dose)	Younger Laboratories, 1972 b
Rabbit	1	male female	dermal (24 hours, occlusive)	14	> 2000 < 3160 (minimum lethal dose)	Younger Laboratories, 1971
Rabbit	1–2	male female	dermal (24 hours, occlusive)	14	> 2000 < 3160 (minimum lethal dose)	Younger Laboratories, 1973
Rabbit	1–2	male female	dermal (24 hours, occlusive)	14	> 5010 < 7940 (minimum lethal dose)	Younger Laboratories, 1972 a
Rabbit	1–2	male female	dermal (24 hours, occlusive)	14	> 7940 (minimum lethal dose)	Younger Laboratories, 1972 c
Rat	n. d.	n. d.	intraperitoneal	n. d.	> 1000	Mallette and von Haam, 1952
Rat	n. d.	male	intraperitoneal	n. d.	> 851	Weeks and Pope, 1974
Rat	n. d.	female	intraperitoneal	n. d.	> 1272	Weeks and Pope, 1974
Hen	5	n. d.	intraperitoneal	42	> 6000	Bayer, 1976
n. d. no data						

End of Table 1

Upon single oral and dermal administration to rats and rabbits, a decline in general health, reduced food consumption, reduced motility and activity, bloody secretions from the eyes, dishevelled coat, tremors, diarrhoea and paralysis were reported as signs of intoxication (for neurotoxicity, see Section 7.10; Mallette and von Haam, 1952; Younger Laboratories, 1958, 1971, 1972 a, b, c, 1973; Bayer, 1977).

Macroscopic examination of the deceased animals revealed hyperaemia of the lung, slightly lighter colour of the liver and kidneys, inflammation of the gastrointestinal tract, enlarged gall bladder, haemorrhages in the lungs and liver as well as oedema and haemorrhages in the brain (Mallette and von Haam, 1952; Younger Laboratories, 1958, 1971, 1972 a, b, c, 1973).

One sheep (approx. 30 kg) per dose level received an oral dose of 500, 1000 or 2000 mg/kg body weight as a 50-percent diphenyl cresyl phosphate solution in olive oil. The 500 and 1000 mg/kg body weight doses caused no appreciable signs of toxicity within a period of 30 days. In contrast, the 2000 mg/kg body weight dose resulted in convulsions shortly after administration and death of the animal within several minutes (Bayer, 1964).

A single oral dose of 1230 mg diphenyl o-cresyl phosphate/kg body weight had no effect on the copper level in the blood and plasma of 4 hens. The observation period was 11 days (Lotti et al., 1988).

The acute inhalation toxicity of diphenyl cresyl phosphate was assessed in the inhalation risk test conducted in groups of 6 male rats. Single exposures lasted for periods of 6 and 7 hours. Neither during exposure nor during the 10 to 14-day observation period were any substance-related signs of toxicity observed, with the exception of mild mucous membrane irritation (Younger Laboratories, 1958, 1971).

Two sheep inhaled an aerosol of undiluted diphenyl cresyl phosphate for one hour. The mean concentration was 0.35 mg/l. During the study, the concentration of the substance was so high at times that the animals were not discernible. Diphenyl cresyl phosphate caused transient minor signs of mucous membrane irritation, but no other appreciable symptoms occurred during the study and the subsequent 6-week observation period (Bayer, 1964).

In rats, a single intraperitoneal injection of 300 mg technical grade diphenyl cresyl phosphate/kg body weight (composition of the product: 45% diphenyl cresyl phosphate, 35% triphenyl phosphate, 18% dicresyl phenyl phosphate, 2% tricresyl phosphate; relative to total cresyl isomer content, the percentage of o-cresyl isomer was less than 0.09%) resulted in a significant decrease in pseudocholine esterase activity to 38 and 26% at 4 and 24 hours, respectively. A decrease was also observed following administration of 150 mg/kg body weight (no further details), but was not seen after a dose of 75 mg/kg body weight. No effect on acetylcholine esterase was de-

tectable in the brain and skeletal muscle in any of the three dose groups. In the liver, significant increases occurred within 24 hours in the activities of cytochrome P 450, cytochrome b_5, ethoxycoumarin O-deethylase as well as ethoxyresorufin O-deethylase. Seven days after administration, the activities had returned to the initial values. Cytochrome c reductase activity was significantly reduced throughout the entire 14-day observation period at the high dose level. In the kidney, there was no detectable effect on these enzyme systems. The 2',3'-cyclic nucleotide-3'-phosphohydrolase activity in the brain was significantly inhibited for the entire duration of the 14-day post-observation period. The tail nerve tissue showed isolated foci of swollen myelin sheath segments associated with widening of the nodes of Ranvier. The high dose led to an increase in lipid droplets in the hepatocytes. Electron microscopy demonstrated a proliferation of the smooth endoplasmic reticulum as well as enlarged mitochondria with an increased number of cristae. All hepatic findings had normalised 14 days after administration (Vainiotalo et al., 1987).

