COVER PAGE

US EPA HPV Challenge Program

Test Plan Submission

S,S',S'-tributyl phosphorotrithioite

CAS No. 150-50-5

January 2008

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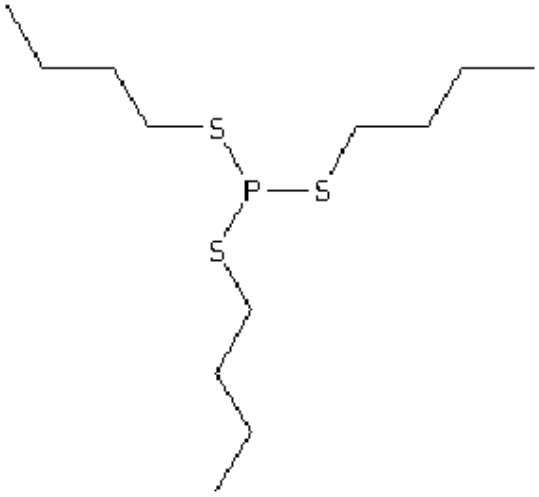
S,S',S'-tributyl phosphorotrithioite

CAS No. 150-50-5

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 150-50-5
IUPAC Name: S,S',S'-tributyl phosphorotrithioite
Molecular Formula: $C_{12}H_{27}PS_3$
Structural Formula:



Molecular Weight: 314.51
Synonyms: Butyl phosphorotrithioite ((bus)3p)

Chemagro B-1776

Delef defoliant

Easy off-D

Folex

Folex 6ec

Folex/Def

Merphos

Phosphorotrithious acid, S,S,S-tributyl ester

Phosphorotrithious acid, tributyl ester

S,S,S-Tributyl phosphorotrithioite

S,S,S-Tributyl trithiophosphite

1.2 Purity/Impurities/Additives

The typical purity for the marketed substance is >95%. The product marketed as Folex is 72% merphos and 28% inert ingredients (Bayer CropScience, 2007). Both have been tested and are considered to represent the sponsored substance.

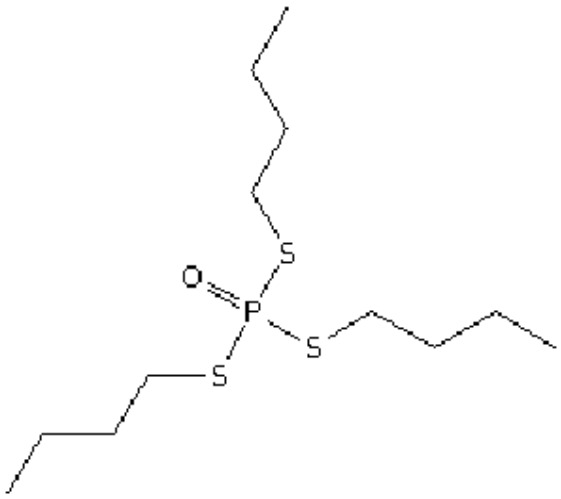
1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Merphos	Reference	Tribufos	Reference
Physical state	Liquid		Liquid	
Melting point	83°C (estimated)	EpiWin, v.3.20	--	--
Boiling point	115 - 134 °C at 10.66 hPa	Worthing and Walker, 1987	270-276°C	Bayer, 2001
Relative density	1.02 g/cm³ at 20 °C	CRC , 2002	1.06 g/cm³	Bayer, 2001
Vapour pressure	0.00001773187 hPa at 25 °C (estimated)	EpiWin, v.3.20	.00000079 hPa at 25 °C	Battelle, 1991
Water solubility	Sparingly soluble .00352 mg/L at 25 °C (estimated)	Worthing and Walker, 1987 EpiWin, v.3.20	2.3 mg/L at 20 °C	Mobay, 1980
Partition coefficient n-octanol/water (log value)	ca. 7.67	Meylan and Howard, 1995	6.02 at 25 °C	Battelle, 2001
Henry's law constant	2.27E-005 atm-m3/mole (estimated)	EpiWin, v.3.20	--	--

2 ANALOGUE JUSTIFICATION

Tributyl trithiophosphite (merphos; CAS# 150-50-5) is a chemical intermediate used to make the pesticide S,S,S-tributyl phosphorotrithioate (tribufos; DEF; CAS# 78-48-8):



These substances are structurally analogous; the only difference is the oxidation state. Merphos is readily oxidized to tribufos (US EPA, no date; Obrist and Thronton, 1978). Data from tribufos is used to fulfil several HPV endpoints for Merphos.

3 GENERAL INFORMATION ON EXPOSURE

3.1 Environmental Exposure and Fate

3.1.1 Sources of Environmental Exposure

3.1.2 Photodegradation

The hydroxyl radical reaction for merphos was calculated using EpiWin, v.3.20. The overall OH rate constant for merphos is 78.8E-12 cm^3/molecule-sec with an estimated half-life of 0.136 days.

3.1.3 Stability in Water

Merphos does not have any hydrolyzable groups; standard hydrolysis studies have not been conducted. EpiWin cannot estimate hydrolysis for this substance.

3.1.4 Transport between Environmental Compartments

Level III Fugacity modeling, using loading rates of 1000 kg/h each for air, soil, and water, shows the following percent distribution of merphos when it is released simultaneously to all three compartments: Air = 0.2%; Soil = 30.2%; Water = 5.8%; Sediment = 63.8% (EpiWin, v.3.20).

3.1.5 Biodegradation

Data were not available for the biodegradation of merphos; studies with the analogous substance, tribufos are used to fill this endpoint.

