United States Environmental Protection Agency

Volume 2
Chemical Hazard Reviews

Environmentally Preferable Options for Furniture Fire Safety

Low-Density Furniture Foam

DRAFT

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Introduction

This volume contains detailed hazard reviews of available information for each of the chemicals in the 14 flame-retardant formulations evaluated through the Furniture Flame Retardancy Partnership.

These detailed hazard reviews are the basis for the summary assessments in section 4 of volume I. The summary assessments were in turn used as the basis for summary table 4.1, which provides top-level information on all of the alternatives.

The goal of the Furniture Flame Retardancy Partnership is to enable informed decision making during the process of selecting alternatives to pentaBDE. Production of pentaBDE will cease at the end of 2004. The industry is now considering alternative flame retardants to meet performance requirements. Given the large quantities of flame retardants used in foam and furniture manufacture, their potential for adverse effects to health and the environment should be addressed.

EPA developed this flame-retardant alternatives evaluation through stakeholder participation. The Partnership plans to follow a process similar to that used by the Voluntary Children's Chemical Evaluation Program (VCCEP) (http://www.epa.gov/chemrtk/vccep/index.htm). The objective of the VCCEP is to ensure that there are adequate information available to assess the potential risks to children.

The information in this volume represents the first phase of data collection. The data were collected in a manner consistent with the HPV Chemical Challenge Program guidance on searching for existing chemical information and data (http://www.epa.gov/chemrtk/srchguid.htm). This information was collected and data were evaluated for adequacy following HPV data adequacy guidelines (http://www.epa.gov/chemrtk/datadfin.htm). The evaluation protocol differed from the HPV program in that EPA reviewed the experimental studies and developed the summaries. In the HPV Program, EPA and the public participate in the review of the robust summaries developed by HPV Challenge Program sponsors. EPA plans to update the presentation of study summaries in future drafts based on the HPV robust study guidelines (http://www.epa.gov/chemrtk/robsumgd.htm). The purpose of data collection in this Partnership was to identify data gaps, not determine data needs.

EPA used EPA's New Chemicals Program criteria to interpret the data contained in the detailed hazard reviews and identify potential hazard concerns in volume 1 for the purposes of informing decision making. When measured data were not available, estimates for chemicals were determined when possible to identify areas with a potentially high hazard concern. EPA also identified potentially low and moderate hazard concerns.

The information presented in this volume will provide an appropriate starting point for longer-term efforts to fully characterize hazard, exposure and risk issues associated with

flame-retardant alternatives. The next step in this process is to work with the Partnership to set goals and a path forward to implement a VCCEP-like program.

Flame Retardant Alternatives

Triphenyl Phosphate

Draft Hazard Review

December 2004

Triphenyl Phosphate:
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	✓
Dermal	✓
Inhalation	*
Eye irritation	✓
Dermal irritation	✓
Skin sensitization	*
Subchronic Toxicity	
28-Day oral	*
90-Day oral	*
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	*
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	*
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	✓
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✓
Neurotoxicity screening battery (adult)	✓
Developmental neurotoxicity	
Additional neurotoxicity studies	✘
Immunotoxicity	
Immunotoxicity	✓
Genotoxicity	
Gene mutation in vitro	✓
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	✓

Triphenyl Phosphate:
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	✓
Octanol/water partition coefficient	✓
Oxidation/reduction	
Melting point	✓
Boiling point	✓
Vapor pressure	✓
Odor	✓
Oxidation/reduction chemical incompatibility	
Flammability	✓
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	✓
Viscosity	
Density/relative density/bulk density	✓
Dissociation constant in water	✘
Henry's Law constant	✓

Environmental Fate	
Bioconcentration	
Fish	✓
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	*
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	✓
Photolysis in soil	
Aerobic biodegradation	✓
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	*
Hydrolysis as a function of pH	✓
Sediment/water biodegradation	✓
Soil biodegradation w/ product identification	✓
Indirect photolysis in water	
Sediment/soil adsorption/desorption	✓

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	✓
Daphnia acute EC50	✓
Mysid shrimp acute LC50	*
Green algae EC50, NOAEC, LOAEC	✓
Fish chronic NOAEL, LOAEC	*
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Sediment organisms	*
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Triphenyl phosphate
CAS 115-86-6
MF $C_{18}H_{15}O_4P$
MW 326.29
SMILES c1ccccc1OP(=O)(Oc2ccccc2)Oc3ccccc3

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401).

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Several acute oral lethality studies were available in a variety of species: rats, mice, rabbits, guinea pigs, and hens. These studies were from the older (pre 1980) literature, and do not fully conform to OPPTS or OECD guidelines, but together may be adequate to support the evaluation of acute oral toxicity. The toxic potency of TPP tended to be somewhat lower when it was administered in aqueous vehicle (usually as a suspension) than when administered in oil. Deaths generally did not occur following administration in aqueous vehicle ([LD50 >5,000-20,000 mg/kg), and were seen at relatively high doses (LD50 = 10,800 mg/kg) from administration in oil. Two of the better studies in the preferred species (rat), one using an aqueous vehicle and the other using an oil vehicle, and one each in mice and rabbits using an aqueous vehicle, are summarized below as the critical studies.

Critical Studies:

Type: Acute oral limit test
Species, strain, sex, number: Rat, Wistar, 5 male and 5 female
Dose: 20,000 mg/kg
Purity: Not reported, Monsanto commercial TPP
Vehicle: Water: 25% aqueous “solution”
Method: Similar to limit test, but higher dose; 24-hour fasting period prior to dosing; 14-day post-dosing observation period; observations limited to mortality and necropsy
Results: No deaths, therefore LD50 >20,000 mg/kg. Necropsy revealed sporadic visceral hemorrhages.

Reference: Food and Drug Research Labs, 1976

Type: Acute oral LD50
Species, strain, sex, number: Rat, Sprague-Dawley, male and female, number not specified
Dose: Up to 15,800 mg/kg
Purity: GC-verified, but not specifically reported
Vehicle: Corn oil
Observation period: 14 days post dosing
Method: LD50 calculated according to DeBeer (1945); not specified whether fed or fasted at time of dosing; 14-day post-exposure observation period; mortality only
Results: LD50 = 10,800 mg/kg; actual mortality data not reported
Reference: Johannsen et al., 1977

Type: Acute oral limit test
Species, strain, sex, number: Mouse, strain not specified, male and female, 5 total/dose
Doses: 2,500 and 5,000 mg/kg
Purity: Not specified
Vehicle: Emulsion in aqueous gum acacia
Method: Similar to limit test; not specified whether fed or fasted at time of dosing; 8-day observation period; observations limited to mortality and overt signs
Results: No deaths at either dose; therefore, LD50 >5,000 mg/kg; slight stupor
Reference: Ciba-Geigy Ltd., 1954

Type: Acute oral limit test
Species, strain, sex, number: Rabbit**,** strain and sex not specified, 1/dose
Purity: Technical grade TPP
Doses: 3,000 and 5,000 mg/kg
Vehicle: Suspended in aqueous gum acacia
Method: Preliminary limit test, observation was for "several days", observations limited to clinical signs and mortality
Results: Neither rabbit died, indicating LD >5,000 mg/kg; both had diarrhea
Reference: Dow Biochemical Research, 1934

Additional Studies and Information:

Other studies that were of lesser quality or were reported in less detail are generally consistent with the above studies (Houghton EF & Company, no date; Kettering Lab, 1945; Smith et al., 1932; Sutton et al., 1960).

Specific organ toxicity was generally not observed in the studies that include gross pathological examinations. Some signs possibly indicative of neurotoxicity (lassitude incoordination, tremors, or weakness) were observed in a few studies (Ciba-Geigy Ltd. 1954; Kettering Lab, 1945; Smith et al., 1932). It has been suggested that at the very high doses employed in these

acute toxicity studies, even small amounts of impurities could be responsible for the apparent neurotoxicity, which has not been seen with purified TPP (see section on neurological effects), or that the signs may have been secondary to other effects.

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged adequate to meet the endpoint.

***Basis for Conclusion*:**

The available studies predate the preferred study guidelines, and lack details including purity and discussion of necropsy results, but together indicate a low order of toxicity (LD50>7,900-10,000 mg/kg), consistent with the acute oral studies.

Type: Acute dermal toxicity
Species, strain, sex, number: Rabbit, albino, sex not specified, 10
Dose: 10,000 mg/kg
Purity: No data, commercial product provided by Monsanto, white flakes
Vehicle: Not reported, but the concurrent acute oral study used water
Method: U.S. Federal Hazardous Substances Act Regulations study guideline16 CFR 1500.40; 5 rabbits tested with intact skin and 5 with abraded skin; 14-day observation period
Results: Mortality after 14 days 0/5 intact, 0/5 abraded. Therefore, LD50 >10,000 mg/kg.
Reference: Food and Drug Research Labs, 1976

Type: Acute dermal toxicity
Species, strain, sex, number: Rabbit, New Zealand albino, sex and number not specified
Dose: Highest dose = 7,900 mg/kg
Purity: No data, prepared from pure phenol
Vehicle: None (“undiluted”)
Method: Intact skin, occlusive dressing, test material washed off after 24 hours, 14-day observation period. Necropsy.
Results: No deaths; therefore, LD50 >7,900 mg/kg; necropsy results not discussed.
Reference: Johanssen et al., 1977

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300 (OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint, unless data regarding particle size in the TPP powder study are provided.

Basis for Conclusion:

The available studies on TPP predate the preferred guidelines, but the study using TPP powder (Food and Drug Research Labs, 1976) was reported to be conducted according to a guideline that was relevant at the time. The duration was shorter than currently recommended and the concentration was much higher, but no signs of toxicity and no deaths were observed. Analysis of particle size, however, was not mentioned, so it is not known whether the size was respirable. Necropsies apparently were not performed. The other available study, on TPP vapor (Sutton et al., 1960), was conducted at an exposure level lower than recommended for a limit test, the observation period was inadequate, and it appears that the chamber was a closed chamber, which is not according to guideline.

Type: Acute inhalation toxicity
Species, strain, sex, number: Rat, Wistar, 5 males and 5 females
Doses: 200 mg/L (nominal); administered as a powder; particle size not reported
Purity: No data, commercial product provided by Monsanto, white flakes
Vehicle: None
Duration: 1 hour
Method: 16 CFR 1500.3; 300 mL chamber with air flow of 5 L/minute. Observation period = 14 days. Observed daily for signs of toxicity and for mortality.
Results: Mortality after 14 days 0/5 males, 0/5 females; no overt signs of toxicity
Reference: Food and Drug Research Labs, 1976

Type: Acute inhalation toxicity
Species, strain, sex, number: Mouse, Carworth Farms CF 1, male
Doses, duration, number: 363 mg/m^3 (6 hours exposure, 5 mice) and 757 mg/m^3 (2 and 4 hours exposure, 7 mice/duration)
Purity: Practical Grade Eastman
Vehicle: None
Method: The mice were exposed to TPP vapor in a battery jar following generation of the vapor by flowing preheated air through molten TPP at 175-180°C. Observation period = 24 hours. The mice were observed for signs of cholinergic toxicity and blood cholinesterase was measured at termination.
Results: No overt signs of toxicity; cholinesterase determinations not considered valid because controls did not appear to have been sham exposed.
Reference: Sutton et al., 1960

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Two reasonably adequate studies report similar results in rabbits: mild reversible irritation primarily of the conjunctiva. The studies are summarized below.

Type: Acute eye irritation
Species, strain, sex, number: Rabbit, albino, sex not specified; 9
Doses: 100 mg
Purity: No data, commercial product provided by Monsanto, white flakes
Vehicle: Not reported
Method: Patterned after U.S. Federal Hazardous Substances Act Regulations study guideline 16 CFR 1500.42, except 6 rabbits–eyes not washed after instillation of TPP, 3 rabbits–eyes washed 4 seconds following instillation of TPP; eyes examined at 24, 48, and 72 hours, and 7 days after instillation of TPP.
Results: Mild conjunctival effects (slight redness 6/6, slight discharge 4/6) at 24 hours in the eyes that were not washed out, which cleared by 72 hours; no effects in eyes that had been washed out (incidence 0/3).
Reference: Food and Drug Research Labs, 1976

Type: Acute eye irritation
Species, strain, sex, number: Rabbit, New Zealand, 3 males and 3 females
Doses: 100 mg
Purity: No data, commercial product provided by Monsanto, white flakes
Vehicle: None
Method: Patterned after U.S. Federal Hazardous Substances Labeling Act Section 191.12 (February 1965). Eyes of 3 (of the 6) rabbits were washed out 30 seconds following instillation of TPP; eyes examined at 1, 24, 48, and 72 hours and 6 days after TPP instillation.
Results: Mild conjunctival effects (slight redness 6/6) at 24 hours in all exposed eyes, which cleared in all but 1 (unwashed) eye by 72 hours; and in that eye by 6 days. Slight corneal opacity was seen in one unwashed eye at 24 hours, which cleared by 48 hours.
Reference: Ciba-Geigy Pharmaceuticals Division, 1983a

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Two reasonably adequate studies, patterned after guidelines in effect at the time, provide similar results, indicating that TPP was not a skin irritant in rabbits. Additional studies provide support. The studies are summarized below.

Critical Studies:

Type: Acute dermal irritation
Species, strain, sex, number: Rabbit, albino, sex not specified, 6
Doses: 500 mg
Purity: No data, commercial product provided by Monsanto, white flakes
Vehicle: Not reported, but acute oral study used water
Method: Patterned after U.S. Federal Hazardous Substances Act Regulations study guideline 16 CFR 1500.41; shaved back, each rabbit tested on intact and abraded skin, semiocclusive dressing removed after 24 hours, observations at 24 and 72 hours.
Results: No erythema or edema on intact or abraded skin in any of the 6 rabbits.
Reference: Food and Drug Research Labs, 1976

Type: Acute dermal irritation
Species, strain, sex, number: Rabbit, New Zealand, 3 males and 3 females
Doses: 1.0 mL of suspension of 10,000 mg/20 mL = 500 mg
Purity: No data, white flakes
Vehicle: 50% aqueous solution of polyethylene glycol
Method: U.S. Federal Hazardous Substances Labeling Act Section 191.12 (February 1965); shaved back, each rabbit tested on intact and abraded skin, occlusive dressing removed after 24 hours, observations at 24 and 72 hours.
Results: No erythema or edema on intact or abraded skin in any of the 6 rabbits.
Reference: Ciba-Geigy Pharmaceuticals Division, 1983b

Additional Studies:

Other studies, reported in less detail, also reported no effects in rabbits from dermal exposure on intact skin to the dry powdered TPP, and only slight dryness during repeated application as a saturated solution in ethanol (13 times in 16 days) (Dow Biochemical Research, 1933).

Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)

Conclusion:

The available skin sensitization data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No experimental studies of skin sensitization in animals were located in the published literature. A few human cases of TPP allergic dermatitis have been reported. An example is a case of allergy to TPP from cellulose acetate eyeglass frames that contained TPP as an additive (Carlsen et al., 1986). Patch testing of dermatological patients, however, has not generally implicated this chemical as a sensitizer. For example, of 343 patients tested because of suspected sensitivity to plastics and glues components, none reacted to TPP (Tarvainen, 1995). In a study of 23,192 patents with eczema who were patch tested with cellulose acetate film containing 7-10% TPP and 4-5 % phthalic acid, positive reactions were observed in only 15 (0.065%) (Hjorth 1964).

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

Conclusion:

The available subchronic oral toxicity data were judged inadequate to meet the endpoint, but an existing unpublished Food and Drug Administration (FDA) study, if provided, could address this data gap.

Basis for Conclusion:

A single 35-day study in rats (Sutton et al., 1960) provides limited relevant information. The study was not adequate to characterize this endpoint because of the small number of rats in each dose group, testing of only one sex, lack of clinical chemistry and histopathology data, and lack of detailed reporting. A set of concurrent approximately 120-day studies performed by FDA investigated general toxicity, reproductive and developmental toxicity, neurotoxicity, and immunotoxicity (Hinton et al., 1987, 1996; Sobotka et al., 1986; Welsh et al., 1987). The general toxicity study, however, was not published, and the associated studies do not report adequate information on the general toxicity of this chemical.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

The only relevant available study is a 35-day repeated oral study that does not satisfy the guideline. A summary of the study is as follows:

Type: 35-Day repeated oral
Species, strain, sex, number: Rat, Holtzman, male, 5/dose
Doses: 0, 0.1, and 0.5% in the diet (the 0.1% group received 5% for the first 3 days, but refused to eat, and therefore was switched to a lower dietary concentration)
Purity: Practical Grade Eastman Organic, purity not specified

Vehicle: None; added to diet
Exposure period, frequency: 35 days, daily
Post Exposure Period: 2 weeks
Method: Two rats/group killed at end of 35 days; 3 rats/group observed for 2 week recovery period; body weight, hematology (hemoglobin, cell volume, red and white cell count, and differential), necropsy with organ weights.
Results: Slight depression in body weight gain in high dose group at day 35, but not after 2-week recovery period. Slight but statistically significant increase (Student's t test) in mean relative liver weight in high dose group–not specified whether all 5 rats/group were included in organ weight determinations. No gross abnormalities seen at necropsy. No statistically significant differences in hematological values.
Reference: Sutton et al., 1960

- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**

The only ≥90 day subchronic studies of TPP toxicity were specialized studies of reproductive, developmental, neurological, and immunological endpoints in the rat conducted by the FDA (Hinton et al., 1987; Sobotka et al., 1986; Welsh et al., 1987). These studies provide only limited information on other systemic toxicities, and therefore do not satisfy the guideline.

- In the reproductive and developmental toxicity study in the rat, males and females were fed TPP at dietary levels up to 1% for 91 days prior to mating, continuing through mating, and the females were continued on the diet until day 20 of gestation. This study reported no differences in behavior or gross pathology of the treated dams, a slight but significant decrease on day 0 of gestation in the body weight of the dams fed the 1% diets (690 mg/kg/day), a slight but significant increase in food consumption primarily at 0.5 and 0.75% in the diet(not dose-related), and a non-significant decrease in body weight gain (minus the gravid uterus) at day 20 of gestation in dams fed ≥0.5% (341 mg/kg/day) (Welsh et al., 1987).
- The neurological study, in which male rats were fed up to 1% TPP in the diet for 4 months, provided no evidence of neurobehavioral effects, but also noted a decrease in body weight gain. The NOAEL and LOAEL for this effect were 0.25% in the diet (161 mg/kg/day) and 0.50% in the diet (345 mg/kg/day) (Sobotka et al., 1986).
- In the immunotoxicity study, in which male and female rats were fed up to 1% TPP in the diet for 4 months, the only effects seen were a decrease in body weight gain at 1.0% (approximately 700 mg/kg/day) in the diet, and non-dose related increases in the relative percentages of α-globulins in treated females and β-globulins in treated males, which were interpreted as a possible sign of liver activity of uncertain toxicological significance (Hinton et al., 1987). Because of the lack of dose-response, these findings may not be indicative of a chemical effect. The NOAEL and LOAEL for decreased body weight gain were 0.75% in the diet (517 mg/kg/day) and 1.0% in the diet (700 mg/kg/day).

Details of these studies are provided in the appropriate sections. These studies are not adequate to fulfill the requirements of the 90-day subchronic oral toxicity guideline.

An associated, concurrent FDA subchronic toxicity study, mentioned in the other FDA reports (Hinton et al., 1987, 1996; Sobotka et al., 1986; Welsh et al., 1987), has not been published. The study has been requested for review.

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

No studies of this type were located.

Subchronic Dermal Toxicity (21/28-day or 90-day)

Conclusion:

The available subchronic dermal toxicity data were judged inadequate to meet the endpoint, unless further information is provided for the available 21-day study.