Studies with o-cresyl-free diphenyl cresyl phosphate

In a preliminary subacute toxicity study, groups of 5 male and 5 female CD rats (41 to 48 days old at study initiation) received diphenyl cresyl phosphate (99.87%, containing no o-isomers) in corn oil by oral gavage at doses of 0 (controls), 100, 300 and 1000 mg/kg body weight/day for a period of 7 days. There were no deaths. Administration by gavage of the 1000 mg/kg body weight dose was occasionally associated with salivation. Body weight gains were lower in the male rats of the high dose group. All of the other animals remained without symptoms. Necropsy revealed no substance-related findings (Pharmaco::LSR, 1995 a).

Based on the results of the preliminary study, groups of 5 male and 5 female CD rats (41 to 48 days old at study initiation) received diphenyl cresyl phosphate (99.87%, free of o-isomers) in corn oil by oral gavage at doses of 0 (controls), 62.5, 250 and 1000 mg/kg body weight/day for a period of 4 weeks. The investigations were carried out in accordance with OECD guideline No. 407. Four male and 2 female rats of the 1000 mg/kg group died of substance-related causes during the last study week of treatment. Macroscopic examination of the deceased animals revealed one of the following findings per animal: enlarged and pale kidneys, thickened wall of

the stomach or the urinary bladder, abnormal contents of the urinary bladder (solid, pale material), dark liver and dark foci in the lungs, bronchi and thymus gland. Histopathologically, the deceased animals showed changes in the liver (diffuse hypertrophy), stomach (hyperkeratosis, acanthosis), kidneys (basophilic cortical tubuli, tubular dilatation, hyaline casts) and adrenal glands (fatty vacuolisation) as well as the urinary bladder (hyperplasia). From day 4 of treatment, the animals of the 1000 mg/kg group showed salivation during dosing by gavage. Occasionally, this was also observed in the rats of the 250 mg/kg group. Further symptoms seen in the animals of the 1000 mg/kg group included ungroomed coat, and in the females general hairloss. Clinical signs indicating neurotoxicity were not observed. In the 1000 mg/kg group, the male rats exhibited delayed body weight gain while for the male and female rats reduced food intake was recorded during the last week of treatment. Water intake was increased in both sexes in the 1000 mg/kg group and slightly increased in the female rats of the 250 mg/kg group. After 24 days, haematology revealed that in the top dose group both sexes had reduced mean cell volumes with marginally low packed cell volumes and the female rats also had marginally low haemoglobin concentrations. Total leukocyte and lymphocyte counts were elevated in the males and females of the 1000 mg/kg dose group. Clinicochemical serum analysis of the animals in the top dose group revealed elevated creatinine levels and lowered chloride concentrations, and in the top and mid dose groups there were changes in protein concentrations (elevated α-2 and β-globulin, lowered albumin). In the rats of the 62.5 mg/kg dose group the changes were only marginal. The females receiving the 1000 mg/kg dose exhibited elevated calcium and phosphorus concentrations and aspartate aminotransferase activity while the males of that dose group had elevated alanine aminotransferase activity. After 22 days, urinary volumes were increased in the rats receiving the 1000 mg/kg dose, and specific gravities were slightly low. Urinary protein content was slightly increased in both sexes in the two higher dose groups and the urine sediments were found to contain epithelial cells and leukocytes. At necropsy, both sexes of the 1000 mg/kg dose group had increased absolute and relative liver, kidney and adrenal weights, and increased absolute and relative liver weights were seen in the males of the 250 mg/kg group. Histopathological examination revealed changes in the renal tubules (basophilic cortical tubules, tubular dilatation, hyaline casts) of the male rats receiving the 250 mg/kg dose and of both sexes in the 1000 mg/kg dose group. The livers of the

animals treated with the 1000 and 250 mg/kg doses additionally exhibited diffuse hypertrophy. Furthermore, there was an increased incidence of cortical fatty vacuolation in the adrenal glands of the 1000 mg/kg animals. Histopathological examination of the central and peripheral nervous system, the testes and epididymides and the ovaries revealed no substance-related findings. There were no changes in sperm numbers, motility or morphology compared with controls. The *no observed adverse effect level* was reported as being 62.5 mg/kg body weight/day (Pharmaco::LSR, 1995 a).

7.3 Skin and mucous membrane effects

Skin irritation

The skin irritation findings for diphenyl cresyl phosphate are shown in Table 2. In the majority of the studies, diphenyl cresyl phosphate proved not to be irritating to the intact skin (FhG, 1982 a; Weeks and Pope, 1974; FDRL, 1976 a; Younger Laboratories, 1958, 1972 a, b, c, 1973), whereas 2 studies report the chemical to be mildly irritating (FDRL, 1976 b; Younger Laboratories, 1971) and one study describes it as a moderate irritant (Mallette and von Haam, 1952). The signs of irritation were mostly reversible within 72 hours. Thus, on the whole, diphenyl cresyl phosphate is predominantly not irritating to the intact skin. On the scarified skin, diphenyl cresyl phosphate was mildly irritating (Weeks and Pope, 1974).

Mucous membrane effects

The studies on the irritating effects of diphenyl cresyl phosphate on the mucous membranes are summarised in Table 3. These are mostly older studies in which diphenyl cresyl phosphate proved not to be irritating (FhG, 1982 b; FDRL, 1976 a, b; Weeks and Pope, 1974) or to be only mildly irritating (Ciba-Geigy, 1984 b; Younger Laboratories, 1958, 1971, 1972 a, b, c, 1973). The signs of irritation were mostly reversible within 48 hours. On the basis of the available data, diphenyl cresyl phosphate on the whole proved to be mildly irritating to the eye.