Tribufos: The aerobic degradation of tribufos was studied in five soils. A continuous flow-through system was used for incubation of treated soils in the dark at 20 ^{o}C (Bayer, 1991). The soils used were from Georgia, Mississippi, California, Texas, and Arkansas. The recommended maximum application rate for tribufos was used in the study. Significant quantities of $^{14}CO_2$ evolved by the end of the study, ranging from 37.6% of the applied radioactivity in Mississippi soils to 72.3% in Texas soil. Soils with more neutral pH (> 6.3) had greater CO_2 evolution. These data suggest that tribufos goes directly to CO2, without the accumulation of intermediate degradates. The metabolism of tribufos in sandy loam (pH > 6.5) under aerobic conditions in the dark at 25 ^{o}C was determined at 7 ppm at intervals of 0, 3, 7, 14, 29, 59, 91, 181, 272, and 360 days (Mobay, 1991a). The only major metabolite formed in the soil was (1-butane sulfonic acid). The 360-day sample still contained greater than 65% of the applied radioactivity as parent tribufos. A maximum of 7.6% of the applied radioactivity was evolved as $^{14}CO_2$ during the study. The calculated half-life was 745 days. The metabolism of [^{14}C] tribufos was evaluated in sandy loam soil under anaerobic conditions at a concentration of 3.2 ppm (Mobay, 1989). Incubation was under aerobic conditions for 30 days followed by a 60 day incubation period under anaerobic conditions at a temperature range of 18.0 - 26.5 ^{o}C. The parent compound degraded to $^{14}CO_2$ and unidentified product(s). At the end of the 90 day incubation period [^{14}C] tribufos and $^{14}CO_2$ accounted for 26.1% and 14.1% of the applied radiocarbon, respectively; 21.2% remained in the soil. The half-life of [^{14}C] tribufos under anaerobic conditions was 64.8 days. A 6-month long (181-day) anaerobic aquatic metabolism study with 1.0 ppm ^{14}C-tribufos (= dose of 12.6 ug/mL) was conducted in the dark with pond sediment which was flooded with pond water at 25 ^{o}C (Miles, 1994). Sediment samples and test water were analyzed for residues of [^{14}C] tribufos and its degradation products. Samples were collected at 0, 1, 3, 7, 14 days and 1, 2, 3, 4, and 6 months after dosing. Residues of the parent compound decreased from 86.2% at day 0 to 11.6% at 6 months. A metabolite identified as 1-butane sulfonic acid increased from 6.0% at day 0 to 19.1% at 3 months, then decreased to 14.7% at 6 months. The half-life of tribufos under anaerobic aquatic conditions was calculated to be 65.1.

3.1.6 Bioaccumulation

Merphos is not expected to bioaccumulate; the estimated BCF = 245.3 (EpiWin, v.3.20).

4 HUMAN HEALTH HAZARDS

4.1 Effects on Human Health

4.1.1 Acute Toxicity

Merphos and the analogous substance, tribufos, have been tested for acute toxicity by the oral and dermal routes. Tribufos has also been tested for acute inhalation toxicity. Table 2 presents a summary of these data.

Studies in Animals

Inhalation

Tribufos: Groups of six rats/sex were exposed for four hours under nose-only exposure conditions to concentrations ranging from 1590 to 6030 mg/m^3 (Mobay, 1990a). Exposure-related signs included: abnormal body position, adipsia, anorexia, apparent paralysis, ataxia, bloody urine, dyspnea, excitability, hypoactivity, increased vocalization, lacrimation, muscle fasciculations, nasal discharge, rales, red and yellow eye discharge, red nasal discharge, red oral discharge, red vaginal discharge, tremors, and urine staining. These signs were first observed shortly after exposure (day 0) and a complete recovery by day 6 was observed. A substantial reduction in weight gain, as

compared to controls, was observed from all exposed groups through day 14. Exposure-related gross lesions from animals that died during the 14-day observation period included: evidence of salivation and lacrimation, ventral staining, nasal stain, reddened lungs, mottled thymus and reddened nasal turbinates. The LC_{50} values were estimated to be = 4650 mg/m^3 (males) and 2460 mg/m^3 (females).

Dermal

Merphos was administered undiluted to the clipped, intact skin of five groups of rabbits (2 sex/dose level) at dose levels of 400, 500, 600, 900 and 1350 mg/kg bw under an occlusive cover for 24 hours (Industrial BIO-TEST, 1973). Red, well-defined erythema; moderate edema and chemical burns were observed at all dose levels. No adverse behavioral reactions were noted among the rabbits dosed at 400 mg/kg bw. Hypoactivity, muscular weakness, and salivation were exhibited by animals exposed at dose levels of 500, 600, 900 and 1350 mg/kg bw. Onset of the reactions was noted 24 hours after dosing. The reactions persisted until the animals died. Necropsy examination of the animals that died revealed pale brown discoloration of the lungs. No gross pathologic alterations were noted among the animals that survived to study termination. The LD_{50} was = 450 mg/kg bw. The acute dermal toxicity of merphos was determined in a two phase dermal toxicity study (Medical College of Virginia, 1980). The first phase involved four dose groups for the females (0, 750, 1640, 2020 and 2500 mg/kg bw) and four dose groups for the males (2000, 2500, 3200, and 4000 mg/kg bw). The second phase included five dose groups (0, 750, 1000, 1500, and 2500 mg/kg bw) for both males and females (12/sex/dose; 6 intact/dose and 6 abraded/dose). Control animals were also included. The test article was applied undiluted to the clipped, intact and abraded sites on the back/trunk of each rabbit under an occlusive cover for 24 hours. Typical signs of toxicity included salivation and erythema. At higher doses typical signs included hunched posture, prostration, excitability, malaise, sedation, muscle tremors, loss of or slow righting reflex, respiratory problems, skin irritation, analgesia, changes in relative body temperature, nasal exudate, watery salivation and diarrhea. Necropsy revealed a variety of abnormalities including excess saliva in the oral cavity, erythema (sometimes edema and eschar), perianal staining, vascularization of the brain and full bladders. Noted less often were several instances of fulminating pneumonia, icteric livers, enlarged gall bladders, and nasal exudate. Skin samples taken from animals in phase 2 showed some degree of histopathologic change in all male and female rabbits. The most prevalent histological changes were surface debris, changes from normal in the dermal collagen, and dermal inflammation. The acute dermal LD_{50} (intact skin) was = 950 mg/kg bw (sexes combined).

