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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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Triisobutyl phosphate

No. 112

CAS No. 126-71-6

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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Triisobutyl phosphate

1 Summary and assessment

The available acute toxicity data show triisobutyl phosphate to be of low toxicity in animals following oral administration (LD_{50} rat oral approx. 4250 mg/kg body weight and > 5000 mg/kg body weight, depending on the source of information; LD_{50} rabbit dermal > 5000 mg/kg body weight; LC_{50} rat, 4 hours > 5140 mg/m³ air).

In the rabbit triisobutyl phosphate has no effect or a moderately irritant effect on the skin, depending on the source of information, and it is not irritating to the eye.

In the guinea pig skin, triisobutyl phosphate shows a clear sensitising potential in the maximisation test. In two Buehler tests in guinea pigs one positive and one negative result was obtained with triisobutyl phosphate.

In a 13-week feeding study in rats triisobutyl phosphate led to reduced neutrophil counts and increased cholesterol levels (male rats) at the highest test concentration of 5000 ppm (equivalent to approx. 346 mg/kg body weight and approx. 404 mg/kg body weight for the male rats and the female rats, respectively). The no observed effect level was reported as being 1000 ppm (equivalent to approx. 68 mg/kg body weight and approx. 84 mg/kg body weight for the male and the female animals, respectively). Under the given experimental conditions no evidence of neurotoxic effects was reported.

Triisobutyl phosphate showed no mutagenic effect in three independently conducted Salmonella/microsome assays with and without metabolic activation and no clastogenic effects in the mouse micronucleus test following intraperitoneal administration.

In the rat no embryotoxic or teratogenic effects were seen upon oral administration of triisobutyl phosphate up to the highest test dose of 1000 mg/kg body weight/day.

In the domestic chicken no neurotoxic effects were observed following oral administration of triisobutyl phosphate up to the highest test dose of twice 5000 mg/kg body weight with an interval of 21 days between doses and a total study duration of 42 days.

In humans, no cases of skin sensitisation have been observed so far in connection with the production and handling of triisobutyl phosphate.

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft has designated triisobutyl phosphate with "Sh" for skin-sensitising substances in the List of MAK and BAT Values.

2 Name of substance

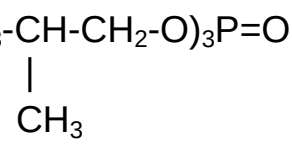
2.1	Usual name	Triisobutyl phosphate
2.2	IUPAC name	Phosphoric acid triisobutyl ester
2.3	CAS No.	126-71-6
2.4	EINECS No.	204-798-3

3 Synonyms, common and trade names

Etingal
Phosphoric acid tris(2-methylpropyl) ester
Phosphorsäuretriisobutylester
Triisobutylphosphat

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_{12}H_{27}O_4P$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	266.32	
5.2	Melting point, °C	< –50	(BASF, 1997)

5.3	Boiling point, °C	272.5 (at 1013 hPa) 264	(BASF, 1991) (Lide and Frederikse, 1996)
5.4	Vapour pressure, hPa	2 (at 103 °C) 10 (at 133 °C) 50 (at 170 °C) 130 (at 200 °C)	 (BASF, 1991) (BASF, 1997)
5.5	Density, g/cm³	0.96–0.965 (at 20 °C) 0.9681 (at 20 °C)	(BASF, 1991) (Lide and Frederikse, 1996)
5.6	Solubility in water	264 mg/l (at 25 °C) Dissolves well	(BASF, 1991) (Lide and Frederikse, 1996)
5.7	Solubility in organic solvents	Dissolves well in ethanol, diethyl ether, benzene	(Lide and Frederikse, 1996)
5.8	Solubility in fat	Partition coefficient n-octanol/water log P_{ow}: 3.72	(BASF, 1991)
5.9	pH value	8.5 (at 100 g/l, 20 °C)	(BASF, 1997)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 10.87 mg/m³ 1 mg/m³ ≙ 0.09 ml/m³ (ppm) (at 1013 hPa and 25 °C)	

6 Uses

As a paper and textile auxiliary (BASF, 1991).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

Acute toxicity

Following a single oral administration in an exploratory study in rats, an LD_{50} of approx. 4.4 ml/kg body weight was found, which is equivalent to approx. 4250 mg/kg body weight (no further details; BASF, 1953).

In a further study in the rat, the acute oral LD_{50} was found to be > 5000 mg/kg body weight (no further details; Levin and Gabriel, 1973).