Beginning of Table 2

Table 2. Irritating effects of diphenyl cresyl phosphate on the dorsal skin of the rabbit

Product	Guideline and/or dose, route, duration*	Findings	Reversibility	Assessment (by the authors)	Reference
Reomol CDP (no indication of purity)	OECD guideline No. 404	mild to marked erythema in 3 animals after 30 to 60 minutes	reversible within 72 hours	no information	Ciba-Geigy, 1984 a
Disflamoll DPK (no indication of purity)	OECD guideline No. 404	no effects after 1, 24, 48, 72 hours and after 8 days (irritation score 0)	–	not irritating	FhG, 1982 a
Kronitex 300, SS-578 (no indication of purity)	according to Draize (16 CFR 1500.41), 24-hour application of 0.5 ml to the intact and the scarified skin	at 24 hours, intact skin: erythema 3/6, oedema 0/6; scarified skin: erythema 6/6 (score 1 to 3), oedema 1/6 (score 1); overall average irritation score 0.46	reversible after 72 hours	not irritating	FDRL, 1976 a
Kronitex CDP, SS-578 (no indication of purity)	according to Draize (16 CFR 1500.41), 24-hour application to the intact and the scarified skin	at 24 hours, intact skin: erythema 3/6 (score 1), oedema 2/6 (score 1); scarified skin: erythema 3/6 (score 1), oedema 4/6 (score 1); scarified skin after 72 hours: oedema 2/6 (score 1); scarified skin: 2/6 (score 1), oedema 0/6; overall average irritation score 0.67	not fully reversible after 72 hours (not observed for longer periods)	mildly irritating	FDRL, 1976 b
Santicizer 140 (no indication of purity)	24-hour application of 0.5 ml to the intact and the scarified skin	at 24 and 72 hours and at 7 days, intact skin: no irritation; scarified skin: at 24 hours, very mild erythema around the abrasion site in one animal	scarified skin: reversible after 72 hours and after 7 days	intact skin: not irritating; scarified skin: mildly irritating at the most	Weeks and Pope, 1974
Santicizer 140 (no indication of purity)	according to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	no irritation within 7 days	–	not irritating	Younger Laboratories, 1973

Table 2. Irritating effects of diphenyl cresyl phosphate on the dorsal skin of the rabbit					
Product	Guideline and/or dose, route, duration*	Findings	Reversibility	Assessment (by the authors)	Reference
Santicizer 140 (no indication of purity)	according to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	no irritation within 7 days	–	not irritating	Younger Laboratories, 1972 a
Santicizer 140 (no indication of purity)	according to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	no irritation within 7 days	–	not irritating	Younger Laboratories, 1972 b
CP31862-2-AG143546	according to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	no irritation within 7 days	–	not irritating	Younger Laboratories, 1972 c
Cresyl diphenyl phosphate Ciba-Geigy (no indication of purity)	according to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	at 24 hours mild irritation in 3/3 animals (score 1 of a maximum of 8)	reversible after 48 hours	mildly irritating	Younger Laboratories, 1971
“OS-104” (no indication of purity)	according to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	no irritation within 72 hours	–	not irritating	Younger Laboratories, 1958
Santicizer 140 (no indication of purity)	no information	moderately irritating (no further details)	not investigated	moderately irritating	Mallette and von Haam, 1952
* where indicated					

End of Table 2

Beginning of Table 3

Table 3. Irritating effects of diphenyl cresyl phosphate on the mucous membranes of the rabbit eye

Product	Guideline and/or dose, route, duration*	Findings	Reversibility	Assessment (by the authors)	Reference
Reomol CDP (no indication of purity)	OECD guideline No. 405	very mild conjunctival irritation in 3/4 animals (no further details)	reversible after 72 hours	mildly irritating	Ciba-Geigy, 1984 b
Disflamoll DPC (no indication of purity)	OECD guideline No. 405	discharge in 2/3 animals after one hour, no other effects	reversible after 24 hours	not irritating	FhG, 1982 b
Kronitex 300, SS-578 (no indication of purity)	according to 16 CFR 1500.42, 0.1 ml neat substance for 24 hours, 6 animals with eyes unwashed, 3 animals with eyes washed after 4 seconds	no effects after 24, 48, 72 hours and after 7 days in the unwashed and the washed eyes	–	not irritating	FDRL, 1976 a
Kronitex CDP, SS-578 (no indication of purity)	according to 16 CFR 1500.42, 0.1 ml neat substance for 24 hours, 6 animals with eyes unwashed, 3 animals with eyes washed after 4 seconds	no effects after 24, 48, 72 hours and after 7 days in the unwashed and the washed eyes	–	not irritating	FDRL, 1976 b
Santicizer 140 (no indication of purity)	0.1 ml neat substance for 24 hours	no effects on the cornea, iris and conjunctivae (6 rabbits)	–	not irritating	Weeks and Pope, 1974
Santicizer 140 (no indication of purity)	according to Draize, 0.1 ml neat substance for 24 hours	at 10 minutes and one hour mild to moderate erythema, very mild oedema, discharge, at 24 hours slight erythema, slight discharge; average score 11.3 out of 110	reversible after 48 hours and after 7 days	mildly irritating	Younger Laboratories, 1973
Santicizer 140 (no indication of purity)	according to Draize, 0.1 ml neat substance for 24 hours	at 10 minutes slight erythema, moderate discharge, at one hour slight erythema, discharge, average irritation score 8/11; at 24 hours discharge, average irritation score 4/110	reversible after 48 hours	mildly irritating	Younger Laboratories, 1972 a