Tribufos: The acute dermal toxicity of tribufos was tested in groups (5/sex/dose) of New Zealand White rabbits (Mobay, 1991c). The undiluted test substance was applied at doses of 500 to 2000 mg/kg bw to and covered with an occlusive patch. Treatment-related signs of toxicity (tremors, muscle fasciculations, decreased motor activity, erythema and/or dry flaking skin at the dose site, increased reactivity, ataxia, diarrhea, perianal stain and various secretions and stains about the head) were apparent on day 0 and resolved in surviving animals by day 13. Body weight gain decreased from days 0-7 in a dose-related manner in surviving males and females, with recovery evident by day 14. Reddened thymus, erythema of the treated skin, salivation/oral stain, dark perianal stain and nasal stain in both males and females and pale zones in small intestines and red fluid in abdominal cavity in females only, were considered treatment-related gross lesions in animals found dead. The only treatment-related gross lesions observed in animals that survived to day 14 were crusty zones on the treated skin of two males and one female at the 1000 mg/kg bw dose level. The dermal LD_{50} was = 1093 mg/kg bw (sexes combined).

Oral

Groups of male and female rats (number not specified) were exposed to merphos in corn oil by oral gavage (doses not specified; Gaines, 1969; Hayes, 1982). The LD_{50} (males) was = 1475 mg/kg bw;

for females the LD_{50} was = 910 mg/kg bw. No additional details were available. Merphos was administered undiluted by gavage to groups of rats (2/sex) at dose levels of 900, 1350, 2025 and 3038 mg/kg bw (Industrial BIO-TEST, 1973). Signs of toxicity included hypoactivity and ruffled fur at all dose levels; muscular weakness and tremors at the 3 highest doses; convulsions and vocalization at 3038 mg/kg bw. Necropsy examination of the animals that died revealed enteritis. No gross pathologic alterations were noted among the animals that survived until study termination. The acute oral LD_{50} was= 2480 mg/kg bw.

Tribufos: The acute oral toxicity of tribufos was tested in groups of five rats/sex (Mobay, 1991b) at doses of 294, 429 and 552 mg/kg bw (males) and 192, 235 and 294 mg/kg bw (females). The incidence of mortality increased with dose for both males and females, with all deaths occurring within days 1 through 5. A variety of signs of toxicity (decreased activity, lacrimation, lacrimal stain, clear nasal discharge and stain, red nasal stain, salivation, oral stain, diarrhea, perianal stain, urine stain, decreased reactivity, tremor and convulsions) were evident within the first two days following exposure with recovery in surviving animals by day 6. Body weight gain was decreased only in the one male that survived the high dose. Evidence of salivation, lacrimation and ventral staining, as well as fluid and dark discolored zones in the stomach and duodenum, nasal stain and pale liver were considered treatment-related gross lesions in animals found dead. There were no gross lesions observed in animals that survived to day 14. The acute oral LD_{50} for males was = 435 mg/kg bw and for females was = 234 mg/kg bw. The acute oral toxicity of merphos was determined in a two phase dermal toxicity study (Medical College of Virginia, 1980). The first phase involved five dose groups for both males and females (six rats/dose). The second phase was necessary to obtain more refined acute toxicity data to define the LD50 and involved three dose groups for the females and two dose groups for the males (six rats/dose). The test article was administered diluted in distilled water by gavage in the first phase at dose levels of 1000, 1500, 2000, 2500, and 3000 mg/kg to fasted rats, and in phase two at dose levels of 2500, 3000, and 3300 mg/kg to fasted females and dose levels of 1000 and 2000 mg/kg to fasted male rats. Typical signs of toxicity included hunched posture, prostration, ruffled fur, sedation, muscle relaxation and depressed respiration. The pain threshold was alternately depressed and increased, sometimes in the same animal at different times during the study. Also noted were relative hypothermia, lacrimation, occasional blood from the eyes or nose, watery excessive salivation, diarrhea, and urine present on the coat. Necropsy revealed a variety of abnormalities in the test animals, including blood tears in the eyes and /or blood or exudate from the nose; atrophy of several organs, including liver, thymus, and spleen; enlargement of the adrenals; hemorrhaging or hyperemia of the brain; thin yellow fluid present in the duodenum, jejunum and colon; and greenish-yellow fluid in the stomach. The acute oral LD_{50} was = 1870 mg/kg bw (sexes combined). Groups of male and female rats (number not specified) were exposed to merphos in corn oil by oral gavage (doses not specified; Gaines, 1969). The LD_{50} (males) was = 150 mg/kg bw; for females the LD_{50} was = 233 mg/kg bw.

Table 2 Summary of the acute toxicity

Species, Route	**Substance**	**Value**	**Reference**
Rat, 4 hr inhalation	Tribufos	LC_{50} = 4650 mg/m^3 (males) and 2460 mg/m^3 (females)	Mobay, 1990
Rabbit, dermal	Merphos	LD_{50} = 450 mg/kg bw (sexes combined)	Industrial BIO-TEST, 1973
Rabbit, dermal	Merphos	LD_{50} = 950 mg/kg bw (sexes combined)	Medical College of Virginia, 1980
Rabbit, dermal	Tribufos	LD_{50} 1093 mg/kg bw (sexes	Mobay, 1991c

		combined)	
Rat, oral gavage	Merphos	LD_{50} = 1475 mg/kg bw (males); = 910 mg/kg bw (females)	Gaines, 1969; Hayes, 1982
Rat, oral gavage	Merphos	LD_{50} = 2480 mg/kg bw (sexes combined)	Industrial BIO-TEST, 1973
Rat, oral gavage	Tribufos	LD_{50} = 435 mg/kg bw (male); = 234 mg/kg bw (females)	Mobay, 1991b
Rat, oral gavage	Tribufos	LD_{50} = 1870 mg/kg bw (sexes combined)	Medical College of Virginia, 1980
Rat, oral gavage	Tribufos	LD_{50} = 150 mg/kg bw (males); = 233 mg/kg bw (females)	Gaines, 1969

Conclusion

The acute dermal toxicity of merphos and the analogue substance, tribufos, is similar, with LD_{50} values from standardized guideline studies approximately = 1000 mg/kg bw. Merphos appears to be less acutely toxic by the oral route than the analogue substance, tribufos. LD_{50} values for merphos range from 1475-2480 mg/kg bw, while values for tribufos range from 150 – 1870 mg/kg bw.