In another report, the acute oral LD_{50} in the rat was also given as > 5000 mg/kg body weight. The acute dermal LD_{50} in the rabbit was also reported as being > 5000 mg/kg body weight (no further details; Monsanto, 1989).

In the cat, salivation and imbalance were seen following a single oral administration of triisobutyl phosphate at a dose of 1 ml/kg body weight (equivalent to approx. 968 mg/kg body weight; no further details; BASF, 1953).

An acute inhalation toxicity study (LC_{50} determination) of triisobutyl phosphate was carried out in 5 male and 5 female Wistar rats (strain: Hoe:WISKf/SPF71) with an average initial weight of 205 and 188 g in accordance with OECD guideline No. 403 (head-nose exposure). The analytically determined aerosol concentration was 5140 mg/m³ of air, the median aerodynamic diameter being 1.3 µm (with a geometric standard deviation of 1.6). During the experiment, the animals showed dyspnoea, tremor, uncoordinated movements, a reduced level of spontaneous activity, ruffled fur, reduced startle reflexes and pinch reflexes, noses with bloody encrustations, sneezing, narrow palpebral fissures as well as reddish saliva and nasal discharge. Body weight gain was impaired in the first week of post-exposure observation. After 21 days the rats were free of symptoms again, with the exception of one female rat, and their body weight had returned to normal. There were no deaths. At necropsy at the end of the observation period approximately half of the animals exhibited discolorations of the lungs (no further details). The LC_{50} (4 hours) for triisobutyl phosphate was thus found to be > 5140 mg/m³ of air (Hoechst, 1989 a).

Three rats survived a single 6-hour exposure to 122 ppm of triisobutyl phosphate, equivalent to 1326 mg/m³ (no further details; Levin and Gabriel, 1973).

The less recent findings from exploratory acute inhalation toxicity studies using vapour or aerosol exposure are summarised in Table 1 (BASF, 1953).

Table 1. Acute inhalation toxicity of triisobutyl phosphate (BASF, 1953)

Species	Nominal concentration (mg/m³)	Exposure	Mortality (deceased/used)	Symptoms
Mouse	1700[1)] (≙153 ppm)	6 hours	2/10	no signs of toxicity
Rat	1700[1)] (≙ 153 ppm)	6 hours	0/4	no signs of toxicity
Rabbit	1700[1)] (≙ 153 ppm)	6 hours	0/1	no signs of toxicity
Cat	1700[1)] (≙ 153 ppm)	6 hours	0/1	salivation
Mouse	52000[2)]	30 minutes	1/10	marked dyspnoea
Rat	52000[2)]	30 minutes	1/4	marked dyspnoea
Rabbit	52000[2)]	30 minutes	0/1	no signs of toxicity
Cat	52000[2)]	30 minutes	0/1	severe mucous membrane irritation in combination with salivation as well as clouding of the cornea and lateral position; on termination of exposure these symptoms were reversible

[1)] vapour
[2)] aerosol

In a further exploratory study of the acute inhalation toxicity of triisobutyl phosphate, one cat and one rabbit were exposed to the substance once for 8 hours during which they inhaled, upon cooling, the vapours formed at 80 °C. The nominal concentration was calculated on the basis of the difference in substance weight before and after the experiment, and an average concentration of 4850 mg/m³ of air was determined. During exposure, the cat made attempts to escape and exhibited salivation, blinking and lacrimation. After the experiment body weight loss, rhinorrhoea, lacrimation and proteinuria and glycosuria were observed. The cat died 12 days later. Histopathology revealed changes in the lungs (hyperaemia, marked dilation of the alveoles), the heart, the kidneys, the adrenal glands (necrosis) and the blood vessels (degenerative changes). In the rabbit experiment, the animal showed wiping of the snout, attempts to escape as well as depressed res-

piration and immediate recovery after the experiment (IG Farben, 1939). The calculated vapour concentration of 4850 mg/m³ of air cannot have been attained by vaporisation, however, in view of the very low vapour pressure of triisobutyl phosphate, which is only 2 hPa even at 103 °C. It seems likely, therefore, that in actual fact this experiment involved an aerosol rather than vapour.

Subacute toxicity

In an exploratory study in the rabbit with oral administration by gavage over a period of 5 days, 3 doses of 1 ml triisobutyl phosphate/kg body weight/day (equivalent to approx. 968 mg/kg body weight/day) had a lethal effect. Whereas after the first administration no clinical signs of toxicity were seen, diarrhoea occurred after the second administration. At necropsy, severe necrosis of the gastric mucosa was observed (no further details; BASF, 1953).