Basis for Conclusion:

The only study available for this endpoint, a 21-day dermal toxicity study, has a design similar to that of the OPPTS guideline, but the reporting of the study is deficient. Only the text portion of the results was available, but the tables summarizing the data were omitted, as were data regarding the outcome of tests of purity of the TPP. Because it is the only relevant study, more detailed reporting of information from this study is needed if it is to be used to satisfy the endpoint. The study is summarized below.

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**

Type: 21-Day dermal toxicity
Species, strain, sex, number: Rabbit, New Zealand white, 10 males and 10 females/dose
Doses: 0 (vehicle control), 100, and 1,000 mg/kg body weight
Purity: Determined at start and end of test but results not reported
Vehicle: Absolute ethanol
Exposure period, frequency: 21-23 days, 5 days/week
Post Exposure Period: none
Method: Similar to 870.3200 but functional observational battery omitted, number of tissues/organs examined histopathologically was not as extensive, and histopathological examinations were performed on all control and high dose rabbits and “as required” on low dose rabbits. The skin of 5 males and 5 females in each dose group was abraded twice a week; the

skin of the other 5 males and 5 females in each group was not. No dressing was used after application of the vehicle or test substance, but collars were used to prevent contact with the material, and the excess was removed after 6 hours.
Results: No treatment-related changes were seen in clinical signs, mortality, body weight, hematology, gross or histopathology, or routine clinical chemistry. Low-dose females had decreased mean thyroid/body weight ratio and increased mean kidney weight. Dose-related depressions in serum, erythrocyte, and brain cholinesterase were observed. The tables summarizing the actual data were omitted from the report.
Reference: Bio/Dynamics, Inc., 1970

- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

No studies of this type were located.

Subchronic Inhalation Toxicity: 90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)

Conclusion:

The available subchronic inhalation toxicity data for nonrodents were judged inadequate to meet the endpoint.

Basis for Conclusion:

No repeated-exposure inhalation toxicity studies were located.

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A study of reproduction and development in rats exposed for 91 days prior to mating, and continuing through mating until day 20 of gestation (Welsh et al., 1987) partially characterizes this endpoint, but is not fully adequate. No other data relevant to this endpoint were located.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

A study of reproduction and development in rats exposed for 91 days prior to mating, and continuing through mating until day 20 of gestation (Welsh et al., 1987) partially satisfies the reproductive screening component of this guideline, but is not fully adequate, primarily because it lacks histopathology of male and female reproductive organs. The study is summarized below under Developmental Toxicity. Findings relevant to reproduction were that there were no significant differences in number of corpora lutea, implants, implantation efficiency, viable fetuses, and number of early or late deaths at dietary levels as high as 1.0% TPP (690 mg/kg/day). Because both sexes were treated, and there were no effects on litter size (as measured by number of viable fetuses), the study provides some evidence that fertility is not affected by TPP in the rat.

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

No studies with this specific design were available.

- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

No studies with this specific design (two-generation reproduction) were available.

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

A study of reproduction and development in rats exposed for 91 days prior to mating, and continuing through mating until day 20 of gestation (Welsh et al., 1987) appears to fulfill the requirements of the Prenatal Developmental Toxicity Study guideline, and is adequate to characterize developmental toxicity. Details of this study are as follows:

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**

Type: Reproductive screen, prenatal developmental toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 40 males and 40 females/dose
Purity: Commercial grade, Aldrich, 98% pure
Doses: 0, 0.25, 0.50, 0.75, or 1.00% in the diet (0, 166, 341, 516, and 690 mg/kg/day based on food consumption and body weight of pregnant females)

Exposure duration, frequency: Starting at 4 weeks post weaning, males and females exposed for 91 days prior to mating, continuing through mating and, for the dams, through gestation day 20; daily
Method: Body weight, food consumption, clinical signs, and necropsy of dams; uterine contents at day 20 of gestation; fetal weight, crown-rump length, external, visceral, and skeletal abnormalities; extensive statistical analyses.
Results: The body weights of the females fed the 1.0 % diets were slightly but significantly lower than those of controls on day 0 of gestation. During gestation, the dams that consumed TPP in the diet generally consumed slightly more food than controls; but their body weight gains during gestation and the adjusted body weight gain (excluding gravid uterus) at day 20 were not significantly different from controls. No differences in behavior or gross pathology were reported. Fertility (pregnancy rate) was higher in the treated females than in controls, but control fertility was relatively low. No significant differences between treated and control groups were seen for numbers of corpora lutea, implants, implantation efficiency, viable fetuses, or resorptions (total or early or late deaths). Male and female fetuses from the treated groups tended to weigh more than control fetuses, but the differences were minimal (<10% increase in fetal weight), not dose-related, and significant ($p<0.05$) only for the males in the 0.50 and 1.00% groups (but not the 0.75% group). Significant, slight increases in visceral variations (moderate hydroureter, enlarged ureter proximal to kidney) were seen in litters of all treated groups, but the increases were not dose-related, and the controls had a relatively high incidence of moderate hydroureter. Given the lack of dose response and uncertain biological significance of the slight fetal changes in this study, the highest dose level (1.0% TPP in the diet, 690 mg/kg/day) may be a NOAEL for fetotoxicity. TPP did not produce teratogenic effects in this study. This study suggests a minimal LOAEL for decreased body weight gain of 1.0% TPP in the diet (690 mg/kg/day) for the dams. Although the highest dose in the study (1.0% in the diet, 690 mg/kg/day) is not as high as a limit dose of 1,000 mg/kg/day, it did produce slight body weight depression in the dams, and in the two associated studies (on neurotoxicity and immunotoxicity), produced more striking depressions in body weight gain in male and female rats at the same dietary level, particularly in the first few weeks on test, and in the absence of a depression in food consumption. A higher dietary level (5%) was tested in a 35-day study in rats and resulted in food refusal (Sutton et al., 1960). Thus testing with dietary levels substantially higher than 1.0% TPP may not be advisable.
Reference: Welsh et al., 1987

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

No studies with this specific design were available.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

A study of reproduction and developmental toxicity is available (Welsh et al., 1987); the developmental toxicity portion of the study is consistent with a full prenatal developmental toxicity study, and was discussed previously under that category.

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No relevant studies were located.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**

No studies of this type were located.

- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

No studies of this type were located.

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available study, a strain A mouse pulmonary adenoma study, is not a suitable type of study to characterize the potential carcinogenicity of chemicals for chronic oral exposure. The study is summarized below.

Type: Strain A mouse pulmonary adenoma
Species, strain, sex, number: Mouse, strain A/St, 20 males/dose
Identity: Uncertain—reported as triphenyl phosphate, and also as phosphorous acid, triphenyl ester (which is triphenyl phosphite, a different chemical)
Purity: Not reported, Aldrich, reagent grade
Doses: 0 (vehicle control), 20, 40, and 80 mg/kg
Vehicle: Tricaprylin
Route: Intraperitoneal injection

Exposure duration, frequency: 3 injections/week; for 20 mg/kg–18 injections (6 weeks), for 40 mg/kg–3 injections (1 week), for 80 mg/kg–1 injection (the experimental design was to give 24 injections, but fewer injections were given for the "more toxic chemicals".
Method: 24 weeks after the first injection, the mice were killed and the lungs were examined for surface nodules; a few of the nodules were examined histologically to confirm that they were adenomas; positive controls received urethan; Student t test.
Results: Survival at 24 weeks was 46/50 for controls, 18/20 at 20 mg/kg (18 injections), 3/20 at 40 mg/kg (3 injections), and 12/20 at 80 mg/kg (1 injection). No increase in the number of pulmonary adenomas/mouse was seen.
Reference: Theiss et al., 1977

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**

No studies of this type were located.

- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

No studies of this type were located.

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged not fully adequate to meet the endpoint.

Basis for Conclusion:

Some components of this endpoint—delayed neurotoxicity and neurotoxicity screening (in adult animals)—are satisfied by the existing data, but no study of developmental neurotoxicity has been conducted. This endpoint could be addressed in combination with the reproductive toxicity endpoint. TPP gave negative results in several acute oral delayed neurotoxicity studies in the hen as well as a subcutaneous study in the cat, and also in a subchronic oral neurotoxicity screening study in the rat. Further information is provided in the following subsections.

Delayed Neurotoxicity

Conclusion:

The available delayed neurotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available acute delayed neurotoxicity studies in the hen and in the cat (another sensitive species), summarized below, give no evidence of acute cholinergic toxicity or of delayed neurotoxicity. These studies, performed prior to the existence of the guidelines, do not entirely conform to the guidelines, and lack detail including, in the hen studies, purity of the TPP sample. Nevertheless, together they indicate a lack of delayed neurotoxicity for TPP. Neurotoxic esterase (NTE) assays were not conducted in these studies. In a separate unpublished study, summarized in a review of structure-activity studies, an NTE assay in brain homogenate following a single oral dose of 700 mg/kg TPP (>99% purity) to the hen (Johnson, 1975) gave negative results. This dose is lower than those used in the critical studies of delayed neurotoxicity in hens but given the lack of signs and histopathological evidence for delayed neurotoxicity, additional NTE assays do not appear necessary.

Because of the lack of signs or histopathology indicating delayed neurotoxicity in the acute studies, 28-day studies are not required. In addition, structure-activity studies indicate that TPP would not be expected to cause delayed neurotoxicity (Johnson, 1975).

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Critical Studies

Type: Delayed neurotoxicity
Species, strain, sex, number: Hen, White Leghorn, 9 for TPP
Purity: Not reported, prepared from pure phenol
Doses: 5,000 mg/kg twice daily; thus, 10,000 mg/kg/day
Vehicle: Corn oil
Route: Gavage
Exposure duration, frequency: Twice a day on days 1-3 and 21-23 of the study (6 days of dosing); interval between doses not reported.
Method: Dosing twice daily for 6 days was needed because of the low toxicity of TPP (no lethality at 5 mg/kg, the largest feasible dose). Hens were fasted for 16 hours before dosing (further explanation not provided). Daily observations for deaths and signs of neurotoxicity were conducted from day 1 through day 42, at which time hens were necropsied. Brain, sciatic nerve, and spinal cord were examined histopathologically. Tricresyl phosphate (mixed o-, m-, p-) was tested concurrently.
Results: For TPP, no overt signs of neurotoxicity and no histopathological effects in the nervous tissues were observed (0/9). Although the hens were weighed at 0, 21, and 42 days, no body weight results were presented. Tricresyl phosphate, a known delayed neurotoxicant, resulted in overt signs and histopathological evidence of delayed neurotoxicity in 6/6. Details of the histopathological data were not provided.
Reference: Johannsen et al., 1977

Type: Delayed neurotoxicity
Species, strain, sex, number: Hen, Rhode Island Red x Light Sussex, 2/dose
Purity: Not reported, white flakes
Doses: 2,000, 3,000, 5,000, 8,000, or 12,500 mg/kg
Vehicle: Arachis oil
Route: Gavage
Exposure duration, frequency: Single dose
Method: Hens were not fasted. Post-dosing observation period was 21 days. Daily observations for deaths and signs of neurotoxicity. Necropsy but not histopathology.
Results: No overt signs of neurotoxicity. Necropsy results not mentioned.
Reference: Ciba-Geigy Pharmaceuticals Division, 1980

Type: Delayed neurotoxicity
Species, strain, sex, number: Hen, Rhode Island Red x Light Sussex, 2
Purity: Not reported, white flakes
Doses: 12,000 mg/kg
Vehicle: Arachis oil
Route: Gavage
Exposure duration, frequency: Single dose
Method: Hens were not fasted. Post-dosing observation period was 21 days. Daily observations for deaths and signs of neurotoxicity. Necropsy but not histopathology.
Results: No overt signs of neurotoxicity, and no abnormalities at necropsy.
Reference: Ciba-Geigy Pharmaceuticals Division, 1981a

Type: Delayed neurotoxicity
Species, strain, sex, number: Cat, not further specified, 5
Purity: Zone-refined triphenyl phosphate, purity 99.99%
Doses, number: 400 mg/kg in propylene glycol (2 cats), 700 mg/kg in corn oil (2 cats), and 1,000 mg/kg in corn oil (1 cat)
Vehicle: Propylene glycol (1 cat), corn oil (2 cats)
Route: Subcutaneous injection
Exposure duration, frequency: Single dose
Method: Post-dosing observation period was 4 months. Daily observations for deaths, general behavior, eating, and drinking. Weighed at intervals. Whole blood, plasma, and erythrocyte cholinesterase determined for cats given 700 mg/kg of TPP and their controls. Complete necropsies on cats given 700 mg/kg. Brain stem and spinal cord examined histopathologically in all cats.
Results: All except one on the lowest dose lost weight (due to cessation of eating); the other on the lowest dose lost weight initially and then regained it. These cats had no overt signs of toxicity and were not necropsied or examined further. At 700 mg/kg, the cats stopped eating during the first week after injection, became moribund, and were euthanized. Cholinesterase activities in these cats were similar to those in the controls. No evidence of axonal degeneration, demyelination, or other adverse change was seen in sections from 11 levels of the nervous

system extending from cerebral cortex to peripheral nerve in the 700 mg/kg group. The cat that received 1,000 mg/kg became anorexic 1 week after injection and was necropsied at 3 weeks after injection. Sections of this cat's brain stem and spinal cord did not reveal any abnormalities. Actual data were not presented.
Reference: Wills et al., 1979

Additional studies

Additional oral studies at lower doses in the chicken [one at 500 mg/kg in the hen (Aldridge and Barnes, 1961), and another at 1,000 mg/kg in the cockerel (young rooster) (Hine et al., 1956)] also reported no signs of delayed neurotoxicity. Two delayed neurotoxicity studies that reported some axonal lesions in the spinal cord of hens following 5,000 mg/kg/day of TPP (unknown purity) for 5 days are considered invalid because the doses were so high that most of the hens died or were killed in extremis during the study, severe weight loss occurred in the hens, and the same mild axonal lesions were seen in both controls and treated hens (Ciba-Geigy Pharmaceuticals Division, 1982), or because no controls were used (Ciba-Geigy Pharmaceuticals Division, 1981a).

Neurotoxicity (Adult)

Conclusion:

The available adult neurotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available study of neurobehavioral effects following subchronic feeding of TPP to rats (Sobotka et al., 1986) predates the guidelines, but fulfills some of the criteria for a Neurotoxicity Screening Battery. It includes some of the observations from the functional observational battery, and a few additional measures (rearing activity, rotorod, negative geotaxis). It does not include neurohistopathological examinations, and testing was conducted in only one sex rather than both sexes as recommended. In other reasonably well-conducted studies of this chemical, however, there is no evidence that one sex is significantly more sensitive than the other or that the chemical is neurotoxic. Structure-activity studies do not indicate neurotoxic potential for TPP (Johnson, 1975). Therefore, the existing study, in context with the other information regarding TPP toxicity, may be adequate to satisfy the adult neurotoxicity component of the neurotoxicity endpoint. The study description follows:

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Type: Neurotoxicity screening, oral
Species, strain, sex, number: Rat, Sprague-Dawley, 10 males/dose

Doses: 0, 0.25, 0.50, 0.75, or 1.0% in the diet; 0, 161, 345, 517, or 711 mg/kg/day
Vehicle: None
Purity: 98% (commercial grade, Aldrich); homogeneity and stability of TPP diets confirmed by gas chromatography
Exposure duration, frequency: 4 months, daily
Method: Observations included food consumption, body weight, in-cage observation for overt signs, open-field exploratory behavior (motor activity and rearing), rotorod, forelimb grip strength, and negative geotaxis. Extensive statistical analysis.
Results: Overt signs and test results for neurobehavioral endpoints were not statistically significantly different in treated versus control rats. Body weight gain, but not food consumption, was statistically and toxicologically significantly lower (>10% decrease) in the 0.5, 0.75, and 1.0% dietary groups than in controls, and there was a negative dose-related linear trend for weight gain. Thus, no LOAEL for neurotoxicity was demonstrated. The NOAEL and LOAEL for effects on body weight gain were 0.25% in the diet (161 mg/kg/day) and 0.50% in the diet (345 mg/kg/day).
Reference: Sobotka et al., 1986

Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)

Conclusion:

The available developmental neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies of this type were located.

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat)
  - OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent)
  - OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred)
  - OPPTS Harmonized Guideline 870.6855

These studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Conclusion: These endpoints do not appear to be applicable to TPP.

Basis for Conclusion: Although there are no studies addressing these endpoints, there are no reliable data for TPP, and no structure-activity considerations, that indicate a need for these follow-up studies.

IMMUNOTOXICITY

***Conclusion*:**

The available immunotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The potential immunotoxicity of TPP was examined in a subchronic dietary study in rats (Hinton et al., 1987, reprinted as Hinton et al., 1996) which predates the guideline for immunotoxicity. This study appears to satisfy most of the requirements of the guideline, although no positive control was included, and the anti-sheep red blood cell assay is not the currently recommended assay. The study, which was negative for immunotoxicity, is summarized below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

Type: Immunotoxicity, oral subchronic
Species, strain, sex, number: Rat, Sprague-Dawley, 10 males and 10 females/dose
Doses: 0. 0.25, 0.50, 0.75, or 1.00% TPP in the diet; approximately equivalent (based on measured dosages in the related studies by Sobotka et al., 1986 and Welsh et al., 1987) to 0, 163, 343, 517, and 700 mg/kg/day. No positive control.
Purity: Aldich, 98% pure, confirmed by gas chromatography, stable under the experimental conditions of this study
Exposure duration, frequency: 120 days, daily
Method: Observations included body weight, food consumption, midterm and terminal sacrifice, necropsy, spleen and thymus weights, histopathology of spleen, thymus, and mesenteric lymph nodes, immunohistochemical evaluation of B- and T-lymphocyte regions in these tissues, total serum protein and electrophoretic analysis of serum proteins, humoral response to sheep red blood cells (relative antibody titers by hemolytic assay). Extensive statistical analysis.
Results: The only statistically significant effects were a decreased growth rate (>10% difference in body weight) during the first 4 weeks in males and females of the 1.00% dietary group, and non-dose related increases in the relative percentages of α-globulins in treated females and β-globulins in treated males, which were interpreted by the study authors as a possible sign of liver activity but of uncertain toxicological significance. Because of the lack of dose-response, these findings may not be indicative of a chemical effect. This study did not demonstrate a LOAEL for immunotoxicity. The NOAEL and LOAEL for decreased body weight gain were 0.75% in the diet (517 mg/kg/day) and 1.0% in the diet (700 mg/kg/day).
Reference: Hinton et al., 1987

GENOTOXICITY

Conclusion: The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

Three studies of gene mutation *in vitro* report negative results. These studies, two in bacteria and one in mammalian cells, predate the relevant guidelines, but were conducted in a manner similar to them, and together, characterize the gene mutation *in vitro* endpoint. Studies of chromosomal aberrations were not available, however, and are needed for adequate characterization of the genotoxicity endpoint.

Gene Mutation in Vitro:

- **Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)**

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537
Metabolic activation: Tested with and without Aroclor 1254-induced liver S9 from male Syrian hamsters (10% in S9 mix for all strains and also 50% for TA1535 and TA1537), and male Sprague-Dawley rats (10% for all strains)
Concentrations: 0, 100, 333, 1,000, 3,333, and 10,000 µg/plate. Solvent was 95% ethanol. A precipitate was present in the plates at ≥3,333 ug/plate; tested in triplicate; plus replicate
Purity: 98% +
Method: Preincubation (20 minutes) and plate incorporation (48 hours) at 37°C. Positive controls were 2-aminoanthracene for all strains with S9, and sodium azide (TA1535 and TA100), 9-aminoacridine (TA1537), and 4-nitro-o-phenylenediamine (TA98) in the absence of S9.
Results: No increase over negative control at any concentration; no apparent cytotoxicity; the two highest concentrations tested may have exceeded solubility limits.
Reference: Zeiger et al., 1987

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538
Metabolic activation: Tested with and without Aroclor 1254-induced liver S9 from male Sprague-Dawley rats
Concentrations: 0, 10, 100, 500, and 1,000 µg/plate. Solvent was DMSO; tested in triplicate; plus replicate
Purity: No data, white crystals
Method: Plate incorporation, 48 hour incubation at 37°C; apparently only one plate for each concentration. Negative and positive controls.