4.1.2 Irritation

Skin and eye irritation studies are available for merphos and the analogue substance, tribufos.

Skin Irritation

Studies in Animals

0.5 ml of undiluted merphos was applied to the intact and abraded skin of each of six rabbits (two application sites) under an occlusive cover for 24 hours (Industrial BIO-TEST, 1973). Merphos was considered moderately irritating.

Tribufos: 0.5 ml of undiluted analogue substance, tribufos, was held in contact with the skin of three rabbits/sex under an occlusive patch for four hours (Mobay, 1991d). Tribufos was considered moderately irritating.

Eye Irritation

Studies in Animals

0.1 ml of undiluted merphos was instilled into the conjunctival sac of the right eye of each of 6 rabbits (Industrial BIO-TEST, 1973). The left eye served as a control. Merphos was considered minimally irritating to the eye.

Tribufos: 0.1 ml of undiluted analogue substance, tribufos, was instilled into the conjunctival sac of the right eye of each of 6 rabbits (Miles, 1992a). The test substance did not produce corneal or iridal lesions. Conjunctival redness (grade 1), chemosis (grade 1) and discharge (grade 3) were observed in all six animals one hour after dosing. On day 7 there were no signs of irritation in any animal. Tribufos is a minimal eye irritant.

Conclusion

Merphos, and the analogue substance, tribufos are moderate skin irritants and minimal eye irritants.

4.1.3 Sensitisation

Skin sensitization data was not available for merphos. A standard skin sensitization study was available for the analogue substance, tribufos.

Studies in Animals

Skin

Tribufos: The potential for tribufos to produce a dermal sensitization response was tested in guinea pigs using the Buehler Topical Closed-Patch Technique (Miles, 1990). A total of 35 adult male Hartley albino guinea pigs were assigned to one of five groups: tribufos test group (15 animals), tribufos non-induced control group (five animals, for challenge), tribufos non-induced control group (five animals, for re-challenge), DNCB (positive control) test group (five animals) and DNCB non-induced control group (five animals). The tribufos was administered as a 10% solution for the three induction doses and the challenge dose and as a 1% solution for the re-challenge dose. Animals in the test groups received three topical induction applications of the appropriate formulation on study days 0, 7 and 14, followed by a 13-day "rest" period and a challenge application on day 27. Animals in the two non-induced control groups (tribufos challenge and DNCB) received only the challenge dose on day 27. A re-challenge dose of tribufos was applied on day 34 (test and non-induced control groups) in order to verify that the erythema present in the test group after the challenge dose was due to local irritation rather than to a sensitization reaction. The results of this study indicate that tribufos does not cause a dermal sensitization reaction in guinea pigs using the Buehler Topical Closed-Patch Technique.

Conclusion

The analogue substance, tribufos is not a skin sensitizer; merphos is expected to give the same result.

4.1.4 Repeated Dose Toxicity

Data are available for the repeated dose oral toxicity of merphos and tribufos.

Studies in Animals

Inhalation

No data available.

Dermal

No data available.

Oral

Merphos: Groups of three rats/sex were treated by oral gavage doses of merphos (undiluted) at 88, 131, 197, 296, 444, 666, and 1000 mg/kg bw; groups of three rats/sex were treated by oral gavage doses of merphos (in corn oil) at 88, 131, 197, 296, 444, 666, and 1000 mg/kg bw (Mobil, 1980). Toxic signs observed were the same for the neat and diluted substance and included decreased activity, ocular/nasal/oral discharge, perianal discharge, diarrhea, hunching, dehydration, emaciation, prostration, rough coat, decreased body temperature, aggressiveness, hyperactivity and diuresis. The 5-d oral LD50 (combined sexes) was = 452 mg/kg bw for the neat material and was = 375 mg/kg bw in corn oil.

In a series of dietary studies, groups of 25 rats/sex were fed merphos for periods up to 112 days; interim sacrifices and recovery groups were included in most studies (Hazelton, 1958a, b, c, d; Hazelton, 1960; Hazelton, 1961a, b). Table 3 provides a summary of the study protocols.

Table 3 Summary of repeated dose rat dietary study protocols (merphos)

Concentration in diet (ppm)	**Exposure time**	**Interim sacrifice /Recovery groups**	**NOAEL (ppm)**	**Reference**
0, 1 ppm; increased to 10 ppm after 4 wks; 2 ppm increased to 50 ppm after 4 wks	91 days	5/sex/group sacrificed at 21, 47, 63 and 91 d	LOAEL = 10 ppm	Hazelton, 1958a
0, 100, 500 ppm	7 and 13 weeks	Five/sex sacrificed at 24 and 42 d; 5/sex in 100 ppm group sacrificed after 49 d; 5/sex in 500 ppm group sacrificed after 62 d; 5/sex in control and 500 ppm groups sacrificed after 91 d; 5 week recovery group included	100 ppm	Hazelton, 1958b,c
0, 20 ppm	49 days	5/sex/group sacrificed at 21, 42 and 49 d; 25 d recovery group	LOAEL = 20 ppm	Hazelton, 1958d; Hazelton, 1961a
0, 2, 5, 750, 1000, 1250, 1500, and 2000 ppm	112 days	5/sex/group sacrificed on d 22, 43, 64 and 92; 5 males from the 0, 2 and 5 ppm groups were sacrificed d 76; 5 females from the 0, 2 and 5 ppm groups were sacrificed d 98; 5/sex from the 0 and 1000 ppm group formed a 12 d recovery group (d 101-d 112)	5 ppm	Hazelton, 1960; Hazelton, 1961b

In the 91 day study (Hazelton, 1958a), survival, physical appearance, behavior, appetite, body weights and food consumption were within normal limits throughout the study. The female rats fed 50 ppm had increased liver weights and liver/body weight ratios. Plasma and red blood cell cholinesterase activity was decreased at 50 ppm and 10 ppm; female rats fed 10 ppm exhibited this effect after 63 days. Brain cholinesterase activity was unaffected. The NOAEL was 10 ppm in the diet.