Table 3. Irritating effects of diphenyl cresyl phosphate on the mucous membranes of the rabbit eye

Product	Guideline and/or dose, route, duration*	Findings	Reversibility	Assessment (by the authors)	Reference
Santicizer 140 (no indication of purity)	according to Draize, 0.1 ml neat substance for 24 hours	at 10 minutes mild to moderate erythema, very mild oedema in 2/3 animals, discharge; at one hour mild to moderate erythema, discharge, average score 9.3 out of 110; at 24 hours slight erythema and discharge	reversible after 48 hours	mildly irritating	Younger Laboratories, 1972 b
CP 31862-2-AG143546 (no indication of purity)	according to Draize, 0.1 ml neat substance for 24 hours	at 10 minutes mild erythema, very mild oedema, moderate discharge; at one hour moderate erythema, slight oedema and moderate discharge; at 24 hours mild to moderate erythema, moderate discharge	reversible after 48 hours	mildly irritating	Younger Laboratories, 1972 c
Diphenyl cresyl phosphate – Ciba-Geigy UK Limited (no indication of purity)	according to Draize, 0.1 ml neat substance for 24 hours	at 10 minutes moderate discharge; at one hour slight erythema, moderate discharge, average irritation score 6/110	reversible after 24 hours	mildly irritating	Younger Laboratories, 1971
"OS-104" (no indication of purity)	according to Draize, 0.1 ml neat substance for 24 hours	at one hour moderate reddening of the conjunctivae, mild oedema and discharge, average irritation score at one hour 6.6/110, at 4 hours 8.0/110, at 24 hours 4.6/110, at 48 hours 2.6/110	reversible after 72 hours	mildly irritating	Younger Laboratories, 1958
* where indicated					

End of Table 3

7.4 Sensitisation

In a patch test, diphenyl cresyl phosphate (Santicizer 140) caused slight irritation of the skin in 2 to 4 rabbits (no further details). Challenge treatment after 14 days provided no evidence of a sensitising effect (Mallette and von Haam, 1952).

7.5 Subchronic and chronic toxicity

Studies with diphenyl cresyl phosphate (probably) containing o-cresyl isomers

Groups of 4 guinea pigs received dermal applications of diphenyl cresyl phosphate (no indication of purity) at 0.1, 0.2, 0.4, 0.6 and 0.8 ml/kg body weight/day (equivalent to approx. 120, 240, 480, 720 and 960 mg/kg body weight/day) to the shorn skin (exposed area approx. 3 cm^2) for a period of 73 days. A control group of 4 animals was given the vehicle, olive oil. All animals, including those of the control group, showed slight erythema with scale formation. The authors attributed this irritation to the olive oil used as the vehicle. From 0.2 ml/kg body weight there was dose/concentration-dependent alopecia in addition. Body weight gain was reduced from 0.6 ml/kg body weight, whereas liver weight was unchanged. The 0.4 ml/kg body weight dose led to hindlimb paralysis in 2 animals, and higher doses caused paralysis of the hindlimbs and the lower portions of the back muscles in all animals (time of onset of the signs of paralysis not indicated). In the 0.6 and 0.8 ml/kg dose groups, 2 animals per group died during the last study week of the study. In the liver, following 0.4 ml/kg body weight there was considerable plethora, an increase in collagen fibres in the sinusoids, disseminated large drop-like lipid infiltration and moderate glycogen depletion. The 0.6 ml/kg body weight dose caused massive terminal hyperaemia of the liver with intralobular bleeding, considerable glycogen depletion and medium-to-large drop-like central intermediary fatty infiltration. The 0.8 ml/kg body weight dose caused massive terminal hyperaemia with intralobular bleeding, considerable glycogen depletion, medium-to-large drop-like central intermediary fatty infiltration and group necrosis of hepatocytes as well as complete glycogen depletion. In the adrenals, according to the authors' description, at and above 0.4 ml/kg body weight there was hyperpla-

sia and formation of fatty cysts and lipid vacuoles in the cortex as well as hyperaemia in the cortex and medulla. The spinal cord was examined only in those animals in which paralysis occurred. Most prominent was oedema of the white matter, particularly of the ventral funiculus, as well as bleeding in the grey zone (Geffke et al., 1970).

7.6 Genotoxicity

7.6.1 In vitro

Studies with diphenyl cresyl phosphate (probably) containing o-cresyl isomers

Diphenyl cresyl phosphate (no indication of purity) was tested for mutagenic potential in the standard-plate incorporation test in two studies using the Salmonella/microsome assay with *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537. Concentrations ranging from 20 to 12500 µg/plate were employed. The test substance exhibited a dose-dependent bacteriotoxic effect at and above 20 µg/plate and started to precipitate at 2500 µg/plate. The tests were carried out in the presence and absence of metabolic activation (S9 mix from Aroclor 1254-induced rat liver). Neither study gave any indications of mutagenicity (Zeiger et al., 1987; Bayer, 1988 b).