Results: No increase in revertants over negative control at any concentration; highest concentration reportedly produced some evidence of physiological effect. *Saccharomyces cerivisiae* D4 also tested.
Reference: Litton Bionetics, Inc., 1978a

- **In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)**

Type: Mammalian Cell Gene Mutation Test: Forward Mutation
Species, strain: Mouse lymphoma L5178Y
Metabolic activation: Tested with and without Aroclor 1254-induced liver S9 from male Sprague-Dawley rats
Concentrations: 0, 3.13 (only without S9), 6.26, 12.5, 25, 50, and 75 (only with S9) µg/plate. Solvent was DMSO; tested in triplicate; plus replicate
Purity: No data, white crystals
Method: Plate incorporation, 48 hour incubation at 37°C. Negative and positive controls (ethylmethanesulfonate without S9; dimethylnitrosamine with S9).
Results: No increase over negative control at any concentration; highest concentration selected during prescreening as a level that reduced growth potential.
Reference: Litton Bionetics, Inc., 1978b

Other

- **Mitotic Gene Conversion in Saccharomyces cerevisiae (OPPTS Harmonized Guideline 870.5575)**

Type: Mitotic Gene Conversion
Species, strain: *Saccharomyces cerevisiae* D4
Metabolic activation: Tested with and without Aroclor 1254-induced liver S9 from male Sprague-Dawley rats
Concentrations: 0, 10, 100, 500, and 1,000 µg/plate. Solvent was DMSO
Purity: No data, white crystals
Method: Plate incorporation, 3- to 5-day incubation at 30°C (without S9) or 37°C (with S9). Negative and positive controls
Results: No increase over negative control at any concentration; highest concentration reportedly produced some evidence of physiological effect.
Reference: Litton Bionetics, Inc. 1978a

No studies were available on the genotoxicity of triphenyl phosphate in the following types of types of tests:

Gene Mutation in Vivo
Chromosomal Aberrations in Vitro

Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)

Conclusion:

The available acute fish toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available acute fish toxicity studies are summarized in Table 1. Acute 96-hour toxicity studies in freshwater fish species including rainbow trout, fathead minnows, goldfish, bluegill sunfish, medaka, channel catfish, and carp and in saltwater species including silverside and sheepshead minnow were located. Most of the 96-hour LC50 values reported in the available literature are consistent with each other and ranged from 300 to 1,200 µg/L. One study (Dawson et al., 1977), however, reported substantially higher LC50 values for TPP (95,000 µg/L in silverside and 290,000 µg/L in bluegill). A reason for this discrepancy is not clear. However, the data reported by Dawson et al. (1977) were considered unreliable because the reported LC50 values are approximately 50 to 150 times greater than the solubility limit of TPP (approximately 2,000 µg/L). Also, the results reported by Dawson et al. (1977) are inconsistent with results from multiple other studies.

Overall, the available acute fish toxicity endpoint appears to be satisfied by the currently existing database for the following reasons:

- Studies are available in both cold- and warm-water freshwater species and in marine species;
- Numerous studies are available that reported similar LC50 values; and
- Although most of the available studies used static conditions, the results from the only study located that used flow-through conditions and analytically confirmed the test concentrations are consistent with results from static studies conducted in the same species. These data indicate that use of static exposure conditions produces similar results as flow-through studies.

It should be noted, however, that sufficient detail was not included in many of the study reports to allow for a comprehensive and independent evaluation of data adequacy, most studies used static conditions and did not analytically confirm the test concentrations, and many studies were conducted prior to publication of GLP guidelines.

A summary of the available acute toxicity studies in fish that were located as well as selected deficiencies in the studies is presented in Table 1. Studies that were either published in a foreign language or that were not readily available AND that were not critical to the hazard assessment were not retrieved.

Table 1-1. Summary of available acute fish toxicity studies for triphenyl phosphate (115-86-6)[a]									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**96-Hour LC50**	**Study Type**	**Concentration Range Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry[b]**	**Solvent**	**Comments on the Data**
Ahrens et al., 1978	Carp	<1,000 µg/L	Static	Not reported	10	No	**pH:** NR **Temp:** "room" temp. **DO:** NR **Hardness:** NR	Acetone (0.6 mL/L)	The study conduct followed German guidelines. Reporting deficiencies preclude an independent evaluation of data adequacy. LC50 values were not reported. LC100 was 1,000 and 10,000 µg/L with and without acetone, respectively. LC0 without acetone was 5,000 µg/L. LC0 value with acetone was not observed.
Ciba-Geigy, 1981a	Rainbow trout 49 mm; 0.94 g	850 µg/L	Static	5 concentrations; 0.18 to 1,800 µg/L	10	No	**pH:** 7.7-8.2 **Temp:** 14.5-15.6°C **DO:** 5-9 mg/L **Hardness:** 172 mg/L	Mixture of octanol (>0.004 mL/L), tween (>0.07 mL/L), and ethylene glycol monomethyl ether (>0.02 mL/L)	The study reportedly followed OECD Guideline 203. TPP purity was 100%; loading rate was 0.21 g/L. Only minor reporting deficiencies were noted. Sublethal effects included abnormal swimming behavior and loss of equilibrium at all concentrations tested.

Table 1-1. Summary of available acute fish toxicity studies for triphenyl phosphate (115-86-6)[a]									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**96-Hour LC50**	**Study Type**	**Concentration Range Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry[b]**	**Solvent**	**Comments on the Data**
Dawson et al., 1977	Bluegill sunfish	290,000 µg/L Water solubility is approx. 2,000 µg/L	Static	5 concentrations, 125,000 to 560,000 µg/L	Not reported	No	Dilution water was reported to have a pH of 7.6-7.9 and a hardness of 55 mg/L. Target temp. was 23°C for bluegill and 20°C for silverside	Either distilled water or solvent with (reportedly) relatively low toxicity was used. Concentration of solvent, if used, was not reported.	The reported LC50 value from this study is substantially higher than the water solubility of TPP (approx. 2,000 µg/L); therefore, these data are unreliable.
	Silverside	95,000 µg/L Water solubility is approx. 2,000 µg/L	Static	5 concentrations, 75,000 to 560,000 µg/L					
Food and Drug Research Labs, 1979	Rainbow trout	760 µg/L	Static	5 concentrations, 180 to 1,800 µg/L	10	No	**pH:** 7.2-7.5 **Temp:** 12°C±1°C **DO:** 7.8-10 mg/L **Hardness:** 42 mg/L	Unidentified solvent	Study reportedly followed U.S. EPA (1975) guidelines. Solvent and blank controls were used. Loading rate was 0.15 g/L.

Table 1-1. Summary of available acute fish toxicity studies for triphenyl phosphate (115-86-6)[a]									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**96-Hour LC50**	**Study Type**	**Concentration Range Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry[b]**	**Solvent**	**Comments on the Data**
	Fathead minnow	3,800 µg/L Water solubility is approx. 2,000 µg/L	Static	5 concentrations, 1,000 to 10,000 µg/L	10	No	**pH:** 6.8-7.5 **Temp:** 20.6±0.6°C **DO:** 1.3-9.0 mg/L **Hardness:** 43 mg/L	Unidentified solvent	Dissolved oxygen concentrations decreased over the course of the study to as low as 1.3 mg/L. The LC50 determined from this study was greater than the water solubility of TPP.
Geiger et al., 1986	Fathead minnow (17 mm; 0.071 g)	870 µg/L	Flow-through (14.4x per day)	5 concentrations; 180 to 1,150 µg/L (mean measured)	20	Yes (GLC; 99.8% recovery)	**pH:** 7.8 **Temp:** 24.5°C **DO:** 6.4 mg/L **Hardness:** 45.6 mg/L Values are averages over the study duration; ranges were not reported	None used; 1.2 mg/L stock solution in glass wool column	Fish were 29 days old at study initiation. Loading rate was 1.4 g/L, and purity was 98%. In the high-dose group, 19/20 fish were dead by the 24-hour observation, and the remaining fish was dead by the 48-hour observation period. Reporting deficiencies included lack of water chemistry parameter values (e.g., pH, dissolved oxygen, temperature) at each concentration (although mean values were given), and a solvent was not used.

Table 1-1. Summary of available acute fish toxicity studies for triphenyl phosphate (115-86-6)[a]									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**96-Hour LC50**	**Study Type**	**Concentration Range Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry[b]**	**Solvent**	**Comments on the Data**
Huckins et al., 1991	Bluegill sunfish (0.5-1 g)	780 µg/L	Static	5 concentrations, 500 to 10,000 µg/L with and without addition of 1 g/L soil and clay	10	No	**pH:** NR **Temp:** 22°C **DO:** NR **Hardness:** NR	Acetone, unspecified concentration	TPP purity was 99%. Selected reporting deficiencies included concentration of solvent used, pH and dissolved oxygen of the test system during the study, and loading rate.
Industrial Bio Test Labs, Inc., 1972	Rainbow trout	Between 100 and 1,000 µg/L	Static	4 concentrations; 100 to 100,000 µg/L	Not reported	No	**pH:** 7.3-7.9 **Temp:** 12.2°C **DO:** 2.9-7.9 mg/L **Hardness:** NR	Acetone	Very limited information on the study was available. Data were obtained from unpublished EPA submission from TSCATS. Reporting deficiencies preclude an independent evaluation of data adequacy.
	Bluegill sunfish	Between 1000 and 10,000 µg/L Water solubility is approx. 2,000 µg/L	Static	4 concentrations; 100 to 100,000 µg/L	Not reported	No	**pH:** 7.6-8.2 **Temp:** 18.6°C **DO:** 6.9-7.5 mg/L **Hardness:** NR	Acetone	

Table 1-1. Summary of available acute fish toxicity studies for triphenyl phosphate (115-86-6)[a]									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**96-Hour LC50**	**Study Type**	**Concentration Range Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry[b]**	**Solvent**	**Comments on the Data**
Mayer et al., 1981 EG&G Bionomics, 1978a, b	Rainbow trout	400 µg/L	Static	Not reported	10	No	**pH:** 7.2 **Temp:** 12±1°C **DO:** NR **Hardness:** 272 mg/L	Not reported	Data were obtained from Mayer et al., 1981 and from unpublished data reported in TSCATS. Fish age, weight, and length and loading rate were not reported.
	Fathead minnow	660 µg/L	Static	3 concentrations; 280 to 2200 µg/L	10	No	**pH:** 6.3-7.5 **Temp:** 22±1°C **DO:** 2.5-8.7 mg/L **Hardness:** 28-44 mg/L	Triethylene glycol (up to 7.5 mL)	Data were obtained from Mayer et al., 1981 and from unpublished data reported in TSCATS. Fish age, weight, and length and loading rate were not reported.
	Sheeps-head minnow	Between 320 and 560 µg/L	Static	5 concentrations; 56 to 560 µg/L	10	No	**pH:** 7.9-8.1 **Temp:** 20±1°C **DO:** 3.8-6.3 mg/L **Hardness:** NR **Salinity**: 17 parts per thousand	Acetone	Data were obtained from Mayer et al., 1981 and from unpublished data reported in TSCATS. Fish age, weight, and length and loading rate were not reported.
Mayer and Ellersieck, 1986	Rainbow trout	370 µg/L	Static	Not reported	Not reported	Yes	**pH:** 7.4 **Temp:** 12°C **DO:** NR **Hardness:** 40 mg/L	Not reported	Results of analytical monitoring were not reported. General methods were reported in the publication that were not necessarily specific for the test on TPP.

Table 1-1. Summary of available acute fish toxicity studies for triphenyl phosphate (115-86-6)[a]									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**96-Hour LC50**	**Study Type**	**Concentration Range Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry[b]**	**Solvent**	**Comments on the Data**
	Channel catfish	420 µg/L	Static	Not reported	Not reported	Yes	**pH:** 7.5 **Temp:** 22°C **DO:** NR **Hardness:** 38 mg/L	Not reported	Results of analytical monitoring were not reported. General methods were reported in the publication that were not necessarily specific for the test on TPP.
	Fathead minnow	1,000 µg/L	Static	Not reported	Not reported	Yes	**pH:** 7.3 **Temp:** 22°C **DO:** NR **Hardness:** 44 mg/L	Not reported	Results of analytical monitoring were not reported. General methods were reported in the publication that were not necessarily specific for the test on TPP.
Palawski et al., 1983	Rainbow trout (0.11 g; 24 mm)	360 µg/L	Static	3 concentrations; 210, 240, and 290 µg/L	10	No	**pH:** NR **Temp:** NR **DO:** NR **Hardness:** NR	Not reported	TPP was 99% pure. The study followed U.S. EPA (1975) guidelines. Fry, 12 days past swim-up stage, were tested. An EC50 based on immobility, mortality, and loss of equilibrium of 300 µg/L was also determined from this study.

Table 1-1. Summary of available acute fish toxicity studies for triphenyl phosphate (115-86-6)[a]									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**96-Hour LC50**	**Study Type**	**Concentration Range Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry[b]**	**Solvent**	**Comments on the Data**
Sasaki et al., 1981	Goldfish (0.8-2.8 g) Killifish (0.1-0.2 g)	700 µg/L 1200 µg/L	Static Static	Not reported Not reported	7 to 9 7 to 9	No* *In a parallel study, ≈70% of TPP was present in water that contained goldfish after 96 hours.	**pH:** NR **Temp:** 25°C **DO:** NR **Hardness:** NR	Not reported	Neither goldfish nor killifish are recommended species for testing by OECD 203. Reporting deficiencies preclude an independent evaluation of data adequacy. Selected reporting deficiencies included: water chemistry values (pH, hardness, dissolved oxygen), identification of test concentrations, and use of a vehicle to facilitate dissolution. Spine deformation occurred at 1.1 mg/L.
Sitthichai-kasem., 1978	Rainbow trout sac-fry (0.081 g) Rainbow trout fingerlings (0.75 g)	389 µg/L 299 µg/L	Static Static	Control and 180-1000 µg/L Control and 180-1000 µg/L	10 10	No No	**pH:** 7.0-7.2 **Temp:** 12°C **DO:** 7.3-8.5 ppm **Hardness:** 40-48	Acetone Acetone	Fish were acclimated before exposure. Moribund and dead fish were counted at 24, 48, 72, and 96 hours.

[a]Studies that were either published in a foreign language or that were not readily AND that were not critical to the hazard assessment were not retrieved.
[b]Hardness reported as mg/L $CaCO_3$

Acute Toxicity to Freshwater and Marine/Estuary Invertebrates (OPPTS Harmonized Guidelines 850.1010 and 850.1035; OECD Guideline 202)

Conclusion:

- The available acute freshwater invertebrate toxicity data were judged adequate to meet the endpoint.
- The available acute marine/estuary invertebrate toxicity data were judged inadequate to meet the endpoint.
- Based on the environmental fate of TPP, additional data may be needed on sediment dwelling organisms. Currently available studies, although inadequate to meet the endpoint in this review, indicate that TPP may be toxic to sediment-dwelling organisms.

Basis for Conclusion:

Freshwater Organisms

The available data are summarized in Table 2. Four studies in daphnids were located. All studies used static conditions, and none of the available studies analytically confirmed the test concentrations. The reported EC50 values were consistent with each other and ranged from 1,000 to 1,350 µg/L. Sufficient detail was available from three of the four studies located to allow for an independent evaluation of data adequacy. Reporting deficiencies were noted in those three studies that included lack of identity of concentrations tested, TPP purity, concentration of solvent in the test solutions, and water hardness. In the remaining study (Ziegenfuss et al., 1986), even basic study design parameters were not reported. Due to these reporting deficiencies and on study design deficiencies (lack of analytical confirmation of the test concentrations), none of the currently available studies are independently sufficient to be used as the basis to satisfy the acute freshwater invertebrate toxicity endpoint. Collectively, however, the data appear adequate because the four studies that were located reported a narrow range of EC50 values, thus providing confidence in the reported effect levels.

Studies were also located on the toxicity of sediment-dwelling organisms. Two studies using the midge and one study using the scud were located. These studies indicate that sediment-dwelling organisms could be particularly sensitive to the toxicity of TPP. EC50 values ranged from 250 to 1,600 µg/L. All of the studies in sediment-dwelling organisms used static conditions, and none of the studies analytically confirmed the test concentrations. Based on the inconsistencies in the reported toxicity values and the lack of a study that analytically confirmed the test substance concentrations, the currently available data do not appear to be adequate to satisfy the acute toxicity endpoint for sediment-dwelling organisms. Based on the environmental fate of TPP, additional testing on sediment-dwelling organisms may be needed.

Marine/Estuarine Organisms

One acute toxicity study in mysid shrimp was located (Table 2). The study was a 96-hour static study that did not analytically confirm the test concentrations. The dissolved oxygen concentration in this study was <60% of saturation after the 96-hour exposure period. The LC50 from this study was between 180 and 320 µg/L; a discrete LC50 was not calculated. The available data in mysid shrimp do not appear to be adequate to satisfy the marine/estuarine invertebrate toxicity endpoint because only one publically available study was located, and it used static conditions, did not analytically confirm the test concentrations, and dissolved oxygen concentration in this study was below values recommended by standard guidelines. Because only one study was available, and it of questionable reliability, the marine/estuarine invertebrate toxicity endpoint does not appear to be satisfied by existing data.

Table 1-2. Summary of available acute invertebrate toxicity studies on triphenyl phosphate (115-86-6)									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**EC50 or LC50 (µg/L)**	**Study Type**	**Concentration Range Tested**	**No. of Organisms/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Ciba-Geigy Ltd., 1981b	Daphnid	48-hour: 1,350	Static	800-3,700 µg/L	20	No	**pH:** 8.6 **DO:** 7.0-7.2 mg/L **Temp:** 20±1°C **Hardness:** NR	DMF	Although reporting deficiencies were noted, the study conduct appears to be consistent with current standard guidelines. pH and dissolved oxygen were only measured at test termination and only at the lowest and highest test concentrations. TPP purity was not reported.
Food and Drug Research Labs, 1979	Daphnid	48-hour: 1,280	Static	180-3,200 µg/L	20	No	**pH:** 8.4-8.5 **DO:** 7.8-9.4 mg/L **Temp:** 20±0.5°C **Hardness:** 232 mg/L	Acetone	Although reporting deficiencies exist, the details that were reported appear to be consistent with current guidelines. Key deficiencies included lack of analytical monitoring of the test concentrations. TPP purity was not reported.

Table 1-2. Summary of available acute invertebrate toxicity studies on triphenyl phosphate (115-86-6)									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**EC50 or LC50 (µg/L)**	**Study Type**	**Concentration Range Tested**	**No. of Organisms/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Mayer et al., 1981 Analytical Bio Chemistry Labs, 1978	Daphnid	48-hour: 1,000	Static	Not reported	10	No	**pH:** 7.7-8.0 **DO:** 7.2-8.7 **Temp:** 19°C **Hardness:** <250 mg/L	Ethanol	Only 10 daphnids were exposed to each concentration. Otherwise, the details reported on the study conduct appear to be consistent with current standard guidelines. The concentrations tested were not identified. TPP purity was not reported.
Ziegenfuss et al., 1986	Daphnid	48-hour: 1,000	Static	Not reported	Not reported	No	**pH:** NR **DO:** NR **Temp:** NR **Hardness:** NR	Not reported	Even basic study design parameters were not available for evaluation.
Huckins et al., 1991	Midge	48-hour: 360	Static	60-1,000 µg/L	10	No	**pH:** NR **DO:** NR **Temp:** 22°C **Hardness:** NR	Acetone	Study reportedly followed U.S. EPA (1975) guidelines. Results from monitoring water quality parameters were not reported.
Ziegenfuss et al., 1986 Monsanto Env. Science Section, 1982	Midge	48-hour: 1,600	Static	125-2,000 µg/L	10	No	**pH:** 7.6-8.1 **DO:** 8.6-9.3 **Temp:** 21-23°C **Hardness:** 268-284 mg/L	Unspecified solvent	The NOAEC was 1,000 µg/L. The study followed U.S. EPA (1975) guidelines.