In the 7 and 13 wk studies (Hazelton, 1958b,c), apparent growth suppression was noted at 100 and 500 ppm during the first three weeks of feeding, prior to the sacrifice of any animals. There were no effects on survival, physical appearance, behavior and food consumption. Cholinesterase activity determinations were performed in the control and 500 ppm group. Complete inhibition of plasma and red blood cell cholinesterase activity in both male and female rats was noted and brain cholinesterase activity was also markedly depressed. Average liver/body weight ratios were increased in the 500 ppm group; average kidney/body weight ratios for the 500 ppm female rats were increased. There were no findings at gross necropsy or following microscopic exam. The NOAEL was 100 ppm in the diet.

In the 49 d study (Hazelton, 1958d; Hazelton, 1961a) there was no effect on survival, physical appearance, behaviour, food consumption or bodyweights. Body weight gains values for the male rats were lower than the control group during the recovery period only. Plasma and red blood cell cholinesterase activity was depressed during the first 49 days of the study. During the recovery period, plasma and red blood cell cholinesterase activity returned to normal limits. Brain cholinesterase activity was unaffected. Average liver weight and liver/body weight ratios of the female rats were increased after 21 days of feeding. The kidney/body weight ratios were increased for males and females after 21 days; this effect was observed in female rats only, after 42 days. There were no test article related histopathological findings.

In the 112 d study (Hazelton, 1960; Hazelton, 1961b), there were no deaths. There were no test article related clinical signs at 2, 5, and 750 ppm. The rats in the 1000 ppm group, which were fed the test compound at levels which were gradually increased to 2000 ppm, appeared thin and exhibited signs of marked respiratory involvement, rough coats, paleness of the extremities, urine stains on the abdomen, and excitability during the final four weeks. There were no effects on body weight gains for the males fed 2 and 5 ppm; slight growth suppression was noted in the females. There were no effects on food consumption for the 2 and 5 ppm animals. Body weight gains and food consumption were decreased from 0-9 weeks for 750 ppm animals, and from 0-13 weeks 1000 ppm animals. Body weight gains for the males on the recovery study were increased as compared to controls during the 11-day period. No significant plasma, red blood cell or brain cholinesterase depression was noted in the 2 or 5 ppm groups. Marked plasma, red blood cell, and brain cholinesterase activity depression was observed consistently through the course of the study in the 750 and 1000 ppm groups. Plasma, red blood cell, and brain cholinesterase activity recovered rapidly during the 11 d recovery period. Gross necropsies revealed thickened intestinal walls and catarrhal exudate in the lumen of the small intestine, and pale, chalky-colored adrenals in a number of rats from the 750 and 1000 ppm groups, including the recovery group. Adrenal glands from 5 animals/sex at 750 and 1000 ppm groups showed (mild to moderate: 750 ppm) and (slight to marked: 1000 ppm) vacuolation of the cord cells of the zona fasciculate in adrenal cortex. After a 12-day recovery period, slight to severe vacuolation of the cord cells of the zona fasciulata was observed. Organ weights and organ/body weight ratios were unaffected in the 2 and 5 ppm groups; significantly lower terminal body weights and liver and kidney weights and significantly higher liver and kidney/body weight ratios were observed in the 750 and 1000 ppm groups. A re-evaluation of the histopathology of the adrenal sections was conducted several months later, and it was concluded that this reaction is a perfectly normal, physiological response of the animal to an abnormal type of stimulation.

Tribufos: The chronic toxicity and oncogenic potential of technical grade tribufos was examined in the rat (Miles, 1992b). The test substance was administered continuously in the diet on the basis of the active ingredient (AI) at nominal concentrations of 0, 4, 40 or 320 ppm to a one-year interim sacrifice/chronic toxicity group and a two-year oncogenicity group, consisting of at least 10 and 50 animals/dose/sex, respectively. In addition to ophthalmological and electroretinographic exams, hematologic, clinical chemistry and urinalysis parameters were measured at periodic intervals as were body weight, body temperature, clinical signs and food consumption. A complete necropsy was performed on all animals of the chronic/oncogenic groups with all gross lesions and tissues collected being examined histologically. In addition, histopathological examinations were conducted on specific neurological tissue obtained from separate one- and two-year sacrifice groups, which were included in the study. Average monthly body weight gain, based on the entire two years of exposure, was determined to be ~95 and 100% of controls for low-dose males and females, respectively, ~95% of controls for mid-dose males and females, and ~73% of controls for high-dose males and females. Food consumption remained unaffected in both males and females up to and including a dose of 40 ppm. Clinical signs attributed to administration of tribufos were principally noted in the high-dose group of both sexes. These included an increased incidence

relative to control animals of paleness, eye opacity zones, rough coat, rashes and raised zones, urine stain and diarrhea. Survival was not affected. Body temperature was not affected. Ophthalmologic and electroretinographic changes were observed only in the 320 ppm group. Clinical pathology changes were noted in 40 and 320 ppm animals. Gross pathology changes were noted in the small intestine (40 and 320 ppm), adrenal gland (320 ppm) and eye (320 ppm males). Decreased organ weights included spleen and kidney (40 and 320 ppm males), increase in absolute testicular weight (320 ppm males), increase in absolute and relative adrenal weight (320 ppm males and females). Micropathological changes included diffuse, bilateral retinal atrophy, increases in optic nerve atrophy and cataract (320 ppm males and females), hyperplasia and vacuolation animals of the mucosa of the proximal small intestine (40 and 320 ppm) and increased vacuolation of the cortex of the adrenal (320 ppm). A systemic no-observed-effect level (NOEL) of 4 ppm was established.