Repeated oral administration by gavage of 0.5 ml triisobutyl phosphate/kg body weight/day (equivalent to 484 mg/kg body weight/day, 22 treatment days, duration of the experiment: 30 days) led to the death of the one rabbit used in the study. Necropsy revealed pea-size focal haemorrhages of the lung, the peritoneum being covered with a serosanguineous fluid. The intestine exhibited markedly increased perfusion, the small intestine had individual small focal haemorrhages, while the gastric mucosa showed “inflammatory reddening” (no further details; BASF, 1953).

The findings from an exploratory oral toxicity study with repeated administration of triisobutyl phosphate in the cat are summarised in Table 2.

Beginning of Table 2

Table 2. Toxicity of triisobutyl phosphate following repeated oral administration in the cat (1 animal/dosage, exploratory study; BASF, 1953)

Dose (ml/kg body weight)	Treatment	Symptoms
0.05	23 times in 39 days	transient diarrhoea
0.1	25 times in 35 days	lack of appetite, diarrhoea, reversible within a 4-week post-exposure observation period
0.1	38 times in 52 days	lack of appetite, diarrhoea

Table 2. Toxicity of triisobutyl phosphate following repeated oral administration in the cat (1 animal/dosage, exploratory study; BASF, 1953)		
Dose (ml/kg body weight)	Treatment	Symptoms
0.5	3 times in 7 days	salivation, unsteady gait, imbalance, tremor, ataxia, vomiting; symptoms grew stronger with repeated administration; marked decrease in the granulocyte counts, increase in the lymphocyte counts, proteinuria; the findings were reversible within a post-exposure observation period of 51 days
1.0	5 times in 5 days	salivation, imbalance, diarrhoea, severe convulsions, death; doubling of the leukocyte and granulocyte counts, marked decrease in the lymphocyte counts, proteinuria; necropsy showed no macroscopic findings

End of Table 2

In an exploratory toxicity study of triisobutyl phosphate with repeated inhalation (6 hours/day on 4 consecutive days) of nominal triisobutyl phosphate concentrations ranging from 300 to 1000 mg/m³ (equivalent to 27 to 90 ppm), 1 out of 10 mice died, whereas 4 rats, one rabbit, one guinea pig and one cat survived and showed no externally visible findings (BASF, 1953).

7.3 Skin and mucous membrane effects

In a less recent study the effect of triisobutyl phosphate on the rabbit skin was investigated both for the concentrated substance and for a 50-percent formulation in oil (2 animals per treatment). The 20-hour occlusive application was found to cause irritation, whereas with the 20-percent solution in oil the irritant effect was only barely perceptible to slight (no further details; BASF, 1953).

In another study in the rabbit skin, an average irritation index of 3.1 (from a maximum irritation index of 8.0) was found following a single 4-hour dermal exposure to triisobutyl phosphate and the substance was evaluated as being moderately irritating (no further details; Monsanto, 1989).

In a primary skin irritation study conducted in accordance with OECD guideline No. 404, one female and 2 male white New Zealand rabbits (weighing 2.4 to 2.5 kg at the beginning of the experiment) were subjected

to a single semi-occlusive exposure of the shaved dorsal skin to 0.5 ml triisobutyl phosphate (purity: 90%, 10% n-propanol) for 4 hours. Skin reaction was assessed at 1, 24, 48 and 72 hours as well as 7 days after exposure. All animals were observed to have developed slight erythema (average irritancy score 0.78) which was reversible after 7 days at the latest. Based on these results, the authors assessed triisobutyl phosphate as non-irritating (RCC, 1990).

In the rabbit eye (2 animals per treatment) undiluted triisobutyl phosphate caused marked irritation, whereas a 50-percent and a 20-percent solution in oil caused only barely perceptible irritation (no further details; BASF, 1953).

In another study in the rabbit eye triisobutyl phosphate caused slight to moderate transient conjunctival irritation which was reversible within one day in 4 out of 6 animals and after 2 or 3 days in the remaining animals. Triisobutyl phosphate was evaluated by the authors as being non-irritating (no further details; Monsanto, 1989).