Table 1-2. Summary of available acute invertebrate toxicity studies on triphenyl phosphate (115-86-6)									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**EC50 or LC50 (µg/L)**	**Study Type**	**Concentration Range Tested**	**No. of Organisms/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Huckins et al., 1991	Scud	96-hour: 250	Static	10-560 µg/L	Not reported	No	**pH:** NR **DO:** NR **Temp:** 17°C **Hardness:** NR	Acetone	Study reportedly followed U.S. EPA (1975) guidelines. Reporting deficiencies preclude an independent evaluation of data adequacy.
Mayer et al., 1981 EG&G Bionomics. 1978c	Mysid shrimp	96-hour: >180 and <320	Static	56-560 µg/L	10	No	**pH:** 7.8-7.9 **DO:** 43%-56% of saturated **Temp:** 20±1°C **Hardness:** NR	Acetone (1 mL)	Dissolved oxygen was <60% of saturation. Standard guidelines indicate that dissolved oxygen concentration remain >60% saturation throughout the study.
Lo and Hsieh, 2000	Golden apple snail	72-hour: 38,200	Static	10-250 µg/L	30	Yes	**pH:** 7.5 **DO:** NR **Temp:** 26°C **Hardness:** NR	Not reported	Organisms were 35-40 days old at study initiation. Golden apple snail is not a common test organism.

Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)

Conclusion:

The available algal toxicity data were judged tentatively adequate to meet the endpoint, pending the availability of additional information from the studies that were not included in the published articles.

Basis for Conclusion:

Seventy-two-hour static studies in *Selenastrum capricornutum*, *Scenedesmus subspicatus*, *Chlorella vulgaris* (Millington et al., 1988), a 96-hour static study in *Selenastrum capricornutum* (Mayer et al., 1981), and a 22-day study in *Ankistrodesmus falcatus* were located. These data are summarized in Table 3. Taken together, these data may be adequate; however, additional information is needed from the studies before they can be used as the basis for satisfying the algal toxicity endpoint.

Millington et al. (1988) conducted a series of 72-hour static studies that were designed to evaluate the influence of various standard test media (OECD, U.S. EPA, and Bold's basal) on the toxicity of triphenyl phosphate to three algal species, *Selenastrum capricornutum*, *Scenedesmus subspicatus*, and *Chlorella vulgaris*. These static studies followed OECD Guideline 201. Five concentrations ranging from 0.05 to 5 mg/L were tested in triplicate cultures. The test concentrations were not analytically confirmed. The resulting 72-hour NOAEC values ranged from 0.1 to 1 mg/L depending on the algal species tested and the test media used. EC50 values were not derived, and raw data were not available to allow for an independent calculation of EC50 values. Overall, the studies appear to have been adequately conducted. Deficiencies in the data included reporting deficiencies (e.g., raw data, water quality values determined during the study, and growth of control replicates), lack of analytical confirmation of the test concentrations, and lack of EC50 determinations. Provided that the missing study details can be obtained and that an EC50 value can be determined, these data appear adequate to satisfy the algal toxicity endpoint.

Mayer et al. (1981) conducted a 96-hour static test in *Selenastrum capricornutum*. Many details from this study were obtained from the unpublished report submitted to EPA (EG&G Bionomics, 1978d). Five concentrations that ranged from 0.6 to 10 mg/L were tested. Test concentrations were not analytically confirmed. An EC50 of 2 mg/L (95% confidence interval of 0.6-4 mg/L) was derived from this study. A clear NOAEC was not established because a 4% decrease in cell number and a 15% decrease in chlorophyll-α concentration was observed at the lowest concentration of 0.6 mg/L. Although the study appears to have been adequately conducted, initial and final cell concentrations of controls or treated cultures were not reported. Provided that these study details can be obtained, the 96-hour EC50 reported in this study appears to be adequate to satisfy the short-term algal toxicity endpoint. It should be noted that the EC50 determined from this study is at the approximate water solubility limit of TPP (2

mg/L). The lack of a clear NOAEC precludes the use of this study as the sole basis to satisfy the chronic algal toxicity endpoint. However, the low magnitude of the effect observed at 0.6 mg/L in this study appears to be consistent with the NOAEC and LOAEC values reported in the other algal toxicity studies (Mayer et al., 1981; Wong and Chau, 1984).

Wong and Chau (1984) reported a 22-day NOAEC of 0.1 mg/L and a LOAEC of 0.5 mg/L based on algal growth in *Ankistrodesmus falcatus*. Sufficient detail was not reported in this study to allow for an independent evaluation of data adequacy. Virtually no details on the methods or results were reported. The study also reported 4-hour IC50 values based on incorporation of radiolabeled CO_3 as an indication of primary productivity. These IC50 values ranged from 0.2 to 0.5 mg/L in *Ankistrodesmus falcatus*, *Scenedesmus quadricauda*, and Lake Ontario phytoplankton. The 4-hour IC50 values derived from this study were not considered adequate for this hazard assessment because TPP concentrations that caused reductions in primary productivity after 4 hours of exposure did not affect reproduction or growth during a separate 22-day study conducted by the same laboratory. The NOAEC and LOAEC values derived from the 22-day study were considered inadequate to satisfy the chronic algal toxicity endpoint because sufficient detail was not available on the study design or results to allow for an independent evaluation of study adequacy. However, if data are available to demonstrate that the study was adequately conducted, then the data may be sufficient to satisfy the chronic algal toxicity endpoint. Further, if concentration-response data are available to allow for a calculation of a 96-hour EC50, then the data may also be used to support the short-term algal toxicity endpoint.

Taken together, it appears that sufficient data are available to satisfy the algal toxicity endpoint; however, additional information is needed before the currently available data can be considered adequate.

Table 1-3. Summary of available algal toxicity studies for triphenyl phosphate								
			Selected Study Design Parameters					
Study Reference	**Species Tested**	**EC50, NOAEC, and LOAEC**	**Study Type**	**Concentration Range Tested**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Millington et al., 1988	*Selenastrum capricornutum*	**EC50**: NR **72-hour NOAEC:** 0.1-1 mg/L* **72-hour LOAEC:** 0.5-5 mg/L* *A range of NOAEC and LOAEC values is reported because tests were performed using three different test media, and the toxicity of TPP was influenced by the test media used.	Static	0.05-5 mg/L	No	**pH:** NR **Temp:** 22°C **DO:** NR **Hardness:** NR	Acetone (<100 uL/L)	The 72-hour LOAEC was between 0.5 and 5 mg/L depending on the test medium. EC50 values were not determined. Test substance purity was not reported.

Table 1-3. Summary of available algal toxicity studies for triphenyl phosphate								
			Selected Study Design Parameters					
Study Reference	**Species Tested**	**EC50, NOAEC, and LOAEC**	**Study Type**	**Concentration Range Tested**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Millington et al., 1988	*Scenedesmus subspicatus*	**72-hour NOAEC:** 0.1-1 mg/L* **72-hour LOAEC:** 0.5-5 mg/L. *A range of NOAEC and LOAEC values is reported because tests were performed using three different test media, and the toxicity of TPP was influenced by the test media used.	Static	0.05-5 mg/L	No	**pH:** NR **Temp:** 22°C **DO:** NR **Hardness:** NR	Acetone (<100 uL/L)	The 72-hour LOAEC was between 0.5 and 5 mg/L depending on the test medium. EC50 values were not determined. Test substance purity was not reported.
Millington et al., 1988	*Chlorella vulgaris*	**72-hour NOAEC:** 1 mg/L **72-hour LOAEC:** 5 mg/L The toxicity of TPP to Chlorella vulgaris was not affected by test medium.	Static	0.05-5 mg/L	No	**pH:** NR **Temp:** 22°C **DO:** NR **Hardness:** NR	Acetone (<100 uL/L)	The 72-hour LOAEC was 5 mg/L using three different test mediums. EC50 values were not determined. Test substance purity was not reported.

Table 1-3. Summary of available algal toxicity studies for triphenyl phosphate								
			Selected Study Design Parameters					
Study Reference	**Species Tested**	**EC50, NOAEC, and LOAEC**	**Study Type**	**Concentration Range Tested**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Mayer et al., 1981 EG&G Bionomics, 1978d	*Selenastrum capricornutum*	96-hour: 2 mg/L 95% CI: 0.6-4 96-hour LOAEC: 0.6 mg/L 96-hour NOAEC: Not observed	Static	0.6-10 mg/L	No	**pH:** 7.0-8.2 **Temp:** 24±1°C **DO:** NR **Hardness:** NR	Acetone: 0.05 mL	The methods reportedly followed U.S. EPA, 1971 guidelines. Control growth was not reported. A NOAEC did not appear to be observed because a 15% decrease in chlorophyll α and 4% decrease in cell number was observed after 96 hours at the lowest concentration of 0.6 mg/L. Test substance purity was not reported.

Table 1-3. Summary of available algal toxicity studies for triphenyl phosphate								
			Selected Study Design Parameters					
Study Reference	**Species Tested**	**EC50, NOAEC, and LOAEC**	**Study Type**	**Concentration Range Tested**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Wong and Chau, 1984	*Ankistrodesmus falcatus*	22-day NOAEC: 0.1 mg/L 22-day LOAEC: 0.5 mg/L	Static	0.05-5 mg/L	No	**pH:** NR **Temp:** NR **DO:** NR **Hardness:** NR	5 µL	Use of standard guidelines was not indicated. Duplicate cultures were used. Virtually no study details were included in the published article, precluding an independent evaluation of data adequacy. Growth of *A. falcatus* was determined spectrophotometrically. Test substance purity was not reported.

Chronic Toxicity to Fish (OPPT Harmonized Guideline 850.1400; OECD Guideline 210)

Conclusion:

The available chronic toxicity data for freshwater or saltwater fish were judged inadequate to meet the endpoint.

Basis for Conclusion:

Freshwater Fish

The available data are summarized in Table 4. Two chronic studies in fish were located. Both studies were published in Mayer et al. (1981). The study in fathead minnows reported a NOAEC of 87 µg/L and a LOAEC of 230 µg/L. The study used flow-through conditions and analytically confirmed the test concentrations; however, the study is considered invalid due to the large variation in measured concentrations (55-170 µg/L at the NOAEC and 140-390 µg/L at the LOAEC). The study in rainbow trout is considered to be inadequate because the highest concentration tested was 1.4 µg/L, a concentration that did not elicit any effects. Also, the measured concentrations were not given. Therefore, validity of the test could not be independently evaluated.

Saltwater Fish

No chronic toxicity studies in saltwater fish species were located.

Table 1-4. Summary of available chronic fish toxicity studies for triphenyl phosphate (115-86-6)									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**NOAEC/ LOAEC**	**Study Type**	**Concentration Range Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Mayer et al., 1981	Rainbow trout	90-day LOAEC: >1.4 µg/L	Flow-through (20 L/hour)	Nominal: 0.22, 0.38, 0.44, 0.64, 0.91, 1.2, and 1.4 µg/L Measured concentrations not reported	NR, but at least 10 based on the number of fish subjected to vertebrae pathology exams.	Yes (mean measured concentrations were within 62% of nominal)	**pH:** 7.2 **Temp:** 12±1°C **DO:** NR **Hardness:** 272 mg/L	Unidentified solvent at <0.05 mL/L	Measured concentrations were not reported. Endpoints evaluated included mortality, behavior, weight, length, vertebrae pathology, and eye pathology. Test substance purity was not reported.
Mayer et al., 1981 EG&G Bionomics, 1979	Fathead minnow	30-day NOAEC: 87 µg/L LOAEC: 230 µg/L	Flow-through (20 L/hour)	Mean measured: 0, 2.8, 12, 36, 87, and 230 µg/L	60 eggs 40 fry	Yes	**pH:** 6.8-7.6 **Temp:** 25±1°C **DO:** >75% saturation **Hardness:** 38-44 mg/L	TEG, unspecified concentration	Results based on fry survival; other parameter were not affected by treatment. Measured concentrations varied substantially and ranged from 55 to 170 µg/L at the NOAEL and from 140 to 390 µg/L at the LOAEL. Test substance purity was not reported.

Chronic Toxicity to Aquatic Invertebrates (OPPTS Harmonized Guidelines 850.1300 and 850.1350; OECD Guideline 211)

Conclusion:

The available chronic toxicity data for freshwater or saltwater invertebrates were judged inadequate to meet the endpoint.

Basis for Conclusion:

Freshwater and Saltwater Species

No chronic toxicity studies in freshwater or saltwater invertebrate species were located.

Acute Oral, Acute Dietary, and Reproductive Toxicity in Birds (OPPTS Harmonized Guidelines 850.2100, 850.2200, and 850.2300; OECD Guidelines 205 and 206)

Conclusion:

The available acute oral, acute dietary, and reproduction toxicity data for birds were judged inadequate to meet the endpoints.

Basis for Conclusion:

No toxicity studies in relevant bird species were located.

Earthworm Toxicity (OPPTS Harmonized Guideline 850.6200)

Conclusion:

The available earthworm toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No toxicity studies in earthworms were located.

Physical/Chemical Properties

Triphenyl phosphate
CAS 115-86-6
MF $C_{18}H_{15}O_4P$
MW 326.29
SMILES c1ccccc1OP(=O)(Oc2ccccc2)Oc3ccccc3

Physical/Chemical Properties

Water Solubility (mg/L):
Conclusion: The available water solubility data are adequate.
Basis for Conclusion: The two best-documented studies, including one that followed an OECD-guideline test, report solubilities of 1.9-2.1 ppm.

Solubility (mg/L)	Reference
Insoluble	Budavari, 2001 (The Merck Index); Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials); Lide and Milne, 1995 (CRC Handbook of Data on Common Organic Compounds); Lewis, 1997 (Hawley's Condensed Chemical Dictionary)
1.90	Saeger et al., 1979 (shake-flask method using Milli-Q purified water); Huckins et al., 1991; SRC, 2004 (PHYSPROP database)
2.1±0.1	Ofstad and Sletten, 1985 (OECD Guideline 105 (column-elution) from a mixture at 25°C)
1.4-1.6	Howard and Deo, 1979 (in buffered distilled water, pH 4.4-9.5 at 21°C)
0.2-0.3	Howard and Deo, 1979 (in filtered lake or river water, pH 7.8-8.2 at 21°C)
0.73	Hollifield, 1979
0.714	Kuhne et al., 1995

Log K_{ow}:
Conclusion: The available log K_{ow} data are adequate.
Basis for Conclusion: A variety of reputable studies report log K_{ow} values in the range of 4.5-4.7.

Log K_{ow}	Reference
4.59	SRC, 2004 (PHYSPROP database); Hansch et al., 1995
3.9	Unpublished data cited in Bengtsson et al., 1986
4.61	Mayer et al., 1981; Huckins et al., 1991

Log K_{ow}	Reference
4.63	Saeger, 1979 (shake-flask method)
4.67	FMC Industrial Chemical Division, 1979 (shake-flask method)
4.58	Ciba-Geigy, Ltd., 1982
4.62	Monsanto Chemical Co., 1982a Monsanto Chemical Co., 1982b

Melting Point:
Conclusion: The available melting point data are adequate.
Basis for Conclusion: Melting point values within the range of 49-52°C are reported in a variety of reputable secondary sources.

Melting Point (°C)	Reference
50	Lewis, 1997 (Hawley's Condensed Chemical Dictionary); SRC, 2004 (PHYSPROP database)
49-50	Budavari, 2001 (The Merck Index); Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)
50.5	Lide and Milne, 1995 (CRC Handbook of Data on Common Organic Compounds)
50.4	Ciba-Geigy, Ltd., 1982
50-52	Sigma-Aldrich, 2003-2004
49.5-50	Dorby and Keller, 1957

Boiling Point:
Conclusion: The available boiling point data are adequate.
Basis for Conclusion: Most sources report reduced-pressure boiling points of 244-245°C at 10 or 11 torr for triphenyl phosphate. Perry and Green (1984) report a boiling point of 413.5°C at 760 torr, which is consistent with the boiling point extrapolated using the Clausius-Clapeyron Equation and the parameters measured by Dorby and Keller (1957). It has also been reported that triphenyl phosphate decomposes at or near its boiling point (Dorby and Keller, 1957).

Boiling Point (°C/torr)	Reference
245/11	Lewis, 1997 (Hawley's Condensed Chemical Dictionary); SRC, 2004 (PHYSPROP database); Budavari, 2001 (The Merck Index); Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials); Lide and Milne, 1995 (CRC Handbook of Data on Common Organic Compounds)

Boiling Point (°C/torr)	Reference
244/10	Sigma-Aldrich, 2003-2004
413.5/760	Perry and Green, 1984
414/760 dec. >410	Dorby and Keller, 1957 (Extrapolated according to the Clausius-Clapeyron Equation using experimentally-derived parameters: Log P(torr) = -A/T + C, where T is in Kelvin, A= 4253, C=9.07) The decomposition temperature was reported in this same paper.

Vapor Pressure (torr):
Conclusion: The available vapor pressure data are adequate.
Basis for Conclusion: Results from the Clausius-Clapeyron equation as measured by Dorby and Keller (1957) are consistent with the vapor pressure data provided in Perry and Green (1984).

Vapor Pressure (torr/°C)	Reference
6.28×10^{-6}/25 0.90/193.5 8.6/249.8 84.7/322.5 354/379.2	SRC, 2004 (PHYSPROP database, extrapolated); Dorby and Keller, 1957 (Extrapolated according to the Clausius-Clapeyron Equation using experimentally-derived parameters Log P (torr) = -A/T + C, where T is in Kelvin, A= 4253, C=9.07)
1/193.5	Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)
1/193.5 5/230.4 10/249.8 20/269.7 40/290.3 60/305.2 100/322.5 200/349.8 400/379.2 760/413.5	Perry and Green, 1984

Odor:
Conclusion: The odor of this compound has been adequately characterized.

Odor	Reference
Odorless	Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)

Odor	Reference
Slight aromatic odor resembling phenol Phenol-like odor	HSDB, 2004

Oxidation/Reduction: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability:
Conclusion: The flammability (as the flash point) has been adequately characterized.
Basis for Conclusion: Similar values are reported in several reputable secondary sources.

Flash Point	Reference
435°F (223°C)	Sigma-Aldrich, 2003-2004
428°F (220°C)	Lewis, 1997 (Hawley's Condensed Chemical Dictionary)
428°F (cc)	Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption:
Conclusion: The UV/VIS absorption of this compound has been adequately characterized.
Basis for Conclusion: Absorption maxima and coefficients are available for this compound in three solvent systems, and are reported in reputable sources.

Wavelength	Absorption Coefficient	Solvent	Reference
268 nm	912	Hexane	Lide and Milne, 1995 (CRC Handbook of Data on Common Organic Compounds)
262 nm	1175	Hexane	Lide and Milne, 1995 (CRC Handbook of Data on Common Organic Compounds)

Wavelength	Absorption Coefficient	Solvent	Reference
256 nm	955	Hexane	Lide and Milne, 1995 (CRC Handbook of Data on Common Organic Compounds)
288 nm	7.03×10^3 l/mol-cm	MeOH, KOH	Sadtler Standard Spectra, no date No absorption above 320 nm
237 nm	2.62×10^4 l/mol-cm	MeOH, KOH	Sadtler Standard Spectra, no date No absorption above 320 nm
268.5 nm	2.36×10^3 l/mol-cm	MeOH	Sadtler Standard Spectra, no date No absorption above 290 nm
273.5 nm	2.36×10^3 l/mol-cm	MeOH, HCl	Sadtler Standard Spectra, no date No absorption above 290 nm
218 nm	1.78×10^4 l/mol-cm	MeOH, HCl	Sadtler Standard Spectra, no date No absorption above 290 nm

Viscosity: No data

Density/Relative Density/Bulk Density:
Conclusion: The density of this compound has been adequately characterized.
Basis for Conclusion: Similar values for density and relative density are available for this material at different temperatures. Bulk density is also reported in a reputable source.