Conclusion

Following repeated dose exposure to merphos in the diet, the NOAEL was = 5 ppm. Depression of plasma, red blood cell, and brain cholinesterase activity are primary effects of toxicity. Liver, kidney and adrenal gland appear to be target organs of toxicity. Following repeated dose exposure to tribufos in the diet, the NOEL was = 4 ppm. Effects on clinical pathology were similar to those observed for merphos. The eye, adrenal gland and small intestine appear to be target organs of toxicity.

4.1.5 Mutagenicity

In vitro and i*n vivo* mutagenicity data are not available for merphos; data are provided for the structural analogue, tribufos.

In vivo Studies

Tribufos: Mice (5/sex/dose) were dosed by oral gavage with tribufos in corn oil at dose levels of 0, 60, 125, and 250 mg/kg bw (SRI, 1991b). The volume of dose solution administered was 10 ml/kg bw. A solvent control (corn oil) and positive control (benzene) were also included, each with 5/sex. Mice were sacrificed approximately 24, 48, or 72 hours after dose administration and right femur from each mouse was removed and slides prepared for the evaluation of micronucleus. Tribufos did not induce an increase in micronuclei in bone marrow erythrocytes.

In an UDS assay, groups of 3 mice/sex were exposed to 75, 150, and 300 mg/kg bw tribufos (SRI, 1991c). Tribufos did not induce UDS following oral administration to male or female mice. These results suggest that tribufos is not a genotoxic agent in the livers of male or female

In vitro Studies

Tribufos: Tribufos was tested in the *Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenicity Assay using the plate incorporation method. The test article was tested at five dose levels (667, 1000, 3333, 6667 and 10,000 ug/plate and 10, 50, 100, 1000, and 5000 ug/plate, respectively) along with appropriate vehicle and positive controls on tester strains TA98, TA100, TA1535, TA1537 and TA1538 in the presence and absence of S-9 mix (Microbiological Associates, 1989a; SRI, 1991a). Tribufos was negative for mutagenicity in these tests.

Tribufos was tested in the chromosome aberration assay using Chinese hamster ovary cells (Microbiological Associates, 1989b). Dose levels for the chromosome aberration assay were selected following a preliminary toxicity test based upon reduction in mitotic index after treatment relative to the solvent control. CHO cells were exposed to solvent alone and to nine concentrations of test article ranging from 0.004ul/ml to 0.1 ul/ml in the absence and presence of an S-9 reaction

mixture. No statistically significant increase in chromosome aberrations was observed in the non-activated or S-9 activated test systems.

Tribufos was tested for its ability to induce unscheduled DNA synthesis in rat primary hepatocytes as measured by autoradiographic methods (Microbiological Associates, 1989c). The results of the UDS assay indicate that under the test conditions, the test article did not cause a significant increase in the mean number of net nuclear grain counts (i.e., an increase of at least 5 counts over the solvent control), at any dose level. Therefore, the test article is considered negative in this study.

Conclusion

The structural analogue, tribufos, was not genotoxic in *in vitro* or *in vivo* assays; merphos is also expected to produce the same non-genotoxic response.

4.1.6 Toxicity for Reproduction

No data are available for merphos; effects on fertility and developmental toxicity data are available for the analogue substance, tribufos.

Effects on Fertility

Tribufos: Tribufos was administered via the diet to rats for two generations to test for potential reproductive effects at nominal dose levels of 0, 4, 32 and 260 ppm (actual doses were 4.0, 30.2 and 260 ppm; Miles, 1991). The F0 and F1 parents were comprised of 30 rats/sex/group. The F0 and Fl parents received tribufos in the diet throughout the entire study, beginning at eight weeks of age for the F0 parents and at weaning for the Fl parents. Prior to breeding, the animals received treated feed for a ten week period. F0 parents were mated to produce Fla litters and F1 parents (randomly selected Fla pups) were mated to produce F2a litters. During the study, adult animals were evaluated for effects on body weight, food consumption, clinical signs, cholinesterase activity, estrous cycling, mating, fertility, gestation length, and litter size. The offspring were evaluated for compound-related effects on sex ratio, pup viability, body weight gain, clinical signs, and cholinesterase activity. Gross necropsy evaluations were performed on all adults and pups. Histopathologic evaluation of reproductive organs, the pituitary, and gross lesions was performed on all adults. There was a marked increase in the cannibalization and related signs of pups (due to a compound effect on the dams) was observed in the high-dose group. There were no other treatment-related clinical signs. Treatment-related decreased body weights were observed in the Fl high-dose group animals during the pre-mating period. The lower Fl body weights were due to a decrease in pup body weight gain during the Fla lactation period (Fla pups = Fl adults). During the Fla and F2a lactation phases, treatment-related decreased body weights were observed in the F0 and Fl high-dose group females. A significantly lower weight change was also observed in the F0 high-dose group. The food consumption during the Fla and F2a lactation phases were also reduced in the high-dose group. The only effect on adult reproductive parameters was a slight, but treatment-related, increase in the gestation length for the F0 and Fl high-dose groups. In the high-dose group, there was a treatment-related increase in the number of FO and Fl dams with stillborn pups. There was a reduction in pup viability in the high-dose group during the Fla and F2a lactation periods. In the high-dose group, a treatment-related decrease in pup weight gain was observed during the Fla and F2a lactation periods. The cholinesterase no-observable-effect level (NOEL) in adult male and female rats was 4 ppm. A biologically significant cholinesterase depression occurred in the plasma and red blood cell cholinesterase of high-dose group 21-day pups; no biologically significant changes occurred in the four-day pup cholinesterase levels. No treatment-related pathologic effects were observed, other than a treatment-related increase in pup cannibalization and related lesions in the high-dose group for the Fla and F2a pups. The reproductive NOEL for tribufos was = 32 ppm. This is based on an increase in gestation length, the cannibalization of pups, a reduction in pup

viability and a decrease in pup body weight gain during the lactation period in the high-dose group. The overall NOEL for tribufos in adult males and females based on cholinesterase data was 4 ppm.