7.4 Sensitisation

Triisobutyl phosphate (no indication of purity) was tested in the guinea pig (strain: Pirbright White) in accordance with OECD guideline No. 406 for its sensitising potential in the maximisation test using 10 test substance animals and 5 controls. For intradermal induction, the animals of the test substance group were treated with an 0.05-percent formulation in paraffin (DAB quality), whereas dermal induction and dermal challenge were carried out with 4-percent triisobutyl phosphate in white vaseline (DAB). The latter treatment led to a positive reaction in 9 out of 10 animals. Dermal challenge yielded no skin changes in the control group (Hoechst, 1989 b). The test substance thus unequivocally proved to be sensitising in this experiment.

In a further study, triisobutyl phosphate (99.2% pure) was tested for its skin-sensitising potential in the Buehler test in accordance with OECD guideline No. 406. Per group 10 to 20 female Pirbright White Dunkin Hartley guinea pigs (initial weight 313 to 388 g) were used. Dermal induction took place three times a day for 6 hours at a time with a 75-percent solution in olive oil (DAB 10) under occlusive conditions at intervals of one week. This con-

centration caused very slight to well-defined skin irritation (assessment 24 hours after removal of the patches). The dermal challenge took place 14 days after the third induction and was carried out with 0.5 ml of a 50-percent solution in olive oil, again under an occlusive dressing. Similarly, the duration of exposure was 6 hours and the skin findings were assessed 24 hours after removal of the patches. In 9 out of 18 guinea pigs very slight to well-defined skin reactions were observed, while the controls showed no reactions (2 guinea pigs from each of the two groups died intercurrently). Triisobutyl phosphate thus proved also to have a sensitising effect on the skin in the Buehler test (BASF, 1995).

A further Buehler test with triisobutyl phosphate (no indication of purity) was conducted in 10 male Hartley guinea pigs (initial weight 321 to 393 g) per group which were again treated in accordance with OECD guideline No. 406. Dermal induction was carried out three times at intervals of one week by means of occlusive application of 0.5 ml of undiluted triisobutyl phosphate for 6 hours per exposure. Any irritating effects of the induction were assessed 24 hours after removal of the patches. The challenge took place 14 days after the last induction and was also carried out with undiluted triisobutyl phosphate. The exposure sites were assessed 24 and 48 hours after removal of the patches. After induction and after challenge none of the guinea pigs showed skin reactions. The positive control, dinitrochlorobenzene (0.075% in acetone), caused sensitisation in all 10 animals. Triisobutyl phosphate thus proved not to have a sensitising effect on the skin in this experiment (FMC, 1996).

7.5 Subchronic and chronic toxicity

In a 13-week feeding study with groups of 10 male (170 to 218 g) and 10 female (132 to 174 g) Sprague-Dawley (CD) rats per group, the animals were given triisobutyl phosphate (purity: 99.7%) at concentration levels of 0 (controls), 200, 1000 and 5000 ppm (± 10% at each level) in the feed. This was equivalent to a daily substance intake of 0, 13.9, 68.4 and 346.1 mg/kg body weight (male rats) and 0, 16.8, 84.3 and 403.9 mg/kg body weight (female rats). At both the control and the high dose levels, 2 additional groups of 10 male and 10 female rats each were treated for the purpose of histological examination of the urinary bladder after 4 and 21 weeks, and a number of animals were included in the control group and the

top dose group for an 8-week observation period (no further details). No animal died and there were no substance-related symptoms. The ophthalmoscopic examinations were without findings. Throughout the entire duration of the study no changes in body weight were observed. The males of the highest dose group showed a significant decrease in neutrophil counts. The females were also observed to have lower neutrophil counts, but the decrease was not significantly different from the controls. The male rats of the high dose group were found to have significantly increased mean corpuscular haemoglobin and those of the mid and high dosage groups had a significantly increased mean corpuscular haemoglobin concentration. As the latter parameters showed only very slight changes and there were no further findings, the authors considered these changes to be of doubtful toxicological significance. A statistically significant increase in cholesterol in the male rats of the high dose group was considered to be probably treatment-related. No information was given as to the reversibility of the changes. Necropsy and histological examination of approx. 40 organs yielded no treatment-related findings. The *no observed effect level* according to the authors was 1000 ppm, which is equivalent to 68.4 mg/kg body weight/day (males) and 84.3 mg/kg body weight/day (females; Monsanto, 1990). Under the conditions of this study, no findings were reported suggesting neurotoxic effects.