No mutagenic effect of diphenyl cresyl phosphate (no indication of purity) was seen in a further standard-plate incorporation test using *Salmonella typhimurium* strains TA 1535, TA 1538, TA 98 and TA 1537 as well as *Escherichia coli* WP2uvrA with and without metabolic activation (S9 mix from rat liver induced with phenobarbital and 5,6-benzoflavone). The test concentrations were in the range from 312.5 to 5000 µg/plate (solvent DMSO). In two independently conducted tests, diphenyl cresyl phosphate had no mutagenic effect either with or without metabolic activation (Shibuya et al., 1995; JETOC, 1997).

In addition, a Salmonella/microsome assay with preincubation of *Salmonella typhimurium* did not detect any mutagenic properties for diphenyl cresyl phosphate (no indication of purity) either with or without metabolic activation (S9 mix from Aroclor 1254-induced rat or hamster liver; no further details; NTP, 1982).

Studies with o-cresyl-free diphenyl cresyl phosphate

Diphenyl cresyl phosphate (41.9%; 26.2% triphenyl phosphate, 24% phenyl dicresyl phosphate, 7.5% tricresyl phosphate, no detectable amounts of tri-o-cresyl phosphate) was tested in vitro for clastogenic effects in CHL/IU cells of the Chinese hamster. DMSO served as the solvent. In a preliminary experiment, the cytotoxic concentrations (50% inhibition of cell proliferation) found for 6-hour exposure were 0.043 and 0.037 mg/ml in the absence and presence of metabolic activation, respectively. When exposure lasted 48 hours, the corresponding cytotoxic concentration was 0.016 mg/ml. In the main study, 6-hour exposure was used at concentrations of 0.043, 0.022 and 0.011 mg/ml in the absence and presence of metabolic activation. Without metabolic activation, there were no indications of chromosome damage or induction of polyploidy (800 cells/group), likewise in the presence of metabolic activation up to a concentration of 0.022 mg/ml (200 cells/group). With metabolic activation, an increase was seen in the occurrence of chromosome damage at the highest concentration level, but no significant increase was detected in the frequency of polyploidy (Tanaka et al., 1995; JETOC, 1997). However, the evaluability of these observations is limited because the concentrations employed were cytotoxic, as demonstrated in the preliminary experiment. Cytotoxicity was not checked in the main study, but it can nevertheless be deduced from the small numbers of cells evaluated at this concentration in the first test series – as few as 93 and 125 cells for clastogenicity and induction of polyploidy, respectively – that cytotoxicity was high. The main study with 24 and 48-hour exposures was conducted with test substance concentrations of 0.016, 0.008 and 0.004 mg/ml only in the absence of metabolic activation and gave no indications of a chromosome-damaging effect (Tanaka et al., 1995).

7.6.2 In vivo

Studies with o-cresyl-free diphenyl cresyl phosphate

Diphenyl cresyl phosphate (99.9% total phenyl cresyl phosphate, without o-cresol) was investigated for its clastogenic potential in the micronucleus test. Male and female NMRI mice (initial weight from 30.1 to 40.2 g) were given single intraperitoneal doses of 0 (controls), 100, 300 and 1000 mg/kg body weight. Corn oil served as the solvent. The dosages were chosen on

the basis of a toxicity study conducted in advance in which 1000 mg/kg body weight had been found to be the highest tolerable dose. After 16 hours (1000 mg/kg body weight), 24 hours (100, 300 and 1000 mg/kg body weight) and 48 hours (1000 mg/kg body weight), the femoral bone marrow was prepared from 5 animals per dose and sex and the ratios of polychromatic and normochromatic erythrocytes were determined as well as the numbers of micronucleated polychromatic erythrocytes. In each case, 1000 cells were scored. The animals of the 1000 mg/kg group showed signs of toxicity (depressed spontaneous activity, closed eyelids, convulsions), and 1 of 18 mice died. At 24 hours after administration of the highest dose (1000 mg/kg body weight) the number of normochromatic erythrocytes was slightly increased (1033 versus 721 in the control), a finding which was interpreted as a cytotoxic effect. In none of the dose groups and at no time point investigated was there any increase in micronucleated polychromatic erythrocytes. Diphenyl cresyl phosphate thus produced no chromosome-damaging effect in this study (CCR, 1993).

7.7 Carcinogenicity

No information available.

7.8 Reproductive toxicity

Studies with o-cresyl-free diphenyl cresyl phosphate

In a preliminary study on the prenatal toxicity of diphenyl cresyl phosphate (total phenyl cresyl phosphate content 99.9%), groups of 6 female CD rats (initial weights ranging from 211 to 259 g) received daily doses of 0 (controls), 100, 330 and 1000 mg/kg body weight in corn oil by oral gavage on days 6 to 15 of pregnancy. One female of the 1000 mg/kg group had to be killed *in extremis* on day 12 of gestation. The surviving animals of this group exhibited salivation, hypoactivity, hunched posture and piloerection. Body weight gain in the 1000 mg/kg group was delayed in the first half of the study, food intake was marginally reduced, and there was an increase in water consumption during the study and up to termination. The rats of the mid and low dose groups showed no clinical signs and did not differ from the controls in respect of body weight development. At necropsy on

day 20 of the study, there were no treatment-related findings. No embryotoxic or foetotoxic effects were observed. There was a slightly increased incidence of renal cavitation and hydroureter in the foetuses of the 1000 mg/kg group which the authors considered to be possibly related to the treatment. This finding was not observed in the main study even at the highest dose of 900 mg/kg body weight (Pharmaco::LSR, 1995 b).