Developmental Toxicity

Tribufos: In an OECD TG 414 "Teratogenicity" study, the analogue substance, tribufos, was administered orally to 3 groups of 33 inseminated female rats (dams) at doses of 1, 7, or 28 mg/kg bw (Mobay, 1986). A fourth group of 33 dams received the vehicle alone and served as the control. Each group of 33 dams was subdivided into 2 termination phases: Phase I was comprised of 5 dams terminated on Day 16 of gestation and Phase II was comprised of 28 dams terminated on Day 20 of gestation. All dams were dosed, following nidation, on Days 6 through 15 of gestation. There was a toxicologically relevant inhibition of maternal plasma ChE activity on Day 16 that was statistically significant for the mid- and high dose levels; only a borderline inhibition occurred in plasma ChE activity for the low dose level. There was also a toxicologically relevant and statistically significant inhibition of maternal erythrocyte ChE activity (mid- and high dose) and maternal brain ChE activity (high dose) on Day 16. By Day 20, ChE activity for high dose plasma, erythrocyte, and brain and mid-dose erythrocyte, while indicating that recovery was occurring when compared to Day 16, continued to be inhibited at toxicologically relevant and, except for high dose plasma, statistically significant levels. Inhibition of plasma ChE activity for the low dose was neither statistically significant nor toxicologically relevant on Day 20. Fetal brain ChE activity, measured on Day 20, remained unchanged for all groups when compared with the control. Also observed was salivation in 2 animals and a statistically significant reduction in overall maternal body weight gain during gestation for the high dose group. There was no evidence of test article-related embryotoxicity, fetotoxicity, or teratogenicity at any dose level tested; the NOAEL for embryotoxicity, fetotoxicity, or teratogenicity was = 28 mg/kg bw, the highest dose tested.

Tribufos was administered orally to 3 groups of 17 American Dutch rabbits in doses of 1, 3, or 9 mg/kg bw (Miles, 1987). A fourth group received the aqueous CMC vehicle alone serving as the control. All does received the test or control article from Day 7 to Day 19, during the stages of embryogenesis and early fetation. Tribufos promoted a statistically significant reduction in body weight gain and a slight but not statistically significant reduction in food consumption during the treatment period for the high dose group. The test article also produced a statistically significant and toxicologically meaningful inhibition of plasma and erythrocyte (RBC) cholinesterase activity on Day 20 of gestation for all treatment groups; by Day 28 only RBC enzyme was significantly reduced for all groups. The reduction was less, however, indicating recovery for this parameter. By Day 28, plasma enzyme was no longer meaningfully reduced and there was no inhibition of brain cholinesterase for any treatment group. The test article had no adverse effects on any maternal reproductive parameters; all values were comparable between the three treatment groups and the control group. The test article did not augment resorption, promote late gestational death, or reduce fetal weight. In addition the test article did not elicit any evidence of teratogenicity. External, visceral, and skeletal evaluation of the fetuses disclosed no alterations in development which could be attributable to test article administration; the NOAEL for teratogenicity was = 9 mg/kg bw, the highest dose tested.

Conclusion

The reproductive NOEL for the analogue substance, tribufos, was = 32 ppm. This is based on an increase in gestation length, the cannibalization of pups, a reduction in pup viability and a decrease in pup body weight gain during the lactation period in the high-dose group. In an OECD TG 414 conducted with rats, there was no evidence of test article-related embryotoxicity, fetotoxicity, or teratogenicity at any dose level tested; the NOAEL was = 28 mg/kg bw, the highest dose tested. External, visceral, and skeletal evaluation of rabbit fetuses disclosed no alterations in development

which could be attributable to tribufos administration; the NOAEL for teratogenicity was = 9 mg/kg bw, the highest dose tested. Similar findings are expected for merphos.

5 HAZARDS TO THE ENVIRONMENT

5.1 Aquatic Effects

Acute toxicity to fish data is available for merphos and the analogue substance, tribufos. Toxicity to aquatic invertebrates and aquatic plants were not available for merphos; data are presented for tribufos.

Acute Toxicity Test Results

Fish

Groups of ten fish (*Lepomis macrochirus*) were exposed to merphos at concentrations from 0.25 to 25.1 mg/L for 96 hours under static conditions (Hazleton, 1965). The LC_{50} for merphos was = 18.2 mg/L. Groups of fish (*Lepomis macrochirus;* number not specified) were exposed to merphos at concentrations from 3.1 to 10 mg/L for 96 hours under static conditions (Mayer and Ellersieck, 1986). The LC_{50} for merphos to was = 5.6 mg/L. Groups of fish (*Oncorhynchus mykiss;* number not specified) were exposed to merphos at concentrations from 8.4 to 15.8 mg/L for 96 hours under static conditions (Mayer and Ellersieck, 1986). The LC_{50} for merphos to was = 11.5 mg/L. Groups of ten fish (*Oncorhynchus mykiss*) were exposed to merphos at concentrations from 0.25 to 25.1 mg/L for 96 hours under static conditions (Hazleton, 1965). The LC_{50} for merphos was = 5.8 mg/L. Groups of fish (*Lepomis macrochirus;* number not specified) were exposed to merphos at concentrations from 7 to 14 mg/L for 96 hours under static conditions (Johnson and Finley, 1980; Mayer and Ellersieck, 1986). The LC_{50} for merphos was = 7.2 mg/L. Groups of fish (*Lepomis macrochirus;* number not specified) were exposed to merphos at concentrations from 11 to 19 mg/L for 96 hours under static conditions (Mayer and Ellersieck, 1986). The LC_{50} for merphos was = 14.5 mg/L. Groups of fish (*Lepomis macrochirus;* number not specified) were exposed to merphos at concentrations from 20 to 53 mg/L for 96 hours under static conditions (Johnson and Finley, 1980; Mayer and Ellersieck, 1986). The LC_{50} for merphos was = 23.8 mg/L.