In the rat, oral administration (drinking water study) of a saturated aqueous solution of triisobutyl phosphate (approx. 430 mg/kg body weight/day in the females and approx. 440 mg/kg body weight/day in the males, 51 treatment days) led to reduced body weight gain as compared with controls. At necropsy, there were no appreciable macroscopic changes (no further details; BASF, 1953).

7.6 Genotoxicity

7.6.1 In vitro

Triisobutyl phosphate (purity: approx. 98%) was tested in the Salmonella/microsome assay using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation (S9 mix from Aroclor 1254-induced rat liver). The investigations were carried out as standard-plate incorporation and preincubation tests at concentration levels

of 20 to 5000 µg/plate (standard-plate incorporation test) and 15 to 5000 µg/plate (preincubation test). In the standard-plate incorporation test concentration levels ≥ 2500 µg/plate and levels ≥ 100 µg/plate proved to be bacteriotoxic to TA 100 and TA 1535, respectively, and in the preincubation test concentration levels ≥ 500 µg/plate were toxic to all strains. Under these experimental conditions, triisobutyl phosphate showed no mutagenic effects, either with or without metabolic activation (BASF, 1990).

A further Salmonella/microsome assay with triisobutyl phosphate (purity: approx. 98%) was carried out in the *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 with and without metabolic activation (S9 mix from Aroclor 1254-induced rat liver). These investigations were also performed as a standard-plate incorporation test and preincubation test at concentration levels of 10, 33.3, 100, 333.3, 1000 and 5000 µg/plate. Bacteriotoxicity was observed in virtually all strains at the higher concentration levels with and without metabolic activation. Again, triisobutyl phosphate did not exhibit any mutagenic effects in these tests, with or without metabolic activation (CCR, 1992).

Triisobutyl phosphate (99.78%) was tested for mutagenic effects in the standard-plate incorporation test using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537. The tests were carried out with and without metabolic activation (S9 mix from Aroclor 1254-induced rat liver). Anhydrous acetone served as the solvent. Concentrations of 0 (control), 15, 50, 150, 500 and 1500 µg/plate were used. 1500 µg/plate proved to be bacteriotoxic to all strains, both with and without metabolic activation. Triisobutyl phosphate did not show any mutagenic effects in these experiments either (Monsanto, 1992 a).

7.6.2 In vivo

In vivo, triisobutyl phosphate (99.8%) was studied in the micronucleus test in groups of 15 male and 15 female CD1 mice each. They were given 0 (negative control group), 300, 600 and 1200 mg/kg body weight once by intraperitoneal injection of a solution in corn oil (1200 mg/kg body weight corresponding to 69% of the LD_{50} according to preliminary experiments). The positive controls were treated with cyclophosphamide (60 mg/kg body weight). After 24, 48 and 72 hours (positive controls after 24 hours only)

the bone marrow was extracted from the femora of 5 animals per sex and dose and processed into slides. The ratios of polychromatic and normochromatic erythrocytes as well as the numbers of micronuclei in the polychromatic erythrocytes were determined by evaluating 1000 erythrocytes per animal. At no time point did triisobutyl phosphate cause a significant increase in the number of micronucleated polychromatic erythrocytes. No significant change was detected with respect to the polychromatic/normochromatic erythrocyte ratio. Thus triisobutyl phosphate did not show any clastogenic effects in this study (Monsanto, 1992 b).

7.7 Carcinogenicity

No information available.

7.8 Reproductive toxicity

In a preliminary study to an embryotoxicity/teratogenicity study triisobutyl phosphate (purity: approx. 98%) was administered by oral gavage in daily doses of 0 (controls), 150, 450 and 1200 mg/kg body weight to pregnant rats (Crl: CD (SD) BR VAF/Plus strain) from day 6 to day 15 of pregnancy. Caesarean section was performed on day 20 of pregnancy. On administration of 1200 mg/kg body weight per day the dams showed salivation, increased consumption of drinking water and slightly retarded body weight gain up to day 10 of pregnancy. In addition, there was a marginal increase in the incidence of early embryonic deaths, a slight reduction in litter size and litter weight as well as slightly reduced mean foetal weight. At doses of 450 and 150 mg/kg body weight salivation as well as slightly retarded body weight gain were also observed in the dams up to day 8 of pregnancy, and at 450 mg/kg body weight water consumption was increased in addition. The litter parameters showed no apparent effects at these dosage levels. Macroscopic examination of foetuses did not reveal any structural anomalies (HRC, 1991).