Density	Reference
1.268 g/cc (60°C)	Lewis, 1997 (Hawley's Condensed Chemical Dictionary)
Bulk: 10.5 lb/gal	Lewis, 1997 (Hawley's Condensed Chemical Dictionary)
1.2055 g/cc (50°C)	Lide and Milne, 1995 (CRC Handbook of Data on Common Organic Compounds)
Specific gravity, 25°C: 1.2	Cited from Midwest Research Institute, 1979 in Huckins et al., 1991

Dissociation Constant in Water:
Conclusion: This endpoint is adequately characterized
Basis for Conclusion: TPP is not expected to dissociate under environmentally important conditions.

Henry's Law Constant:
Conclusion: The Henry's Law Constant has been adequately characterized for this compound.

Basis for Conclusion: One measured and one estimated value are reported in the literature, and are in reasonable agreement with one another. The estimated value is based on measured vapor pressure and water solubility data.

Henry's Law Constant	**Reference**
1.2×10^{-5} atm-m^3/mole	Cited from Mayer et al., 1981 in Huckins et al., 1991
3.31×10^{-6} atm-m^3/mole	SRC, 2004 (PHYSPROP database, estimated from vapor pressure and water solubility)

Environmental Fate

Bioconcentration

Fish:
Conclusion: The bioconcentration of TPP has been adequately measured in rainbow trout, goldfish, and killifish.
Basis for Conclusion: Similar BCFs are reported for rainbow trout in two key 90-day studies (Monsanto Chemical Company, 1982c; Mayer, 1981). Other studies (Muir, 1984; Muir et al., 1980) are available, but exhibit significant scatter in the data for rainbow trout. The data reported by this author are based on uptake times of 24 hours or less, and may not represent equilibrium conditions. The highest kinetic BCF value reported by this author, 18,960, may be irrelevant because it was calculated based on a "slow" rate of elimination of residual radioactivity by the fish. According to this study, the fish eliminated 98-99% of the initial load of radioactivity (from the uptake of ^{14}C-labeled TPP) in 9 days. The remaining 1-2% was eliminated more slowly. Because only the total amount of radioactivity was measured without identifying specific radioactive compounds present, it is not certain that the residual radioactivity was due to unchanged TPP and not to metabolites.

Adequate studies are available for goldfish and killifish (Sasaki et al., 1981, 1982). In these two studies, the authors measured BCFs under both static and flow-through conditions, with varying TPP concentrations, and over differing lengths of time. The authors found that the measured BCFs for killifish were largely independent of these parameters.

Reference	Species	BCF	Key Design Parameters				Comments
			Exp. Type	Range (ppb)	Study Length	T (°C)	
Monsanto Chemical Co, 1982c	Rainbow Trout	271			90 days		
Mayer, 1981	Rainbow Trout	132-364	Flow-through	0.22, 1.4	90 days		Elimination half life 0.54 days
Muir, 1984	Rainbow Trout	573 931 1368	Static	3.1-50.4	1-24 hours		

Reference	Species	BCF	Key Design Parameters				Comments
			Exp. Type	Range (ppb)	Study Length	T (°C)	
Muir et al., 1980	Rainbow trout	2,590 (fast) 18,960 (slow)	Static	50	6 hours	10	River water mixed with dechlorinated tap water, pH 8.12-8.36. Fish were exposed to TPP+water for 6 hours then transferred to clean water. BCF expressed as k(uptake)/k(elimination). k(uptake) = 46.36/hour. Elimination rate slows down at about 9 days with 98-99% eliminated. k(fast)=0.0179/hour; k(slow)=0.00245/hour.
Muir, 1984	Fathead minnow	218 561 1,743	Static	0.8-34.9	1-24 hours		
Sasaki et al., 1981	Killifish	250-500	Static	250 initial	2-3 days	25	
Sasaki et al., 1981	Goldfish	110-150	Static	250 initial	2-3 days	25	
Sasaki et al., 1982	Killifish	189±90 193±79 84±32	Flow-through (all)	30 20 10	35 days 32 days 18 days	25	BCF is independent of concentration, continuous (flow-through) results correlate to static results (Sasaki, 1981). BCF of phosphate esters tested correlate with Log K_{ow}.

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism:
Conclusion: The metabolism rate in fish has not been adequately characterized, and the metabolites have not been adequately identified.
Basis for Conclusion: None of the studies summarized here identifies any metabolites. All of the studies were designed to monitor the levels of TPP (as either the natural isotope or ^{14}C labeled) in fish to document the rates of uptake and elimination. Although these studies provide information about the rate of elimination of TPP and/or its carbon-containing metabolites from fish, none of these studies adequately describe how TPP is metabolized and what products are formed.

Species	Rate	Comment	References
Rainbow trout	98-99% eliminated in 9 days Rate constant = 0.0179/hour Slower elimination after 9 days Rate constant = 0.00245/hour		Muir et al., 1980
Rainbow trout	Elimination half-life is 0.54 days		Mayer et al, 1981
Killifish	Elimination half-life 1-2 hours		Sasaki et al., 1982
Killifish	Apparent metabolism is much faster in killifish than in goldfish.	Concentration of TPP in water decreased in the presence of fish. 0% applied TPP remains in the water after ~72 hours. Control (no fish) has no change in TPP concentration.	Sasaki et al., 1981
Goldfish	Apparent metabolism is much slower than in killifish.	60-65% applied TPP remains in the water after 100 hours in presence of goldfish.	Sasaki et al., 1981

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in water:
Conclusion: The available studies do not adequately describe the photolysis behavior of TPP in water under normal environmental conditions. However, this endpoint appears to be adequately characterized.

Basis for Conclusion: Since triphenyl phosphate does not absorb light at wavelengths above 290 nm, direct photolysis in sunlight is not expected. Three published photolysis studies were

located. Similar rate constants and half-lives are reported. For two of these studies, the light from the lamps was not filtered to block wavelengths <290 nm in either experiment (Hg lamps emit at 254 nm), and the results are not environmentally relevant. For the third, the rate constant for photolysis was found to be 34 times greater than phenol with a quantum yield of 0.290 at 254 nm (Wan et al., 1994).

Photolysis of Aqueous Triphenyl Phosphate Irradiated with Low-Pressure Hg Lamps		
Initial concentration: 0.1 ppm pH: 3 and 10	Pseudo 1st-order rate constant was >40/hour ($t_{1/2}$ <1.04 minutes) at both pH levels. Some hydrolysis may occur at pH 10	Ishikawa et al., 1992
Initial concentration: 3.0×10^{-4} M pH: 3.4 Time: 6 hours	TPP removed: 100% PO_4^{3-} detected: 60% of theoretical max. Phenol detected: 0%	Ishikawa et al., 1992
Initial concentration: 3.0×10^{-4} M pH: 12 Time: 6 hours	TPP removed: 100% PO_4^{3-} detected: 60% of theoretical max. Phenol detected: 9% of theoretical max.	Ishikawa et al., 1992
Initial concentration: 1.0 ppm	Rate constant: 1.9×10^{-2}/second Half-life: 0.6 minutes	Hicke and Thiemann, 1987

Photolysis in Soil: No data

Aerobic Biodegradation:
Conclusion: The biodegradation of TPP under aerobic conditions has been adequately characterized.
***Basis for Conclusion*:** The key study was performed according to OECD guidelines. Additional studies are available, in which TPP is degraded under a variety of conditions. TPP was also found to be ready biodegradable in experimental studies.

Study Type/ Method	**Innoculum**	**Acclim.**	**Degradation**	**Time**	**Comments**	**Reference**
OECD 303A	Activated sludge	14 days	93.8% as DOC removal	20 days	Initial concentration 5 ppm, emulsified with octanol	Ciba-Geigy, Ltd., 1983
SCAS	Activated sludge		>95%	24 hours		Monsanto Chemical Co., 1980
River die-away			50%	2-4 days		Monsanto Chemical Co., 1980

Study Type/ Method	Innoculum	Acclim.	Degradation	Time	Comments	Reference
CO_2 evolution	Activated sludge	14 days	82%	27 days	Initial concentration 22 ppm	Mayer et al., 1981
CO_2 evolution	Activated sludge	14 days	61.9% 81.8%	7 days 28 days	Initial concentration 18.3 ppm	Saeger et al., 1979
Simulated biological treatment/ SCAS	Activated sludge w/ domestic sewage feed		95%	24 hours		Mayer et al., 1981
Simulated biological treatment/ SCAS	Activated sludge w/ domestic sewage feed		93-96%	24 hours	12-week test duration, acclimation time not reported	Saeger et al., 1979
River die-away	River/lake water	20-day lag time	100% as TPP removal by GC analysis	7-8 days	Seneca River water pH 8.2, Lake Onondaga water pH 7.8, Lake Ontario water pH 8.2, all NY sources; hydrolysis may interfere with measurement at higher pH	Howard and Deo, 1979
River die-away	Mississippi River water		50% primary biodegradation	2-4 days	Initial concentration 0.05 ppm	Mayer et al, 1981
River die-away	Mississippi River water		100%	1.75 days	Initial concentration 1.0 ppm	Saeger et al., 1979
MITI II	Sewage sludge		83-94%	28 days		Chemicals Inspection & Testing Institute, 1992

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis:
Conclusion: The pyrolysis products of triphenyl phosphate have not been adequately described.
Basis for Conclusion: No formal pyrolysis studies have been located in the literature.

Pyrolysis Products	Reference
Products include phosphorous oxide	Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)

Hydrolysis as a Function of pH:
Conclusion: The hydrolysis data are adequate.
Basis for Conclusion: Triphenyl phosphate is rapidly hydrolyzed at high pHs, more slowly hydrolyzed at neutral pH, and only very slowly hydrolyzed at acidic pHs. The rates measured under alkaline conditions (pH ~9) are in good agreement with one another, and the rates measured under acidic conditions (pH ~5 or lower) are in reasonable agreement with one another. The results for hydrolysis at pH 7 have been reported to be 19 days, 1.3 years, and 406 days. There is no apparent reason for this discrepancy in values. It appears that the half-life of 19 days was measured once (Mayer et al., 1981) and has then been repeated in other sources. The longer half-life (ca. 1.3 years) has been reported (within acceptable experimental error) in two independent studies (Mabey and Mill, 1978), and is consistent with the observation in Howard and Deo (1979) that the half-life at pH 6.7 was too slow for accurate measurement over the course of the study (14 days).

$T_{1/2}$	pH	Temp.	Comment	Reference
19 days 3 days	7 9	25°C		Mayer et al., 1981
7.5 days 1.3 days	8.2 9.5	21°C	Half-life was too slow for accurate measurement at pH 4.5 and 6.7. Diphenyl phosphate was the only hydrolysis product identified	Howard and Deo, 1979
1.3 years	7	25°C	Rate constant = 1.7×10^{-9}/sec at pH 7	Mabey and Mill, 1978
>28 days 19 days 3 days	5 7 9			Monsanto Chemical Co., 1980
366 days 406 days <5 days	3 7 9	20°C		Ciba-Geigy, Ltd., 1984
630 days 1,125 days <10 days	3 7 9	10°C		Ciba-Geigy, Ltd., 1984

$T_{1/2}$	pH	Temp.	Comment	Reference
28 days 19 days 3 days	5 7 9	25°C		Mayer et al., 1981, cited in Anderson et al., 1993

Sediment/Water Biodegradation:
Conclusion: The biodegradation of triphenyl phosphate in the presence of pond and/or river sediment under various conditions has been adequately characterized.
Basis for Conclusion: Biodegradation of TPP has been studied under a variety of conditions and temperatures in the presence of both river and pond sediment.

Sediment	Temp.	$T_{1/2}$	Comments	Reference
Pond soil	25	50-60 days	Aerobic conditions. Sediment is described to be hydrosoil from a small pond. Initial concentration, 0.05 ppm Major product is diphenyl phosphate.	Muir et al., 1989
Pond sediment	25 10 2	2.8 days 2.8 days 11.9 days	Static conditions (air/oxygen neither excluded nor added during the test). Sediment was collected from a eutrophic farm pond near Winnipeg, Manitoba. Initial TPP concentration 0.10 µg/mL. Sediment:water ratio 1:10.	Muir et al., 1989
River sediment	25	7.0 days	Static conditions (air/oxygen neither excluded nor added during the test). Sediment was collected from the Red River near Winnipeg, Manitoba. Initial TPP concentration 0.10 µg/mL. Sediment:water ratio 1:10.	Muir et al., 1989
Pond sediment	25	56.7%, 3 days* 13.1%, 40 days*	Aerobic conditions (respirometer, aerated). Initial TPP concentration 0.05 µg/mL Sediment:water ratio 1:20 *Half-life not reported. Values are % TPP remaining over time.	Muir et al., 1989
River sediment	25	68.9%, 3 days* 10.3%, 40 days*	Anaerobic conditions (respirometer, under N_2). Initial TPP concentration 0.05 µg/mL Sediment:water ratio 1:20 *Half-life not reported. Values are % TPP remaining over time.	Muir et al., 1989

Soil Biodegradation with Product Identification:
Conclusion: The biodegradation rate of triphenyl phosphate in soil has been adequately characterized under aerobic and anaerobic conditions. The biodegradation products have been adequately characterized.

Biodegradation of Triphenyl Phosphate in a Loamy Sand Soil at 20°C					
	Percent TPP Remaining Over Time, HPLC				
Conditions	**13 Days**	**32 Days**	**60 Days**	**101 Days**	**Metabolites Identified**
Aerobic	69.3	46.6	30.4	20.2	Diphenyl phosphate, CO_2
Anaerobic		50.2	35.4	31.4	Diphenyl phosphate, CO_2, phenol
Reference: Anderson et al., 1993					

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption:
Conclusion: The K_{oc} has been adequately characterized in a variety of soil types.

K_{oc}	Soil Type	Reference
2514	silty clay	Anderson et al., 1993
3561	loamy sand	All measurements were made at 20°C.
2756	silt loam	

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Flame Retardant Alternatives

Tris(2-Chloroisopropyl) Phosphate

Draft Hazard Review

December 2004

Tris(2-chloroisopropyl)phosphate:
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	✓
Dermal	✓
Inhalation	✓
Eye irritation	✓
Dermal irritation	✓
Skin sensitization	
Subchronic Toxicity	
28-Day oral	
90-Day oral	*
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	*
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✓
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	✓
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	*
DNA damage and repair	
Other	

Tris(2-chloroisopropyl)phosphate:
Data Availability Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	✓
Octanol/water partition coefficient	✓
Oxidation/reduction	
Melting point	✓
Boiling point	✓
Vapor pressure	✓
Odor	✓
Oxidation/reduction chemical incompatibility	
Flammability	✓
Explosivity	
Corrosion characteristics	
pH	✘
UV/visible absorption	
Viscosity	✓
Density/relative density/bulk density	✓
Dissociation constant in water	✘
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	✓
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	✓
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	*
Hydrolysis as a function of pH	*
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	✓
Daphnia acute EC50	✓
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	*
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	✓
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm EC50, LC50, NOAEC, LOAEC	

Chemical Identity

2-Propanol,1-chloro-, phosphate (3:1)
Synonyms tris(2-chloroisopropyl) phosphate; tris(1-chloro-2-propyl) phosphate; TCPP
CAS 13674-84-5
MF $C_9H_{18}Cl_3O_4P$
MW 327.57
SMILES ClCC(C)OP(=O)(OC(C)CCl)OC(C)CCl

Note on the identities of substances tested for human health endpoints: According to the UNEP (no date) SIAR, tris(2-chloroisopropyl) phosphate was manufactured to a purity of about 75% +/-10%, with major impurities being bis(1-chloro-2-propyl)-2-chloropropyl phosphate (20-30%) and bis (2-chloropropyl)-1-chloro-2-propyl phosphate (3-5%). Tested commercial products, Fyrol PCF and Antiblaze 80, had similar compositions and purity (UNEP, no date); tris(2-chloroisopropyl) phosphate was the major component (NRC, 2000).

A recent MSDS for Fyrol PCF lists a composition of 99.5% tris(2-chloroisopropyl) phosphate (Akzo Nobel, 2002). Thus, the composition of this commercial product may have changed, but the pure product is not likely to have been used in the available studies, which are not recent.

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401).

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint..

Basis for Conclusion:

Several studies on materials containing a large proportion of tris(2-chloroisopropyl) phosphate are consistent with guidelines and indicate acute oral LD50 values exceeding 1,000 mg/kg in rats.