Tribufos: Groups of ten marine fish (*Cyprinodon variegatus*) were exposed to tribufos at concentrations of 0, 0.14, 0.23, 0.39, 0.65, 1.08, 1.8, and 3.0 mg/L for 96 hours under flow through conditions (Mobay, 1991e). The LC_{50} for tribufos was = 0.77 mg/L. Groups of ten fish (*Pimephales promelas*) were exposed to tribufos at concentrations of 0, 0.08, 0.16, 0.31, 0.63, and 1.25 mg/L for 96 hours under flow through conditions (Bayer, 2002a). The LC_{50} for tribufos was = 0.92 mg/L. The acute toxicity of tribufos to rainbow trout (*Salmo gairdneri*, syn. *Oncorhynchus mykiss*) was determined in a 96-hour flow-through-test according to OECD TG 203 (Bayer, 1990c). Groups of ten fish were exposed to concentrations of 0, 0.33, 0.58, 1.02, 1.82, 3.24, and 5.77 mg/L. An additional group of ten fish was maintained as solvent control. The 96 hr LC_{50} was = 1.52 mg/L. Groups of fish (*Lepomis macrochirus;* number not specified) were exposed to tribufos at concentrations from 0.5 - 0.78 mg/L for 96 hours under flow though conditions (US EPA, 1995). The LC_{50} for tribufos to was = 0.63 mg/L. Groups of fish (*Lepomis macrochirus;* number not specified) were exposed to tribufos at concentrations from 0.5 - 0.78 mg/L for 96 hours under static conditions (US EPA, 1995). Temperature and hardness were varied across several experiments. The LC_{50} range for tribufos with varying hardness and temperature was = 0.245 – 0.78 mg/L. Groups of ten fish (*Lepomis macrochirus*) were exposed to tribufos for 96 hours under static conditions at concentrations of 0, 0.16, 0.29, 0.51, 0.91, 1.63, and 2.89 mg/L (corresponding to 0, 0.17, 0.30, 0.53, 0.95, 1.69 and 3.00 mg/L; Bayer, 1990a). The LC_{50} for tribufos to was = 0.72 mg/L.

Table 4. Summary of the toxicity of merphos and tribufos to fish

Organism	Substance	96 hr LC_{50} (mg/L)	Reference
Lepomis macrochirus	merphos	18.2	Hazleton, 1965
Lepomis macrochirus	merphos	5.6	Mayer and Ellersieck, 1986
Oncorhynchus mykiss	merphos	11.5	Mayer and Ellersieck, 1986
Oncorhynchus mykiss	merphos	5.8	Hazleton, 1965
Lepomis macrochirus	merphos	7.2	Johnson and Finley, 1980; Mayer and Ellersieck, 1986
Lepomis macrochirus	merphos	14.5	Mayer and Ellersieck, 1986
Lepomis macrochirus	merphos	23.8	Johnson and Finley, 1980; Mayer and Ellersieck, 1986
Cyprinodon variegatus	tribufos	0.77	Mobay, 1991e
Pimephales promelas	tribufos	0.92	Bayer, 2002a
Oncorhynchus mykiss	tribufos	1.52	Bayer, 1990C
Lepomis macrochirus	tribufos	0.63	US EPA, 1995
Lepomis macrochirus	tribufos	0.245 – 0.78	US EPA, 1995
Lepomis macrochirus	tribufos	0.72	Bayer, 1990a

Aquatic Invertebrates

Tribufos: In an OECD TG 202 study, *Daphnia magna* were exposed to tribufos at concentrations of 0.01, 0.032, 0.056, 0.10, 0.32, 0.56 and 1.00 mg/L, a test medium control, and a solvent control (0.1 ml acetone/L) under static conditions for 48 hours (Bayer, 1990b). The EC_{50} for *Daphnia magna* was = 0.12 mg/L after 48 hours. *Daphnia magna* were exposed to tribufos at concentrations of 0.05 - 0.73 mg/L under static conditions for 48 hours (US EPA, 1995). The EC_{50} for *Daphnia magna* was = 0.061 mg/L after 48 hours.

Aquatic plants

Tribufos: A static renewal 14-day duckweed growth test was conducted to determine the growth effects of the analogue substance, tribufos (Bayer, 2002b). Duckweed was exposed for 14 days under static renewal conditions; test solutions were renewed on Day 7. Nominal concentrations were 0, 20.5, 51.2, 128, 320, 800, 2000 ug/L. Growth was determined by count of fronds on days 0, 2, 5, 7, 9, 12 and 14. The 14-day EC_{50} - standing crop and growth rate were = 866 and >1555 ug/L, respectively. The 14-day EC_{50} - cumulative biomass and frond dry weight were = 1176 and 1249 ug/L, respectively. The EC_{50} in the 14-day exposure of Duckweed to tribufos was = 866 ug/L. *Selenastrum capricornutum* was exposed over a 7-day period to six concentrations (nominal: 0.0312, 0.0625, 0.125, 0.25, 0.5 and 1.0 mg/L) of tribufos (Mobay, 1990). Biomass was determined by cell counts on days 2, 3, 4, and 7. The 7-day EC_{50} was = 0.179 mg/L.

Conclusion

The acute aquatic toxicity to several species of fish of merphos (96 hr LC_{50} = 5.6 – 23.8 mg/L) appears to be less than that of tribufos (96 hr LC_{50} = 0.245-0.92 mg/L). This difference may be due to several factors. All of the mephos data were generated using static systems without analytical verification while most of the tribufos data was based on measured concentrations in flow-through systems. Further, acetone was used in several of the tribufos studies to better sobulize the test material while the merphos studies do not indicate the use of any vehicle. Considering the low

water solubility of these compounds, the tribufos values are likely to be a better indicator of true toxicity based on the certainty of the actual exposure concentrations. In the absence of data for aquatic invertebrates and aquatic plants, the toxicity of merphos is conservatively accepted to be the same as tribufos (48 hr EC_{50} for *Daphnia* = 0.061-0.12 mg/L; EC_{50} in aquatic plants = 0.866 mg/L (14-d); 0.179 mg/L (7-d)).

6 RECOMMENDATIONS FOR THE MERPHOS TEST PLAN

All physical/chemical, environmental fate and toxicity and human health endpoints have been met for merphos, either directly or through read across to the analogous substance, tribufos.

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