In the subsequent main study conducted to assess the reproductive toxicity of triisobutyl phosphate (purity: approx. 98%) in accordance with OECD guideline No. 414, 25 female Charles River rats (178 to 223 g) each received by oral gavage 0 (controls), 100, 300 and 1000 mg/kg body weight as an aqueous suspension in 0.5% sodium carboxymethylcellulose from

day 6 to day 15 after mating. On day 20 of gestation, Caesarean section was performed on the dams and approximately half of the foetuses in each litter were examined for visceral and skeletal malformations. The 1000 mg/kg body weight dose caused marginal maternal toxicity with initial retardation of body weight gain, increased water consumption and post-dosage salivation. The latter symptom was also observed in the animals of the 300 and 100 mg/kg body weight dose groups. In the rats of the high dose group a marginal increase in the incidence of early embryonic deaths was observed, but the number of litters affected was low and in the overall comparison with the controls the finding lacked statistical significance. Triisobutyl phosphate had no effect on embryonic and foetal development and caused no significant visceral and skeletal anomalies or skeletal variants. A slight increase in bilateral forelimb flexures was confined to only two litters of the high dose group and was not considered not to be treatment-related (HRC, 1991).

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

In a 13-week feeding study in rats, there were no indications of neurotoxicity up to the highest daily dose of approx. 400 mg of triisobutyl phosphate per kilogram body weight (cf. Section 7.5; Monsanto, 1990).

The neurotoxicity of triisobutyl phosphate (purity: 99.7%) was studied in accordance with OECD guideline No. 418 in groups of 5 adult hens (approx. 12 to 14 months of age). One group per dose received by gavage a single oral dose of 0 (controls), 500 or 1000 mg/kg body weight (solution in olive oil), followed by an observation period of 42 days. Additional groups received single doses of 2000 and 5000 mg/kg body weight and were re-exposed to the same respective doses 21 days later. The second administration was then followed by an observation period of 21 days. As a positive control, 5 hens received by gavage a single oral dose of 500 mg of tri-o-cresyl phosphate (in olive oil)/kg body weight and were also placed under observation for 42 days after treatment. Whereas treatment-related deaths (5 out of 15) as well as severe and extremely severe signs of neurotoxicity

(7 out of 15) and body weight loss occurred amongst the positive controls, no treatment-related impairments were observed in the hens receiving triisobutyl phosphate even after two doses of 5000 mg/kg body weight. Terminal macroscopic examination did not yield any findings (BASF, 1987). Thus the study did not produce any evidence of neurotoxicity from triisobutyl phosphate.

The neurotoxic potential of triisobutyl phosphate was additionally investigated by measuring the specific enzymes in hens (White Leghorn). A group of 10 adult animals (approx. 17 months old and weighing approx. 1.6 kg) were given a single oral dose of 5000 mg/kg body weight of the undiluted substance. Two groups of 5 hens each received no treatment or a single 750 mg dose of tri-o-cresyl phosphate/kg body weight as a positive control, respectively. Twenty-four hours after treatment, plasma butyrylcholinesterase, brain acetylcholinesterase and brain neurotoxic esterase activities were determined. The latter enzyme has been proposed as a marker for organophosphate-induced delayed neurotoxicity. Triisobutyl phosphate did not inhibit acetylcholinesterase and neurotoxic esterase activities in the brain but did result in inhibition of plasma butyrylcholinesterase. The activities of acetylcholinesterase and neurotoxic esterase were 93 and 100% of the controls, respectively, whereas plasma butyrylcholinesterase activity was reduced to 2%. Following administration of tri-o-cresyl phosphate, activities of 79%, 14% and 11% were found for acetylcholinesterase, neurotoxic esterase and plasma butyrylcholinesterase, respectively. In the authors' opinion, these results suggest that triisobutyl phosphate does not produce delayed neurotoxicity in hens (no details of the clinical signs of neurotoxicity; Laboratory of Neurotoxicology, 1990).

7.11 Other effects

No information available.

8 Experience in humans

No cases of skin sensitisation have been observed so far in connection with the production and handling of triisobutyl phosphate in two chemical plants. As regards acute exposure of the skin and mucous membranes, one case of eye irritation and two cases of skin irritation were recorded

following acute local exposure to the substance during work-related handling in the period from 1989 until June 1997 (BASF, 1998).

9 Classifications and threshold limit values

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft has designated triisobutyl phosphate with "Sh" for skin-sensitising substances in the List of MAK and BAT Values (DFG, 2000).

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