Based on the results of the preliminary study, groups of 22 female CD rats (initial weights ranging from 212 to 266 g) received diphenyl cresyl phosphate (total phenyl cresyl phosphate content 99.85%) doses of 0 (controls), 100, 300 and 900 mg/kg body weight in corn oil by oral gavage on days 6 to 15 of gestation. The investigations were carried out in accordance with OECD guideline No. 414. In order to determine haematology and blood chemistry parameters on day 16, 5 female rats per group were included in the study as satellites. On day 20 of the study, caesarean section was carried out. The rats in the groups receiving 300 and 900 mg/kg displayed dose-dependent salivation following administration, those of the 900 mg/kg group additionally showing hairloss, piloerection as well as an ungroomed and brown-stained coat. Furthermore, observations included body weight stasis or loss over days 7 to 10 of gestation and reduced food consumption for the first few days of treatment in 900 mg/kg dose group as well as a marked increase in water consumption throughout the entire treatment period at and above 300 mg/kg body weight. Necropsy of the dams was without substance-related findings. Haematological examination of the dams revealed signs of anaemia in all dose groups, although these were only marginal in the 100 mg/kg group. Leukocytosis was seen in the animals receiving 300 and 900 mg/kg, and at 900 mg/kg polychromasia and/or hypochromasia were also observed. Blood chemistry findings included low albumin concentrations as well as slightly high α-globulin and high β-globulin concentrations in the mid and high dose groups. At 900 mg/kg body weight, additionally there were high alanine and aspartate aminotransferase activities as well as marginally low plasma glucose levels. At all dosages, foetal survival rates, growth and development *in utero* and other parameters of reproductive toxicity were unaffected by treatment. No teratogenic effects were seen. The maternal *no observed adverse effect level* was reported as 100 mg/kg body weight and the *no effect level* for foetuses was given as 900 mg/kg body weight (Huntingdon Life Sciences, 1996).

In a modified reproductive toxicity study, groups of 10 male and 10 female SD rats (initial weights 290 to 316 and 180 to 225 g, respectively) received technical-grade diphenyl cresyl phosphate (41.9%, containing no tri-o-cresyl phosphate or other o-isomers) in olive oil by oral gavage at 0 (controls), 12, 60 and 300 mg/kg body weight/day. The treatment period for the male and female rats encompassed the 14-day pre-mating period as well as the mating period, and treatment was continued in the males up to the day prior to planned sacrifice, i.e. for a total of 45 days, while the females received treatment throughout gestation and up to day 3 of lactation, i.e. for a total of 41 to 45 days. Dosages were based on the results of a 2-week preliminary study, in which doses of 500 and 1000 mg/kg body weight had proved toxic (reduced motility, gait ataxia, salivation, slow respiration, deaths, increased liver and adrenal weights), testicular atrophy had been noted in the males, and the females had failed to become pregnant. The rats of the 300 mg/kg group developed salivation during dosing by gavage. Body weight gain in the males and females of the 300 mg/kg group and in the females of the 60 mg/kg group was slightly retarded, while retardation was marked in the female rats of the 60 mg/kg group during the last third of gestation. Food consumption was increased in the male rats of the 300 mg/kg and 60 mg/kg groups up to study days 28 and 7, respectively. Water intake in the 300 mg/kg group was higher than controls in both sexes. Haematological and blood chemical examination was carried out only in the male rats. In the top dose group signs of anaemia with leukocytosis were noted. Cholinesterase activities in serum, erythrocytes and the brain were significantly reduced in a dose-dependent manner in the 60 and 300 mg/kg body weight dose groups. In the top dose group, the alanine aminotransferase and γ-glutamyl transferase activities and calcium levels were increased, while aspartate aminotransferase activity as well as triglyceride and albumin levels and the albumin/globulin ratio were decreased. Increases in total cholesterol were noted in the two top dose groups. In the top dose group, an increase in urine volume and decreases in specific gravity and pH were found. At study termination, the 300 mg/kg group of male rats exhibited higher relative organ weights of the liver, kidneys and adrenals, the animals of the 60 mg/kg group having increased liver and adrenal weights. The top dose female rats had higher relative liver and adrenal weights. Macroscopically, all top dose animals were noted to have enlarged adrenals, and in 5 males rats enlargement of the liver was seen. The stomachs of 7/10 male rats were found to have erosions. Enlarged adrenals were also