Critical Studies:

Type: Acute oral toxicity
Species, strain, sex, number: Rat, CD, 5/sex/dose for main study
Doses: 2,500, 3,200, 4,000, and 5,000 mg/kg for main study

Purity: Huntingdon (1987) report names the test material trichloropropyl phosphate. According to product data sheet (Courtalds, 1988), 'trischloropropyl phosphate' is a synonym for trischloroisopropyl phosphate (90-95% isopropyl and 5-10% n-propyl phosphates).
Vehicle: None for pilot study, corn oil for main study
Method: Doses were chosen based on results of a pilot study (2/sex/dose) for rats tested at 2,000 or 4,000 mg/kg and observed for 5 days. In the main study after dosing, rats were observed daily for clinical signs, and body weights were recorded on day 1, 8, and 15 (for survivors) or premature death, after which gross necropsy was performed.
Results: Most deaths occurred within hours of dosing and all within the first 2 days. Mortality within 14 days was 0/5, 0/5, 5/5, and 3/5 for males and 0/5, 1/5, 5/5, and 4/5 for females in the lowest-to-highest dose groups, respectively. Clinical signs observed in most animals included piloerection, hunched posture, abnormal (waddling) gait, lethargy, decreased respiratory rate, pallor of extremities, increased salivation; ptosis was observed in most rats at ≥3,200 mg/kg and clonic convulsions at ≥4,000 mg/kg. No compound-related gross lesions were found at terminal necropsy. The acute oral LD50 values were 3,600 mg/kg (range 3,300-3,900 mg/kg) for male and female rats combined, 3,800 mg/kg (range 3,300-4,500 mg/kg) for males, and 3,400 mg/kg (range 3,000-3,900 mg/kg) for female rats.
Reference: Huntingdon, 1987 for Courtalds Chemicals

Type: Acute oral toxicity
Species, strain, sex, number: Rat, CD Sprague-Dawley, 1 or 5/sex/dose for 6 doses between 320 and 5,000 mg/kg. Eight other doses tested in one sex: 4 or 5 males or 1 or 5 females.
Doses: 320, 500 (females only), 630, 700 (females only), 1,000, 1,250, 1,300 (males only), 1,400 (females only), 1,700 (males only), 2,000 (females only), 2,300 (males only), 2,500, 30,00 (males only), and 5,000 mg/kg
Purity: Not reported; tris(2-chloroisopropyl) phosphate, lot PP-2B, typically about 75%
Vehicle: Not reported
Method: Incomplete description. "Standard" method with observation period of 14 days and terminal gross necropsy.
Results: For males, mortality was observed at ≥1,300 mg/kg and all died at ≥2,300 mg/kg; for females, mortality occurred at ≥1,000 mg/kg and all died at ≥1,250 mg/kg. Most deaths occurred within hours of dosing; sporadic deaths between 13,00 and 2,300 mg/kg occurred between days 6 and 11. Clinical signs observed in animals surviving treatment included increasing or decreasing activity, discharge (oral, nasal, perianal, and ocular), hunched posture, rough coat, aggression, diarrhea, dehydration, decreased body temperature, alopecia, emaciation, decreased excreta, anorexia, sporadic twisting, and teeth chattering. Rats dying after treatment also showed signs of prostration, clonic convulsions, ataxia, and sensitivity to touch. No compound-related gross lesions were found at terminal necropsy. The acute oral LD50 values were 1,546 mg/kg (95% C.I. 1,066-2,241 mg/kg) for males and 1,017 mg/kg (95% C.I. 727-1,423 mg/kg) for female rats.
Reference: MEHSL, 1980c

Type: Acute oral toxicity

Species, strain, sex, number: Rat, Wistar, 5/sex
Dose: Both sexes treated with 200 and 500 mg/kg; females only at 2,000 mg/kg
Purity: 67% tris(2-chloroisopropyl) phosphate; 27.2% bis(2-chloroisopropyl) mono(2-chloro-n-propyl) phosphate; 4.4% bis(2-chloro-n-propyl)phosphate mono(2-chloroisopropyl) phosphate; 0.5% tris(2-chloro-n-propyl) phosphate; 3.5% trischloropropylphosphate-ether; 1.3% unknown.
Vehicle: Corn oil
Observation period: 14 days
Method: Council of European Communities Directive 67/548/EEC, Annex V, Part B.1. (acute toxicity (oral)). Animals were examined for clinical signs or mortality several times on day of dosing and twice daily thereafter (once daily on weekends). Body weights were recorded on days 1, 8, and 14. Gross necropsy of all animals.
Results: Clinical signs observed in females at 2,000 mg/kg included apathy, palmospasm, blood-encrusted snout, and lateral position; observed at slight severity within 20 minutes of dosing. All females at highest dose died within 3-6 hours of dosing; mottled reddened lungs were observed in these animals at necropsy. No mortality, body weight effects, clinical signs, or gross lesions at necropsy were observed in males and females dosed with 200 or 500 mg/kg. The acute oral LD50 for female rats was 632 mg/kg; the value for males was not determined, but was greater than 500 mg/kg.
Reference: Bayer AG, 1996

Type: Subacute oral toxicity
Species, strain, sex, number: Rat, Wistar, 5 males/dose
Dose: 0, 1, 10, 100, or 1,000 mg/kg/day for 7 consecutive days
Purity: 97.85% tris(2-chloroisopropyl) phosphate and isomers
Vehicle: Peanut oil
Observation period: 14 days
Method: Animals were examined for clinical signs or mortality twice daily during the week and once daily on weekends. Body weights recorded on days 1, 8, and 14. Feed and water intake were monitored daily. Gross necropsy of all animals included measurement of testicular weight.
Results: There were no deaths, no clinical signs of toxicity, and no effect on food intake or body weight gain. Water intake at the highest dose was significantly increased by 30% compared to controls. Treatment had no effect on the incidence of gross pathological lesions or mean testicular weights. The subacute oral LD50 for male rats was greater than 1,000 mg/kg/day.
Reference: Bayer AG, 1993

Type: Acute and subacute oral toxicity
Species, strain, sex, number: Rat, Wistar, 5 females/group
Purity: Not reported. Test material was a commercial tris chloropropyl phosphate flame retardant from Tokyo Kasei Kogyo K.K. containing: tris(2-chloroisopropyl) phosphate; bis (1-chloromethyl)(2-chloropropyl) phosphate; and bis (2-chloropropyl) (1-chloromethyl) phosphate as confirmed by gas chromatography. The test substance may have been essentially the same as that used by Nakamura et al. (1979) (reviewed in the genotoxicity section).
Doses: 945, 1,137, 1,349, 1,633, 2,000, or 3,400 mg/kg (single dose experiment)

0, 8, 40, 200, or 1,000 mg/kg/day (multiple-dose experiment)
Vehicle: Olive oil
Method: (This study was conducted in preparation for a developmental toxicity assay described in the same publication.) Rats were given a single dose or one daily dose for 7 consecutive days. Seven days after the last dose, rats were monitored for clinical signs and body weight effects. LD50 values were calculated for groups receiving a single dose. Body weights and organ weights (brain, heart, lung, liver, spleen, kidney, and adrenal) relative to body weight were measured for groups treated for 7 consecutive days.
Results: Acute test: Thirty minutes after a single dose, rats that later died exhibited tremor and wheezing; clonic convulsions and foamy bleeding from mouth and nose appeared within one hour. Tremor appeared in all groups, wheezing and foamy bleeding at ≥1,137 mg/kg, clonic convulsions at 1,349 mg/kg. Mortality was 0/5, 3/5, 2/5, 3/5, 4/5, and 5/5 for the lowest-to-highest dose groups. High-dose rats died between 2 and 5 hours after dosing. No deaths occurred after 5 hours. The acute oral LD50 was calculated as 1,500 mg/kg in female rats. Subacute test: Rats dosed on seven consecutive days showed no effects on body weight and no clinical signs of toxicity. A single rat died after dosing with 1,000 mg/kg. Statistically significant increases compared to controls were observed in relative kidney weights (+9.8 to 19.7%) at and above 40 mg/kg/day (not dose-related) and in relative liver weight (+9.7%) at 1,000 mg/kg/day. No effects were noted at 8 mg/kg/day.
Reference: Kawasaki et al., 1982

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged adequate to meet the endpoint.

***Basis for Conclusion*:**

Two available studies followed methods similar to guidelines except that group sizes were 3/sex rather than 5/sex. The data appear to be acceptable since no deaths occurred at the limit dose of 2,000 mg/kg even where tris(2-chloroisopropyl) phosphate was applied to abraded skin.

Type: Acute dermal toxicity
Species, strain, sex, number: Rabbit, New Zealand albino, 3/sex
Dose: 2,000 mg/kg
Purity: Not reported; tris(2-chloroisopropyl) phosphate, lot PP-2B, typically about 75%
Vehicle: None
Exposure period: 24 hours
Method: After hair clipped, test material applied dermally to intact skin of 1 male and 2 females and to abraded skin of 2 males and 1 female. Test sites occluded and Elizabethan collars used to avoid oral exposure. Sites were unwrapped and rinsed with saline after 24 hours. Observation period 14 days with gross necropsy at termination.

Results: No rabbits died. Anorexia was noted in 5/6 animals on day 1. All animal showed some erythema and edema at 24 hours that resolved by 72 hours. At necropsy, scaling or scarring of the test site was observed in two animals. No other treatment-related effect was observed. The acute dermal LD50 was greater than 2,000 mg/kg.
Reference: MEHSL, 1980h

Type: Acute dermal toxicity
Species, strain, sex, number: Rabbit, New Zealand albino, 3/sex
Dose: 2,000 mg/kg
Purity: Tris(2-chloroisopropyl) phosphate as Antiblaze 80; typically about 75%
Vehicle: None
Exposure period: 24 Hours
Method: After hair clipped, test material applied dermally: to intact skin of 1 male and 2 females and to abraded skin of 2 males and 1 female. Test sites occluded and Elizabethan collars used to avoid oral exposure. Sites unwrapped and rinsed with saline after 24 hours. Observed frequently on day 1 and daily thereafter for 14 days, with gross necropsy at termination.
Results: No rabbits died and all gained weight. Anorexia and/or decreased activity were noted in four animals on day 1, but all animals were clinically normal by day 2. Test sites of all animals showed some erythema and edema at 24 hours that resolved by 72 hours. At necropsy, scaling or scarring of the test site was observed in two animals. No other treatment-related effects were observed. The acute dermal LD50 was greater than 2,000 mg/kg.
Reference: MEHSL, 1981a

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300; OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

One of the available studies followed methods similar to guidelines, including analysis of the test atmosphere.

Type: Acute inhalation toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 5/sex
Doses: Average aerosol concentration of 5.05 mg/L
Purity: Not reported; tris(2-chloroisopropyl) phosphate as Antiblaze 80 lot 060815000; typically about 75%
Vehicle: None
Duration: 4 hours
Method: Rats were exposed whole-body to aerosol. Rats were examined at 15-minute intervals during exposure and half-hour recovery period, hourly for 4 hours afterwards and daily thereafter

for 14 days. Body weights were recorded on days 0 (before exposure), 1, 2, 4, 7, and 14. Gross necropsy of all rats at termination.
Results: The mass median diameter of aerosol particles was 4.1 μm, with a geometric standard deviation of 2.3 μm; 87% of the cumulative mass of particles was respirable (diameter of 10 μm or less). Mortality was 0/5 for males and 3/5 for females; deaths occurred within 1 hour to day 4. Clinical signs included watery salivation, decreased activity (lasting to day 6-7), eyes half to completely closed, reddish lacrimation, brownish discharge near oral cavity, and slight alopecia; during recovery, one female was prostrate, and convulsing with dyspnea prior to death within 1 hour. Slight depression in body weight gain was observed in males on day 1 and lasted to day 7 in females. One female dying prematurely showed bilateral corneal opacity, but no gross necropsy abnormalities were observed in two other female fatalities or survivors of either sex. The 4-hour acute inhalation LC50 exceeded 5.05 mg/L for males and was approximately 5 mg/L for females.
Reference: GSRI, 1981

Type: Acute inhalation toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 5/sex
Doses: 17.8 mg/L
Purity: Not reported; tris(2-chloroisopropyl) phosphate, lot PP-2B, typically about 75%
Vehicle: None
Duration: 1 hour
Method: Rats were exposed whole-body to aerosol. Rats were examined during exposure, for 4 hours afterwards and daily thereafter for 14 days. Body weights recorded on days 0 (before exposure), 1, 2, 4, 7, and 14. Gross necropsy of all rats at termination.
Results: Particle size of aerosol was not measured, reducing the value of this study. There were no deaths. Clinical signs during exposure included decreased activity, partially closed eyes, swollen eyelids, and lacrimation in all animals and excessive salivation in some animals. Oily and/or matted fur persisted in all rats through day 10, decreasing thereafter. Most rats exhibited dry rales, wet or dry material around the facial area, and excessive salivation; dry rales and dry material on the facial area persisted through day 4. Transient weight losses on day of exposure were resolved by day 2 in males; 3/5 females did not recover pre-exposure weight by day 14.
Reference: Bio/Dynamics, 1980

Additional Studies and Information:

Southwest Research Institute (1991) investigated whether toxic compounds were formed when cyclic phosphonate compounds (CAS Nos. 41203-81-0 and 42595-49-9) were thermally decomposed in the presence of other phosphate compounds in trimethylol polyol-based urethane foam. Convulsive seizures are characteristic responses of rats to toxic bicyclic phosphates or phosphites. Rats were exposed (head only) for 20 minutes to smoke and decomposition gases from foam containing equal proportions of the cyclic phosphonate compounds and tris(2-chloroisopropyl) phosphate as an example of a trialkylphosphate. Preliminary results suggested

that, under these conditions, toxic bicyclic phosphites or phosphates were formed; results for tris(2-chloroisopropyl) phosphate in two tests were “suspect” and “positive”.

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available study and another incompletely reported study appear to have been conducted according to methods consistent with guidelines. Both studies conclude that tris(2-chloroisopropyl) phosphate is not a primary eye irritant.

Type: Acute eye irritation
Species, strain, sex, number: Rabbit, New Zealand White, 3/sex
Doses: 0.1 mL per eye
Purity: Not reported; tris(2-chloroisopropyl) phosphate, lot PP-2B, typically about 75%
Vehicle: None
Method: Substance instilled into one eye/animal. Unwashed eye evaluated for irritation at 1, 24, 48, and 72 hours. Animals checked twice daily for mortality.
Results: No effects were noted in the cornea or iris. Conjunctival effects included redness in 5/6 animals, chemosis in 2/6, and discharge in 1/6 at 1 hour. The average irritation scores were 3.0, 0, 0, and 0 (out of a maximal score of 110) for each time period. Based on the criteria in Fed. Reg. (16 CFR: 1500.42), the test material was negative for eye irritation.
Reference: MEHSL, 1980g

Additional Studies and Information:

As described in a brief summary, 0.1 mL of tris(2-chloroisopropyl) phosphate as Antiblaze 80 was instilled in the eyes of six New Zealand White rabbits, after which scoring of the unwashed eyes was conducted at 1, 24, 48, and 72 hours (MEHSL, 1980f). The average irritation scores were 10.4, 3.7, 2.3, and 0.7 for the respective timepoints. The test material was reported not to be a primary eye irritant as defined by Fed. Reg. (16 CFR: 1500.42).

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available study and another incompletely reported study appear to have been conducted according to methods consistent with guidelines. Both studies conclude that tris(2-chloroisopropyl) phosphate is not a primary skin irritant.

Critical Studies:

Type: Acute (24-hour) dermal irritation
Species, strain, sex, number: Rabbit, New Zealand White, 3/sex
Doses: 0.5 mL per test site (intact and abraded)
Purity: Not reported; tris(2-chloroisopropyl) phosphate, lot PP-2B, typically about 75%
Vehicle: None
Method: Back hair clipped; two sites, one intact, one abraded on each animal. Application sites occluded; animals restrained with collars. After removal of test material, scoring after 30 minutes, 24 hours, and 72 hours. Mortality checked twice daily.
Results: No edema was observed. The primary irritation index was 0.5 out of 8 maximal. Combined scores for intact and abraded skin were 0.9/8 at 24 hours (0.8 for intact and 1.0 for abraded skin) and 0/8 at 72 hours. The report stated that according to Fed. Reg. (16 CFR: 1500:3), the material was not a primary skin irritant (i.e., having a score of 5 or higher).
Reference: MEHSL, 1980d

Additional Studies:

As described in a brief report, 0.5 mL of tris(2-chloroisopropyl) phosphate as Antiblaze 80 was applied to intact and abraded dorsal skin sites and occluded for 24 hours (MEHSL, 1980e). The primary irritation index was 1.0/8 (0.8/8 for intact skin and 1.1/8 for abraded skin). The combined readings for intact and abraded skin were 1.3/8 at 24 hours and 0.6/8 at 72 hours. The material was defined as not a primary skin irritant.

- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

No studies were located that followed or were similar to the guideline listed above or otherwise addressed skin sensitization.

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

***Conclusion*:**

The available subchronic oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

Subchronic oral toxicity studies were not available in a verifiable form.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

No study of this type was located.

90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)

No verifiable study of this type was located.

Additional studies

As described in a robust summary, groups of CD rats were administered Fyrol PCF (70% tris(2-chloroisopropyl) phosphate and 22% 2-chloropropanol phosphate) in the diet at concentrations of 0, 800, 2,500, 7,500, or 20,000 ppm for 3 months (Stauffer Chemical Company, 1981). No deaths or clinical signs of toxicity were noted except for reduced body weight gain in both sexes at the highest dose. Significant increases in absolute and relative liver weights were observed in all treated male groups and in females at ≥7,500 ppm. Mean kidney weights were significantly increased in males at ≥7,500 ppm, but not in females. Histopathological lesions were observed in the liver (periportal swelling) of high-dose males only, in the kidney (mild cortical tubular degeneration) of males at ≥7,500 ppm and females at 20,000 ppm, and in the thyroid (very mild follicular hyperplasia) in all treated males and in high-dose females. Sternal bone marrow of three high-dose rats (sex not specified) was mildly hypoplastic. There were no treatment-related effects on hematology, clinical chemistry, or cholinesterase activity of brain, plasma, or erythrocytes. The lowest exposure level, 800 ppm, was a LOAEL for males, based on increased liver weight and thyroid histopathology. In females, the NOAEL was 7,500 ppm and the LOAEL was 20,000 ppm based on kidney histopathology.

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

No studies of the type were located.

Subchronic Dermal Toxicity (21/28-day or 90-day)

Conclusion:

The available subchronic dermal toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No study was located that followed or was similar to the two guidelines listed below or otherwise addressed subchronic dermal toxicity.

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**

- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90-day)

Conclusion:

The available subchronic inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No study was located that followed or was similar to the guideline listed below or otherwise addressed subchronic inhalation toxicity.

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No verifiable studies were located that followed or were similar to the guidelines listed below or were otherwise relevant to reproductive toxicity

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

Additional information

As described in a robust summary, there were no histopathological effects on the reproductive organs of male or female CD rats that were exposed to Fyrol PCF in the diet at concentrations between 800 and 20,000 ppm for 3 months (Stauffer Chemical Company, 1981). The composition of the test material and other experimental details are given above under the Subchronic Oral Toxicity endpoint.

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

In the only available developmental study, the group sizes were smaller than stipulated under guideline and no maternal or developmental effects were noted at doses significantly lower than the recommended limit dose of 1,000 mg/kg/day.

Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)

Type: Prenatal developmental toxicity
Species, strain, sex, number: Rat, Wistar, 11-14 pregnant females/dose for prenatal test; 5-7 pregnant females/dose for postnatal test
Purity: Not reported. Test material was a commercial tris chloropropyl phosphate flame retardant from Tokyo Kasei Kogyo K.K. containing: tris(2-chloroisopropyl) phosphate; bis (1-chloromethyl)(2-chloropropyl) phosphate; and bis (2-chloropropyl) (1-chloromethyl) phosphate as confirmed by gas chromatography. The test substance may have been essentially the same as that used by Nakamura et al. (1979) (reviewed in the genotoxicity section).
Doses: Dietary concentrations of 0.01, 0.1, or 1.0 % tris(2-chloroisopropyl) phosphate; intakes calculated as 0, 6, 70, and 625 mg/kg/day (based on reported intakes and average body weight).
Vehicle: Diet
Exposure duration, frequency: 20 gestational days, ad lib
Method: Pregnant female rats exposed via the diet on gestational days (GD) 0 to 20. At termination, dams examined for implantations, fetal sex ratio, and mortality. Two thirds of live fetuses were examined for skeletal abnormalities and one-third for visceral abnormalities.
For postnatal study, groups of 5-7 pregnant females were dosed as above and allowed to litter

normally. Litters were culled to 8 pups each, weaned at 21 days and monitored for 4 additional weeks.
Results: Exposure had no effect on feed consumption or body weight gain and resulted in no clinical signs of toxicity in dams. There were no fetal deaths or gross external abnormalities in any group; treatment had no effect on fetal weights or the incidence of implantations and resorptions. There were no dose-related visceral abnormalities. The incidence of skeletal abnormalities was not statistically different from controls, but a few instances of cervical ribs and missing 13th ribs were observed in treated groups but not controls.
Postnatal observations: Dietary exposure resulted in no effects on birth weight, postnatal growth, or survival.
Conclusion: The highest dose in this study, 625 mg/kg/day, was a NOAEL for maternal, fetal, and postnatal toxicity.
Reference: Kawasaki et al., 1982

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

No studies with the specific designs of the two tests listed above were available.

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies following or similar to the guidelines listed below or otherwise relevant to chronic toxicity were located.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies following or similar to the guidelines listed below or otherwise relevant to carcinogenicity were located.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

Although results of one assay suggest that a high oral dose of tris(2-chloroisopropyl) phosphate does not induce delayed neurotoxicity in hens, the study did not perform a complete assessment of neurological parameters.

Delayed Neurotoxicity

Conclusion:

The available delayed neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The acute study (Assay A) on Fyrol PCF departed from guideline in that enzyme inhibition was assayed 24 rather than 48 hours after dosing. The longer study (Assay B) did not conduct a complete battery of neurobehavioral tests as stipulated under the guideline. However, no neurohistopathology or clinical signs of neurotoxicity were observed at a dose level (13,000 mg/kg) significantly greater than that recommended under the guideline.