noted in one male and 7 females, and an enlarged liver was seen in one male of the 60 mg/kg group. Histopathological examination revealed cortical vacuolation of the adrenals in the top and mid dose animals of both sexes. In addition, fatty change of the proximal tubular epithelium was observed in the 300 mg/kg group of male rats as well as dose-dependently at and above 60 mg/kg body weight in the female rats. In 6 males of the 300 mg/kg group, necrosis of the mucosa in the stomach was diagnosed. Two of the 60 mg/kg and 3 of the 300 mg/kg groups of females showed atrophy of the thymus. The testes of 9 out of 10 rats of the top dose group displayed atrophy of the seminiferous tubules accompanied by reduced sperm counts and degeneration of the germinal epithelium. In the top dose group, 6 nonpregnant females or females without parturition exhibited interstitial cell hypertrophy and hyperplasia in the ovaries. The reproductive toxicity parameters found for the 300 mg/kg group included decreased fertility and nidation rates as well a tendency towards a lower delivery rate, findings which were attributed to inhibition of spermatogenesis in the paternal animals. Copulation rate, gestation length, number of corpora lutea, delivery index and maternal behaviour were not affected by the treatment. Observation of the neonates also revealed no appreciable treatment-related effects in terms of the numbers of live offspring, the sex ratio, general condition, body weight or external features. There were no skeletal or visceral malformations. The *no effect level* reported for the subacute study was 12 mg/kg body weight for male and female rats, while for reproductive toxicity *no effect levels* were given as 60 mg/kg body weight for parental males and 300 mg/kg body weight for both parental females and offspring (Matsuura et al., 1995; JETOC, 1997).

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

Technical-grade diphenyl cresyl phosphate produced delayed polyneuropathy in animals. Only the o-cresyl isomer of diphenyl cresyl phosphate or technical-grade diphenyl cresyl phosphate mixtures containing the o-cresyl isomer appear to be neurotoxic. The o-cresyl isomer is the only isomer ca-

pable of forming phenyl saligenin phosphate, a metabolite considered to be responsible for neurotoxicity (Johnson, 1969, 1975).

In order to form phenyl saligenin phosphate, the phenyl ring must have an o-alkyl substituent and the α-carbon atom of the o-alkyl group must possess at least one hydrogen atom (Johnson, 1975; Johannsen et al., 1977). In the first step, the NTE enzyme (neuropathy target esterase, formerly neurotoxic esterase) is phosphorylated by phenyl saligenin phosphate. In a second stage, the enzyme-substrate complex is ionised by hydrolysis of the ester group. This leads to inactivation ("aging") of the enzyme (Johnson, 1975).

Studies with diphenyl cresyl phosphate (probably) containing o-cresyl isomers

In hens, single and multiple oral and subcutaneous administration of technical diphenyl cresyl phosphate (Santicizer 140) and diphenyl o-cresyl phosphate, respectively, caused signs of neurotoxicity (limping, ataxia, paralysis of the extremities) 2 to 3 weeks after dosing. Histopathological examination revealed focal axonal degeneration and demyelinisation in the cerebrum, the cerebellar folium, the spinal cord as well as the optic nerve (Hine et al., 1956; Henschler, 1959; Aldridge and Barnes, 1966 a; IBT, 1972 a, b, 1975; Lotti and Johnson, 1980; Lotti et al., 1988). The product used by Hine et al. (1956) was $\geq$ 98% pure, whereas that used by Henschler (1959) contained 40.3% by weight o-cresol in the aromatic fraction. No further information was given on the composition of the test substances.

Oral diphenyl cresyl phosphate doses of 100 mg/kg body weight containing approx. 2.2% o-isomer, when administered twice daily on study days 1 to 3 and 21 to 33, produced signs of neurotoxicity in 3 out of 10 hens and resulted in histopathological neural lesions after 42 days. The graphically determined cumulative ED_{50} was given as 1230 mg/kg body weight (Johannsen et al., 1977).

The *no effect level* for a neurotoxic effect (limping and paralysis of the extremities) of diphenyl o-cresyl phosphate was estimated to be 30 mg/kg body weight for a single oral dose in hens (Lotti and Johnson, 1980).

In regard to the inhibition of NTE activity in the brain, spinal cord and peripheral nerves, the effect level in hens for a single oral dose was 10 mg diphenyl o-cresyl phosphate per kilogram body weight. Inhibition occurred within 24 hours (Aldridge and Barnes, 1966 b; Johnson, 1969; Lotti and Johnson, 1980; Caroldi and Lotti, 1982).

In a later study it was also shown that diphenyl o-cresyl phosphate (> 99% pure) after a single oral dose of just 10 mg/kg body weight led to an 86% reduction in NTE activity in the brain of hens after 23 hours, while 1000 mg/kg body weight doses of the m- and p-isomers were without effect (Sprague and Castles, 1985).

Oral administration of 2.5 mg diphenyl o-cresyl phosphate/kg body weight per day to 3 hens for 10 weeks resulted in 60-percent inhibition of NTE activity in the brain and 45-percent inhibition in the spinal cord. A steady-state level established itself approximately after the second to third week of administration. “NTE-like” activity in the spleen was slightly inhibited, while no effect on the “NTE-like” activity in the lymphatic tissue could be observed. Clinically, no neurotoxic symptoms were observed during the period of administration or during the 3-week post-treatment observation period. There were no histopathological changes, either (Johnson and Lotti, 1980; Lotti and Johnson, 1980).