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Critical Studies

Type: Acute oral delayed neurotoxicity

Species, strain, sex, number: Hen, 12-14 months old, White Leghorn, 4/group for 24-hour biochemical assay, 18/group treated with Fyrol PCF, and 10/group for controls for 6-week neurotoxicity assay
Purity: Not reported; Fyrol PCF has a typical tris(2-chloroisopropyl) phosphate content of about 75%
Doses: 10 mL/kg (13,200 mg/kg) undiluted
Vehicle: None
Negative control: 2 mL/kg corn oil
Positive control: 500 mg/kg TOCP
Route: Oral gavage
Exposure duration, frequency: Assay A. Biochemistry: 24 hours, once.
Assay B. Neurotoxicity: once at intervals of 3-weeks; experiment terminated 3 weeks after second dose
Method: Assay A. Biochemistry: Brain neurotoxic esterase (NTE) and plasma cholinesterase (PChE) activities were measured 24 hours after dosing.
Assay B. Neurotoxicity: After dosing, body weight and food consumption measured every 3-4 days; walking behavior assessed weekly. At termination, brain, spinal cord, and sciatic nerve tissues evaluated for neurohistopathology.
Results: Assay A. Biochemistry: Fyrol PCF did not significantly reduce esterase activities 24 hours later, suppressing PChE by 32.8% and NTE by only 3.2%. TOCP significantly suppressed PChE by 70% and brain NTE by 85.3%.
Assay B. Neurotoxicity: compound-specific effects in hens treated with Fyrol PCF included death of 1/18, ~30% reduction of mean body weight, cessation of egg production, and severe feather moult. There was no sign of delayed motor impairment and no neurohistopathology (axonal degeneration in cerebellar peduncles and spinal cord and bilateral degeneration of the sciatic nerve) as observed for TOCP control.
Reference: Sprague et al., 1981

No neurotoxicity studies were located that were relevant to the categories listed below.

Neurotoxicity (Adult)

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity

- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat); OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent); OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred); OPPTS Harmonized Guideline 870.6855

These additional neurotoxicity studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Other Neurotoxicity Data

Cholinesterase inhibition

In an *in vitro* assay, Antiblaze 80 (about 75% tris(2-chloroisopropyl) phosphate) tested at concentrations of 10, 100, and 1,000 ppm did not significantly inhibit cholinesterase activity in homogenates of rat brain (MEHSL, 1980a).

IMMUNOTOXICITY

***Conclusion*:**

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies following or similar to the guideline listed below or otherwise relevant to immunotoxicity were located.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion: The available genotoxicity data were judged inadequate to meet the endpoint

Basis for Conclusion:

Although several adequate studies are available for mutagenicity in bacteria, no verifiable studies were located for chromosomal aberration endpoints.

Gene Mutation in Vitro:

- **Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)**

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA97, TA98, TA100, TA1535, and TA1537
Metabolic activation: S-9 from liver or hamster induced with Aroclor 1254

Concentrations: 3.3-333 μg/plate without activation and 10-1,000 μg/plate with activation.
Purity: Not reported; tris(2-chloroisopropyl) phosphate from Stauffer Chemical Co.
Method: Preincubation method. In duplicate. DMSO solvent negative control. Positive controls included sodium azide, 9-aminoacridine, and 4-nitro-o-phenylenediamine. S-9 from liver from rat or hamster induced with Aroclor 1254.
Results: DMSO and tris(2-chloroisopropyl) phosphate did not induce an increase in mutant frequency in bacteria with or without metabolic activation; results for positive controls were as expected.
Reference: Zeiger et al., 1992

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538
Metabolic activation: Tested with and without S-9 from liver of male rats induced with Aroclor 1254
Concentrations: 0, 0.1, 1.0, 10, 100, 500, or 2,000 μg/plate.
Vehicle: DMSO
Purity: Not reported. Typical mixture of "tris(chloropropyl) phosphate" contains about 75% tris(2-chloroisopropyl) phosphate
Method: Plate incorporation method of Ames. Tests performed on three occasions with duplicate plates. Positive controls included N-methyl-N-nitro-N-nitrosoguanidine, 9-aminoacridine, 4-nitroquinoline-N-oxide and 2-nitrofluorene.
Results: Vehicle control and tris(2-chloroisopropyl) phosphate were not mutagenic, with or without metabolic activation; positive control results were as expected.
Reference: BIBRA, 1977

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA1538
Metabolic activation: Tested with and without S-9 from liver of male Sprague-Dawley rats induced with Aroclor 1254
Concentrations: Cytotoxicity tested at concentrations up to 3.1 μL/50 μL; cytoxicity observed at ≥0.97 μL/50 μL. Based on results of cytotoxicity assay, mutagenicity tested at 0, 0.03, 0.10, and 0.33 μL/100 μL/plate with additional plate at 1 μL/100 μL to confirm cytotoxicity.
Vehicle: DMSO
Purity: 95% pure Fyrol PCF (Stauffer Co.) Purity not reported; typical mixture of "tris(2-chloropropyl) phosphate" contains about 75% tris(2-chloroisopropyl) phosphate.
Method: Pre-incubation assay. Tests performed with duplicate plates for controls and triplicate for test article. Positive controls included N-methyl-N-nitro-N-nitrosoguanidine, 9-aminoacridine, 2-aminoanthracene, and 2-nitrofluorene.
Results: Vehicle control and tris(2-chloroisopropyl) phosphate were not mutagenic with or without metabolic activation; positive control results were as expected.
Reference: MEHSL, 1980b

Additional Studies

Nakamura et al. (1979) reported no mutagenicity in *Salmonella typhimurium* strains TA100 or TA1535 from a mixture containing 67% tris(2-chloroisopropyl) phosphate, 28% bis(1-chloromethyl)(2-chloropropyl)phosphate, and 5% bis(2-chloropropyl)(1-chloromethylethyl) phosphate with or without metabolic activation at doses up to 10 µM (3.3 mg) per plate.

- **In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)**

As described in a brief memorandum, tris(2-chloroisopropyl) phosphate at 0.006 to 0.028 µL/culture, increased the frequency of forward mutations in mouse lymphoma cells in a dose-related fashion in the presence of metabolic activation (rat liver homogenate) (MEHSL, 1981b).

As described in a robust summary, Fyrol PCF at concentrations between 0.08 and 0.48 µL/mL did not increase the frequency of forward mutations in mouse lymphoma cells with or without metabolic activation (Stauffer Chemical Company, 1978a).

Chromosomal Aberration in Vivo

- **Mammalian Bone Marrow Chromosomal Aberration Test (OPPTS Harmonized Guideline 870.5385)**

As described in a robust summary, Fyrol PCF administered as a single oral dose of 0.011, 0.04, or 0.11 mL/kg by gavage in DMSO to groups of 24 male Sprague-Dawley rats did not increase the frequency of chromosomal aberrations in bone marrow harvested 6 to 48 hours after dosing (Stauffer Chemical Company, 1978b). The mitotic index of cells from rats treated with Fyrol PCF (based on counts of 500 cells per animal) was approximately equal to the negative control.

No verifiable genotoxicity studies relevant to the below categories or to other types of genotoxic effects were located.

Gene Mutation in Vivo
Chromosomal Aberration in Vitro
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for freshwater fish and invertebrates were judged adequate to meet the endpoints, but the available acute toxicity data for marine fish or invertebrates, or algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

Data were located for 96-hour acute toxicity studies in bluegill sunfish (*Lepomis macrochirus*), fathead minnows (*Pimephales promelas*) (IUCLID, 2000; OECD SIDS, 2000), zebrafish (*Brachydanio rerio*), and guppies (*Poecilia reticulata*) and for a 48-hour acute toxicity study in killifish (*Oryzias latipes*) (IUCLID, 2000) exposed to tris(2-chloroisopropyl) phosphate. The available study details are provided in Table 1. The data presented in IUCLID (2000) have not undergone any evaluation by the European Commission. The summaries of the studies with killifish and guppies provided acute toxicity values, but did not provide any information regarding the study conditions. The data for killifish and guppies are considered unreliable and will not be discussed further in this report.

Bluegills and fathead minnows were exposed to aqueous dilutions of Antiblaze 80, a commercial formulation that contains tris(2-chloroisopropyl) phosphate. Although the concentration of tris(2-chloroisopropyl) phosphate in Antiblaze 80 was not provided, tris(2-chloroisopropyl) phosphate concentrations in the test waters were analytically verified (OECD SIDS, 2000; IUCLID, 2000). Zebrafish were exposed to aqueous dilutions of a tris(2-chloroisopropyl) phosphate mixture with a reported purity of 97.7%. Tris(2-chloroisopropyl) phosphate concentrations in the study with zebrafish were also analytically verified (IUCLID, 2000). The 96-hour LC50 values for bluegills, fathead minnows, and zebrafish were 84, 51, and 56.2 mg/L, respectively.

The studies with bluegills and fathead minnows were reportedly conducted according to OECD Guideline 203. Although the study details provided in the summaries are insufficient to conduct an independent, thorough evaluation of the studies with bluegills, fathead minnows, and zebrafish, they suggest that the studies were conducted well. Furthermore, the relatively close agreement of the analytically-verified LC50 values in these studies suggests that these values are a good estimate of the toxicity of tris(2-chloroisopropyl) phosphate to freshwater fish. These data are considered adequate to satisfy the acute toxicity endpoint for freshwater fish.

Data were located for a 48-hour acute toxicity study in *Daphnia magna* exposed to tris(2-chloroisopropyl) phosphate in Antiblaze 80 (IUCLID, 2000; OECD SIDS, 2000). Triplicate groups of 10 first-instar daphnids were exposed to aqueous dilutions of Antiblaze 80 for 48

hours under static conditions. Nominal concentrations were 0, 33.5, 67, 335, 502, or 670 mg Antiblaze 80/L. Daphnids were observed for immobilization 24 and 48 hours after the study was initiated. The study was reportedly conducted as indicated by OECD Guideline 202. The analytically-verified 48-hour EC50 (for immobilization of daphnids) was 131 mg/L (95% CI: 65-176 mg/L). The NOEC was 33.5 mg/L. Although the summary provides insufficient details to conduct a thorough, independent evaluation of the study results, the data are considered sufficiently reliable to satisfy the endpoint for acute toxicity to freshwater invertebrates.

A study of the acute toxicity of tris(2-chloroisopropyl) phosphate in the green alga *Selenastrum capricornutum* was located (Sanitized Report, 1992). Exponentially growing algae were exposed to 2, 6, 18, 54, or 162 mg tris(2-chloroisopropyl) phosphate/L (nominal concentrations) for 96 hours. Algal growth in tris(2-chloroisopropyl) phosphate-free media and a potassium dichromate positive control were also evaluated. Algal cell concentrations were determined photometrically after 0, 24, 48, 72, and 96 hours. Algal culture and test conditions largely followed the testing guidelines established in OPPTS Harmonized Guideline 850.5400 and OECD Guideline 201. However, the purity of the tested material was not provided and tris(2-chloroisopropyl) phosphate concentrations in the test water were not analytically confirmed. Furthermore, concentrations of KH_2PO_4 and $NaHCO_3$, which were added to stabilize pH, were higher than recommended in the OECD guideline. Without analytical confirmation of the concentrations of tris(2-chloroisopropyl) phosphate in the test waters, and in the absence of supporting studies, these data are not adequate to satisfy the algal toxicity endpoint.

No additional pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Table 2-1. Summary of available acute fish toxicity studies for tris(2-chloroisopropyl) phosphate (CASRN 13674-84-5)[a]									
			Selected Study Design Parameters[b]						
Study Reference	**Species Tested**	**LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
A) IUCLID, 2000; B) OECD SIDS, 2000	Bluegill sunfish (*Lepomis macrochirus*)	96-hour LC50: 84 mg/L (measured) (A)	Static (A,B)	0, 0.9, 4.9, 9.8, 49, 98 mg/L (nominal) (B)	10 (B)	Yes (A,B)	**pH:** NR **Temp:** NR **DO:** NR **Hardness:** NR **Water volume**: NR **Electrical conductivity**: NR	NR	Fish were observed every 24 hours. Criterion for death was lack of opercular movement. The analytically-confirmed 96-hour LC50 (84 mg/L) corresponded to a nominal concentration of 180 mg/L (A). The NOEC was 9.8 mg/L based on abnormal behavior (surfacing and loss of equilibrium). A binomial probability test yielded a 120-hour LC50 of 85 mg/L (A). The study reportedly followed OECD Guideline 203 (A). This study was also reported in IPCS (1998).

Table 2-1. Summary of available acute fish toxicity studies for tris(2-chloroisopropyl) phosphate (CASRN 13674-84-5)[a]

Study Reference	Species Tested	LC_{50}	Selected Study Design Parameters[b]						Comments on the Data
			Study Type	Concentrations Tested	No. of Fish/ Conc	Analytical Monitoring	Water Chemistry	Solvent	
A) IUCLID, 2000; B) OECD SIDS, 2000	Fathead minnow (*Pimephales promelas*)	96-hour LC50: 51 mg/L (measured) (A,B)	Static (A,B)	0, 0.9, 4.9, 9.8, 49, 98 mg/L (nominal) (B)	10 (B)	Yes (A,B)	**pH:** NR **Temp:** NR **DO:** NR **Hardness:** NR **Water volume**: NR **Electrical conductivity**: NR	NR	Fish were observed every 24 hours. Criterion for death was lack of opercular movement. The analytical confirmed 96-hour LC50 (51 mg/L) corresponded to a nominal concentration of 98 mg/L (A). The NOEC was 9.8 mg/L based on abnormal behavior (surfacing and loss of equilibrium). The 168-hour LC50 (measured) was 74 mg/L (A). The study reportedly followed OECD Guideline 203 (A). This study was also reported in IPCS (1998).
IUCLID, 2000	Zebrafish (*Brachydanio rerio*)	96-hour LC50: 56.2 mg/L	Static	NR	NR	Yes	**pH:** NR **Temp:** NR **DO:** NR **Hardness:** NR **Water volume**: NR **Electrical conductivity**: NR	NR	The material tested was reported to be 97.9% pure. The chemical concentrations in the test water were verified by gas chromatography at 0, 24, 48, 72, and 96 hours. The reported LC0 was 31.6 mg/L and the LC100 was 100 mg/L.

[a]Studies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.
[b]NR: Not reported

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish were judged inadequate to meet the endpoint.

The available chronic toxicity data for freshwater invertebrates were judged adequate to meet the endpoint, but the available chronic toxicity data for marine invertebrates were judged inadequate to meet the endpoint.

Basis for Conclusion:

Data were located for a 21-day reproduction test of tris(2-chloroisopropyl) phosphate in *Daphnia magna* (OECD SIDS, 2000). Daphnids (10 daphnids/replicate, 4 replicates/concentration) were exposed to aqueous dilutions of tris(2-chloroisopropyl) phosphate for 21 days under static conditions with renewal of the test solutions every 3 days. Exposure concentrations were 10, 18, 32, 56, or 100 mg tris(2-chloroisopropyl) phosphate/L. Adult daphnid mortality was assessed daily and mortality of the offspring was assessed every time the test solutions were renewed. A NOEC of 32 mg/L was reported based on adult mortality. Reproductive effects were not observed at lower concentrations. Analysis of the test solutions show that the actual concentrations of tris(2-chloroisopropyl) phosphate in the test solutions were 85% to 102% of the nominal concentrations. The available information in the study summary is insufficient to conduct a thorough and independent evaluation of these results. However, the study appears to have been conducted well and appears sufficient to satisfy the chronic toxicity endpoint for freshwater invertebrates.

No additional pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadquate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideine 207)**

Physical/Chemical Properties

2-Propanol,1-chloro-, phosphate (3:1)
Synonyms tris(2-chloroisopropyl) phosphate; tris(1-chloro-2-propyl) phosphate
CAS 13674-84-5
MF $C_9H_{18}Cl_3O_4P$
MW 327.57
SMILES ClCC(C)OP(=O)(OC(C)CCl)OC(C)CCl

Water Solubility:
Conclusion: The available water solubility data are adequate.
Basis: The literature data supplied below are from reputable sources and are in good agreement with one another.

Solubility (mg/L)	References
1100	OECD SIDS, 2000
1600	World Health Organisation, 1998 (20˚C)
1200	CERI, 1999; SRC, 2004 (PHYSPROP Database)

Log K_{ow}:
Conclusion: The available Log K_{ow} data are adequate.
Basis: The only value found for this endpoint that did not originate from the CITI (1992) data compilation was from a flawed study. The CITI (1992) value is reasonable based on the structure of the chemical.

Log K_{ow}	References/Comments
2.59	CITI 1992; World Health Organisation, 1998; OECD SIDS, 2000; SRC, 2004 (PHYSPROP Database)
3.33	Flawed study, results not reproducible, OECD SIDS, 2000

Oxidation/Reduction: No data

Melting Point:
Conclusion: The available melting point data are adequate.
Basis: Several reputable sources report similar values. In addition, the SIDS pour point value was measured according to a standard method and is reasonably consistent with the melting boint values located.

Melting Point (˚C)	References
-51	(pour point by ASTM D97) OECD SIDS, 2000
-40	CERI, 1999; SRC, 2004 (PHYSPROP database)
-42	World Health Organization, 1998

Boiling Point:
Conclusion: The decomposition temperature is adequate in lieu of a boiling point.
Basis: The key study was performed according to a standard method. Although the other two sources cited here do not mention decomposition, the value reported in the WHO document is consistent with the decomposition temperature in the key study.

Boiling Point (˚C/torr)	References
Dec. 244/700	(by ASTM D2897) OECD SIDS, 2000
235-248	World Health Organization, 1998
>270	CERI, 1999

Vapor Pressure:
Conclusion: The available vapor pressure data are adequate.
Basis: The vapor pressure at 20˚C is cited in two sources, and the available data are reasonably consistent with the value of 40 torr at 110˚C reported in the SIDS summary document for this chemical. The SIDS value was measured according to standard guidelines.

Vapor Pressure (torr/˚C)	Reference
0.75/20	(Converted from 100 Pa) Akzo Nobel, 2002; Leisewitz et al., 2000
40/110 <2/25	(by ASTM D2879) OECD SIDS, 2000
<2/25	World Health Organisation, 1998

Odor:
Conclusion: The odor of this compound has been adequately characterized.
Basis: The phrase used to describe the odor of this material is sufficiently descriptive (as opposed to “characteristic” or “typical”) to convey a sense of this material’s smell.

Odor	Reference
Slightly sweet	Akzo Nobel, 2002

Oxidation/Reduction Chemical Incompatibility: No data

Flammability:
Conclusion: The flammability (as the flash point) has been adequately characterized.
Basis: Both the open- and closed-cup measurements were performed according to standard methods.

Flash Point	Reference
185˚C (Closed cup, ASTM D93)	OECD SIDS, 2000
218˚C (Cleveland, open cup; Open cup ASTM D92)	Akzo Nobel, 2002; OECD SIDS, 2000; World Health Organisation, 1998

Explosivity: No data

Corrosion Characteristics: No data

pH: This chemical does not contain functional groups expected to influence the pH of aqueous solutions. Data for this endpoint are therefore not applicable.

UV/Visible Absorption: No data

Viscosity:
Conclusion: The viscosity of this chemical has been adequately characterized.
Basis: The values reported in the available literature are in reasonable agreement with one another.

Viscosity (cP)	Reference
71 at 25˚C	Akzo Nobel, 2002
61 at 25˚C	World Health Organisation, 1998
57 at 25˚C	OECD SIDS, 2000

Density/Relative Density/Bulk Density:
Conclusion: The density of this compound has been adequately characterized.
Basis: Consistent data are provided in several reputable sources.

Density	**Reference**
1.290 at 25˚C	Specific gravity. OECD SIDS, 2000; World Health Organisation, 1998
1.29 at 25˚C	Specific gravity. World Health Organisation, 1998
1290 kg/m^3 at 25˚C	Bulk density. Akzo Nobel, 2002

Dissociation Constant in Water: This compound does not have functional groups that are expected to dissociate in water. This endpoint is therefore not applicable.