It was possible to produce the clinical symptoms of delayed polyneuropathy in hens by means of a single oral diphenyl o-cresyl phosphate dose of 50 mg/kg body weight or by daily administration of 5 mg/kg body weight from days 22 to 35 of the study following 21 days of administering diphenyl o-cresyl phosphate at 2.5 mg/kg body weight/day. The neuropathy began approx. 2 weeks after the last dose (Lotti and Johnson, 1980).

It was not possible to detect an effect on the acetylcholine esterase and butyrylcholinesterase activities in the brain and spinal cord following single oral administration to hens of up to 70 mg diphenyl o-cresyl phosphate/kg body weight. Plasma butyrylcholinesterase activity was slightly inhibited (Lotti and Johnson, 1980).

In the rat, technical-grade diphenyl cresyl phosphate (composition: 45% diphenyl cresyl phosphate, 35% triphenyl phosphate, 18% dicresyl phenyl phosphate, 2% tricresyl phosphate; relative to total cresyl isomer content, the percentage of o-cresyl isomer was less than 0.09%) given as a single

oral dose caused inhibition of the pseudocholinesterase activity in plasma at and above 150 mg/kg body weight. The acetylcholine esterase activity in the gluteal muscle and brain remained unaffected even on oral administration of 300 mg/kg body weight. The post-treatment observation period was 14 days (Vainiotalo et al., 1987).

The shaved intact and scarified dorsal skin (approx. 10% of the body surface) of each of 10 rabbits per group was treated with daily applications of diphenyl cresyl phosphate (Santicizer 140, no details of the composition) at 617.6 and 1235.2 mg/kg body weight on 5 days/week for 4 weeks. The duration of exposure was 6 hours/day, and the application area was then washed. Ten further animals served as a control group. The cholinesterase activity in plasma and in erythrocytes was measured before the start of the study, on study days 13 and 29 as well as 7, 14, 27 and 41 days after the end of the application period. In the control group, 3 animals died, and in the lower dose group 7 died during post-treatment observation, while in the high dose group 8 deaths occurred during exposure and the remaining 2 animals died during the post-treatment observation period. At the application sites, mild erythema and oedema developed, but these faded during the observation period after treatment. Signs of toxicity included the occurrence of diarrhoea and significant reduction in body weight. The cholinesterase activity levels observed on treatment days 13 and 29 as well as on days 7, 14 and 27 of the observation period were significantly below those in the controls, but had normalised again by day 41 of observation (IBT, 1973).

According to Russian work available in English only as an abstract, it was also possible to elicit neuroparalytic effects in guinea pigs following subcutaneous injection of diphenyl cresyl phosphate (no details of dose and number of injections), but the effects were weaker than those caused by tricresyl phosphate containing 37% o-isomers (Dvorkin, 1973).

In 4 squirrel monkeys, single intraperitoneal administration of diphenyl cresyl phosphate (Santicizer 140, no details of the composition) at 1000 mg/kg body weight caused 89-percent inhibition of plasma cholinesterase activity 24 hours after dosing. Cholinesterase activity in the erythrocytes remained unaffected (Weeks and Pope, 1974).

Studies with o-cresyl-free diphenyl cresyl phosphate

Whereas the above-mentioned studies with o-cresyl-containing diphenyl cresyl phosphate clearly indicated neurotoxic lesions, the studies to be discussed below, which were conducted with o-cresyl-free diphenyl cresyl phosphate, did not produce any such effects.

No neurotoxicity was caused in 8 hens by oral administration of a mixture consisting of only diphenyl m-cresyl phosphate and diphenyl p-cresyl phosphate (no details of the proportions; 10 g/kg body weight twice daily on 3 consecutive days, administration repeated after 21 days). The effects were assessed on day 42 of the study. The total cumulative dose was reported as 120 g/kg body weight (Johannsen et al., 1977).

In another study in hens, single oral administration of technical-grade diphenyl cresyl phosphate (Disflamoll DPK), a technical product based on synthetic cresol low in o-isomers (no further details), no neurotoxicity was observed at dose levels ranging from 250 to 5000 mg/kg body weight. Upon intraperitoneal administration, however, 2 out of 5 animals showed limping and paralysis of the extremities, but these signs were only seen in the highest dose group receiving 5000 mg/kg body weight. During 30-day oral administration of the same batch of diphenyl cresyl phosphate at concentrations of 100, 300, 1000 and 3000 mg/kg feed (equivalent to daily doses of 207, 607, 2118 and 4602 mg/kg body weight; 8 hens per dose group) and throughout the 28 days of post-treatment observation, no signs of neurotoxicity were noted (Bayer, 1971).

Following a single 100 mg/kg body weight oral administration of diphenyl cresyl phosphate (supposedly free from impurities, no further details) no signs of neurotoxicity were seen in 4 hens, and after an observation period of 30 days there were no histopathological changes in the brain, the spinal cord or the sciatic nerve. Another bird exhibited unsteady gait on day 3 and an abnormal curling of the toes after one week, the signs persisting throughout the observation period. This observation, however, was not considered by the investigator to be related to treatment (Hazleton, 1964).

7.11 Other effects

No information available.

8 Experience in humans

In a patch test, 10-percent Santicizer 140 (no further details) caused slight irritation of the skin in 10% of the 15 to 30 subjects (no further details). Challenge treatment after 14 days provided no evidence of a sensitising effect (Mallette and von Haam, 1952).

9 Classifications and threshold limit values

No information available.

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