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish:
Conclusion: The bioconcentration factor has been adequately characterized.
Basis: Two measurements are available for carp; the values are independent of the starting concentration of tris(2-chloroisopropyl) phosphate, and are in good agreement with one another.

Reference	Species	BCF	Key Design Parameters				Comments
			Exp. type	Range (ppm)	Study length	T (˚C)	
CERI, 1999 CITI, 1992	Carp (*Cyprinus carpio*)	0.8-2.8 <1.9-4.6	Flow-through	0.2 0.02	6 weeks		Fat content of the fish averaged 3.5%.

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation:
Conclusion: The biodegradation of ths compound under aerobic conditions has been adequately characterized.
***Basis*:** The results from several different studies are in general agreement that the test substance is not amenable to biodegradation under aerobic conditions.

Study type/ Method	Innoculum	Acclim	Degradation	Time	Comments	Reference
Shake flask test system	Acclimated domestic sewage	14 days	0.1%, 0.0% and 6.7% by CO_2 evolution 9.17%, 18.29%, and 0% by DOC removal	28 days	Samples were run in triplicate at 22˚C. Initial test substance concentration = 10 mg C/L	Albright & Wilson, 1993
Japanese MITI test	Activated sludge		0% by BOD	28 days	Initial concentrations 100 mg/L (test subst.), 30 mg/L (sludge), 25˚C, pH 7	CERI, 1999; CITI, 1992; OECD SIDS, 2000
OECD 302C			21% by O_2 uptake	28 days		World Health Organisation, 1998
OECD 301E			14%	28 days		OECD SIDS, 2000

Anaerobic Biodegradation: No data

Pyrolysis:
Conclusion: The available pyrolysis data are not adequate.
Basis: Although a semi-quantitative description of the pyrolysis products is given in the Choudry and Hutzinger paper, the list of degradates provided accounts for only 43% of the total mass expected and doesn't contain any oxygenated or phosphorus-containing compounds. Therefore, this study does not provide a complete profile of the pyrolysis of tris(2-chloroisopropyl) phosphate.

Pyrolysis Products	Reference
Relative mol.% degradates, 0.1 mole tris(2-chloroisopropyl) phosphate heated at 250-260˚C under reduced pressure (3 mm Hg), overall yield 43 wt%: 1-chloro-1-propene 45.5%, 1-chloro-2-propene 45.5%, 2-chloropropane 9%	Choudhry and Hutzinger, 1982
When heated to decomposition, it emits toxic fumes of Cl^+ and PO_x	Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)

Hydrolysis as a Function of pH:
Conclusion: The hydrolysis data available are not adequate.

Basis: The only experimental studies available in the open literature provide a qualitative assessment of the potential for tris(2-chloroisopropyl) phosphate to hydrolyze. No kinetic data or half-life information were available.

$T_{1/2}$	pH	Temperature	Comment	Reference
			Hydrolyzes slowly under acidic or alkaline conditions	World Health Organisation, 1998; Akzo Nobel, 2002

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

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Flame Retardant Alternatives

Tribromoneopentyl Alcohol

Draft Hazard Review

December 2004

Tribromoneopentyl alcohol:
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	✓
Dermal	
Inhalation	*
Eye irritation	✓
Dermal irritation	✓
Skin sensitization	*
Subchronic Toxicity	
28-Day oral	✓
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✘
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	✓
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	✓

Tribromoneopentyl alcohol:
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	
Daphnia acute EC50	
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

1-Propanol, 2,2-dimethyl-, tribromo derivative

Synonym	Tribromoneopentyl alcohol
CAS	36483-57-5
MF	$C_5H_9Br_3O$
MW	324.84
SMILES	BrC(C(CO)(C)C)(Br)Br

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401).

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Several acute oral lethality studies were available in rats. One study summarized below as a critical study (Ameribrom, Inc., 1982a) conformed to OPPTS and OECD guidelines, but did not report the purity of the test substance. The other study summarized below (Norris et al., 1972a) was performed on a test substance containing a high purity of tribromoneopentyl alcohol (98.6%), but did not report all study details necessary for a full individual evaluation according to OPPTS and OECD guidelines. Although no single acute oral toxicity study was relevant for full individual evaluation, all available acute oral toxicity data report similar results for testing of tribromoneopentyl alcohol and appear to support the evaluation of acute oral toxicity.

Critical Studies:

Type: Acute oral toxicity
Species, strain, sex, number: Charles River CD rats, 5 animals/sex/dose
Dose: 2,575, 3,204, 3,289, 3,501, 3,769, and 4,117 mg/kg
Purity: Not reported, off-white crystals
Vehicle: Corn oil
Observation Period: 14 days
Method: Designed to conform to U.S. EPA, Pesticide Programs, Proposed Guidelines for Registering Pesticides in the U.S., Hazard Evaluation: Humans and Domestic Animals, 163.81-1, dated 22 August, 1978; preliminary test followed by main study

Results: Male mortality was 2/5 at 2,575 and 3,204 mg/kg, 4/5 at 3,289, 3,501, 3,769, and 4,117 mg/kg. Female mortality was 2/5 at 2,575 and 3,501 mg/kg, 3/5 at 3,769 mg/kg, 4/5 at 3,204 and 3,289 mg/kg, and 5/5 at 4,117 mg/kg. LD50 (male) = 2,847 mg/kg (95% CI = 2,050-3,644). LD50 (female) = 2,685 mg/kg (95% CI = 1,415-3,955). LD50 (combined) = 2,823 mg/kg (95% CI = 2,217-3,429). Clinical signs noted included decreased motor activity, proneness, ataxia, brady-pnoea, ptosis, irritability, hunching, reddening, urogenital wetting and bleeding, lachrymation, salivation, haematuria, coat staining, piloerection, and ungroomed appearance. Necropsy findings consisted of gastric mucosa congestion, ulceration, erosion, or hemorrhage, associated with abnormal oily and yellow contents. The small intestine was usually distended with hemorrhagic, pale, or yellow contents. One female at 3,769 mg/kg and one male at 4,117 mg/kg had congestion of the urinary bladder; the bladder contents were blood-stained in the male with bladder congestion.
Reference: Ameribrom, Inc., 1982a

Type: Acute oral toxicity
Species, strain, sex, number: Sprague Dawley albino rat, 5 males/dose
Dose: 1,260, 1,580, 2,000, and 2,520 mg/kg
Purity: 98.6% tribromoneopentyl alcohol
Vehicle: Corn oil
Observation period: 13 days
Method: Test material administered as a 20% solution in corn oil to fasted rats by single dose gavage. Animals were weighed before dosing, the day following dosing, and at weekly intervals for 2 weeks thereafter. Clinical observations made "periodically" for signs of toxicity.
Results: LD50 = 1,630 mg/kg (95% CI = 1,370-1,950). Mortality was 0/5 at 1,260 mg/kg, 4/5 at 1,580 mg/kg, 3/5 at 2,000 mg/kg, and 4/5 at 2,520 mg/kg. Animals at all dose levels were noted as having bloody urine. Necropsy revealed hemorrhagic appearance of the mucosa of the urinary bladder at the highest dose level.
Reference: Norris et al., 1972a

Additional Studies and Information:

Other studies that were of lesser quality (such as a low percentage of tribromoneopentyl alcohol in test substance) or that were reported in less detail are generally consistent with the above studies (Biochemical Research Laboratory, no date; Norris et al., 1972b; Toxicology Research Laboratory, 1976).

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The currently available acute dermal toxicity data were judged inadequate to meet the endpoint.

***Basis for Conclusion*:**

No studies of this type were located.

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300 (OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The only available study of tribromoneopentyl alcohol (Norris et al., 1972a), summarized below, did not fully conform to OPPTS and OECD guidelines. Study details to allow for a full evaluation of study adequacy were missing, and the test atmosphere was not characterized. In addition, only one concentration was tested, which did not produce mortality or toxicity, and was lower than the currently recommended limit dose for single dose testing. An additional study, conducted and reported in the same manner, was performed on a mixture containing only 11.3% tribromoneopentyl alcohol (Norris et al., 1972b).

Type: Acute inhalation toxicity
Species, strain, sex, number: Sprague Dawley rats, 5 males
Doses: 0.714 mg/liter of air (nominal)
Purity: 98.6%
Vehicle: None
Duration: 7-hour exposure
Observation Period: 2 weeks
Method: The test substance (a solid at room temperature) was maintained at 100°C. Air was metered through the test substance and into the 19 L glass exposure chamber at the rate of 1 liter/minute; according to the investigators, this procedure produced a vapor. Whether the substance in the test chamber was exclusively a vapor, or whether aerosol or particulate was formed, is uncertain. The exposure period was 7 hours. Clinical observations were made during the exposure period and up to 2 weeks thereafter (no specification of frequency). Body weight was measured before and after exposure and "periodically" for 2 weeks thereafter. Necropsy was performed on 1 rat 1 day after exposure and on the remaining 4r rats at the end of the observation period.
Results: No mortality, signs of toxicity, respiratory or nasal irritation, or abnormal body weight changes were observed during the exposure or observation period. No abnormalities were noted at necropsy.
Reference: Norris et al., 1972a

Additional Study:

An acute inhalation toxicity study of a mixture containing only 11.3% tribromoneopentyl alcohol (plus 81.1% dibromoneopentyl glycol and 7.6% monobromoneopentyl triol) (Norris et al., 1972b) was performed in a similar manner as the above study. The nominal exposure concentration of this mixture was 2.49 mg/L. The nominal exposure concentration of tribromoneopentyl alcohol would have been 0.28 mg/L, a lower concentration than in the above study of relatively pure tribromoneopentyl alcohol. There were no deaths, but labored breathing and slight signs of nasal irritation were observed in the rats during exposure. The rats appeared normal during the 2-week observation period and no pathological changes were observed during necropsy. The apparent irritant effects in this study cannot be attributed solely to tribromoneopentyl alcohol, which accounted for only a small percentage of the mixture, and which caused no signs of irritation when tested alone at a higher concentration.

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available acute eye irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

The study summarized below as a critical study (Ameribrom, Inc., 1982b) conformed to OPPTS and OECD guidelines, but did not report the purity of the test substance. Other available data, though inadequate for individual evaluation, reported similar results to the critical study summarized below and provide support for the acute eye irritation evaluation.

Critical Studies:

Type: Acute eye irritation
Species, strain, sex, number: New Zealand White albino rabbits, 9/sex
Doses: 100 mg
Purity: Not reported; off-white crystals
Vehicle: None
Method: The study was designed to conform to the U.S. EPA, Pesticides Program, Proposed Guidelines for Registering Pesticides in the U.S.; Hazard Evaluation: Human and Domestic Animals 163.81-4, dated 22 August, 1978. Six rabbits were tested without any washing of test substance from the eye. Three rabbits were tested with irrigation of the eye after 30 seconds of exposure. Eyes were assessed at 24, 48, and 72 hours and 4, 7, 10, and 13 days after test administration.
Results: Almost all animals of both groups (unwashed exposure and washed exposure) exhibited diffuse opacity (Grade 1 on a scale of 1-4) on the cornea at 24 hours after exposure. One rabbit from the unwashed group exhibited Grade 2 opacity. Irridial congestion was also noted in most

animals in the unwashed exposure group. Conjunctival irritation, such as redness and discharge, was observed in both the unwashed and washed exposure groups at varying degrees. All ocular effects were fully reversible by the end of the observation period with many being fully resolved a few days after exposure.
Reference: Ameribrom, Inc., 1982b

Additional Studies and Information:

Other studies that were of lesser quality (such as a low purity of tribromoneopentyl alcohol in test substance) or were reported in less detail are generally consistent with the above study (Keeler et al., 1974; Biochemical Research Laboratory, no date).

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available acute dermal irritation data were judged marginally adequate to meet the endpoint.

Basis for Conclusion:

The study summarized below (Ameribrom, Inc., 1982c) generally conformed to OPPTS and OECD guidelines with only slight derivations and detail omissions, except for the lack of reporting of test substance purity. Although a summary table was also available for another acute dermal irritation study (Biochemical Research Laboratory, no date) that reported similar results to the above mentioned study, few study details were reported in the table.

Type: Acute dermal irritation
Species, strain, sex, number: New Zealand White albino rabbits, 3/sex
Doses: 0.5 g
Purity: Not reported, off-white crystals
Vehicle: Saline, enough to moisten test material
Method: The study was designed to conform with the U.S. EPA, Pesticides Programs, Proposed Guidelines for Registering Pesticides in the U.S.; Hazard Evaluation: Humans and Domestic Animals 163,82-5, dated 22 August 1978. Single application of slightly saline-moistened test material to shaved skin under an occlusive wrap. The skin of one side of each animal was mildly abraded and the skin of the other side was left intact. The test material was applied to both sides. The dressings were removed 24 hours after dosing and residual test material was removed by wiping with towels. Animals were regularly checked for clinical signs of toxicity during exposure and were checked daily from day 2 of the study until study termination. Skin irritation assessments were made 1 hour after removal of the wrap, as well as 72 hours and 4 and 5 days after application of the test material.
Results: At 25 hours after application, very slight to well-defined erythema was displayed in most animals and moderate-to-severe erythema was displayed in two animals. At 72 hours after

application, four rabbits displayed very slight erythema and two rabbits displayed well-defined erythema. One rabbit displayed a very slight edema. At 4 days after application, one rabbit displayed very slight erythema. All skin responses were completely resolved by the final assessment 5 days after application. Exfoliation was observed in three female rabbits from 72 hours after application until study termination. Incidence or severity of dermal irritation was not affected by abrasion of skin before treatment. The authors concluded that the test substance was a mild irritant to the skin.
Reference: Ameribrom, Inc., 1982c

Additional Studies:

Another study, reported with few details (Biochemical Research Laboratory, no date), was generally consistent with the results of the above study. In this other study, undiluted tribromoneopentyl alcohol was applied to the belly of rabbits for 10 applications (intact skin, no irritation occurred) or 3 applications (abraded akin, slight hyperemia on abrasions after each of the first two applications). Slight hyperemia and slight exfoliation occurred after similar applications to intact and abraded belly skin of a 10% solution of tribromoneopentyl alcohol in Dowanol DPM. There was no indication of absorption of acutely toxic amounts (not further explained).

Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)

Conclusion:

The available skin sensitization data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available skin sensitization study was performed on a test substance mixture containing only 13.6 % tribromoneopentyl alcohol (plus 81% dibromoneopentyl glycol and 5.4% monobromoneopentyl triol) (Keeler et al., 1974). Toxicological effects of the individual component chemical, tribromoneopentyl alcohol, may differ from effects produced by the combination of the chemicals in the mixture. The study also did not conform fully to OPPTS and OECD guidelines. Results were negative for dermal sensitization in this study in guinea pigs.

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

Conclusion:

The available subchronic oral toxicity data were judged marginally adequate to meet the endpoint.

Basis for Conclusion:

The only available study for subchronic oral toxicity is a 30-day study in rats (Humiston et al, 1973), which was reasonably comprehensive, and conducted in a manner similar to the guideline specifications. Differences from the guidelines are as follows: the frequency of clinical observations was not reported; not all of the stipulated observations with regard to hematology, clinical chemistry, organ weights, and histopathology were made; and a limited neurobehavioral assessment was not performed. In these hazard reviews on the flame retardant alternatives, however, the adequacy of neurotoxicity data is considered separately, so this data gap will be noted under that topic. The 30-day study included urinalysis, which is not a guideline requirement, but provides valuable information.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

The only relevant available study is a 30-day repeated oral dose study, summarized below, which was conducted in a manner similar to the guidelines for a 28-day oral toxicity study in rodents.

Type: Repeated-dose 30-day oral toxicity
Species, strain, sex, number: Sprague-Dawley rats, 5/sex/dose
Doses: 0, 10, 30, 100, and 300 mg/kg/day
Purity: 98.0%
Vehicle: None
Exposure period, frequency: 30 days, administered daily in diet (food constantly available)
Post Exposure Period: None
Method: The test substance was administered in the diet. The rats were weighed initially then weekly throughout the study, and were observed for clinical signs, but frequency of this observation was not reported. Food consumption was measured weekly, and dietary concentrations were adjusted to maintain the target dosages. Hematologic evaluations (packed cell volume, hemoglobin, total erythrocyte count, total and differential leukocyte counts) and urinalysis (specific gravity, pH, sugar, proteins, occult blood, bilirubin) were performed on study day 24 in the control and high dose groups. Clinical chemistry analyses [BUN, alkaline phosphatase, SGPT (ALT)] were performed on blood samples collected from all the rats at the termination of the study. A complete necropsy was performed, and heart, liver, kidney, testes,

and brain were weighed. A reasonably comprehensive selection of tissues was examined histologically in high dose and control animals. Liver, kidney, and bladder were examined histologically in the low- and mid-dose animals. Statistical analyses were performed on the continuous variables.
Results: A statistically significant increase in BUN in male rats was noted at 300 mg/kg/day. No significant changes were seen in the urinalysis results. Dose-related histopathologic changes in kidney (degeneration and regeneration of renal cortical tubular epithelial cells) and urinary bladder tissue (generalized hyperplasia of the transitional epithelium) were noted only in male rats at ≥100 mg/kg/day. Incidences of each of these effects were 0/5 in controls and in each of the two lower dose groups, 2/5 in the 100 mg/kg/day group, and 5/5 in the 300 mg/kg/day group. Bladder effects were seen in some of the acute oral toxicity studies as well. Because the tissue staining procedures may not have been optimal for visualizing hyaline droplets in renal tissue, the possibility that the renal effects may have been related to $alpha_{2u}$-globulin associated renal toxicity cannot be ruled out. The OPPTS and OECD guidelines, however, do not address the issue of staining techniques. No changes in any of the endpoints were noted in the female rats, and no changes in endpoints other than those noted above were seen in the males. Although $alpha_{2u}$-globulin associated nephropathy is not considered relevant to humans (U.S. EPA, 1991), not all chemically-induced male rat nephropathy is of this type. Therefore, in the absence of additional information, the renal lesions are considered relevant. The NOAEL for bladder and renal effects was 30 mg/kg/day and the LOAEL was 100 mg/kg/day.
Reference: Humiston et al., 1973

- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**

No studies of this type were located.

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

No studies of this type were located.

Subchronic Dermal Toxicity (21/28-day or 90-day)

Conclusion:

The available subchronic dermal toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent subchronic dermal toxicity studies were located that addressed the endpoints in the guidelines listed below.

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity: 90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)

Conclusion:

The available subchronic inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies of this type were located.

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent were located that addressed the chronic toxicity studies endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent neurotoxicity studies were located that addressed the endpoints in the guidelines listed below.

Delayed Neurotoxicity

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**
  Note this guideline is not relevant for tribromoneopentyl alcohol, which is not an organophosphorus substance.

Neurotoxicity (Adult)

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat)
  - OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent)
  - OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred)
  - OPPTS Harmonized Guideline 870.6855

These studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

IMMUNOTOXICITY

***Conclusion*:**

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent immunotoxicity studies were located that addressed the endpoints in the guideline listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

Four studies of gene mutation *in vitro* reported negative results without activation or with activation using liver S9 from rat, rabbit, or monkey. These studies, all bacteria reverse mutation tests, although not individually adequate for characterization of the gene mutation *in vitro* endpoint as they did not conform fully to OPPTS and OECD guidelines or were missing vital study details, report similar results. Therefore, if they are considered together, they provide sufficient support to adequately characterize the gene mutation *in vitro* endpoint. Results of one study indicate that activation with hamster S9 may result in mutagenicity. Studies of chromosomal aberrations were not available, however, and are needed for adequate characterization of the genotoxicity endpoint.

Gene Mutation in Vitro:

- **Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)**

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA-1535, TA-100, TA-1538, TA-98, and TA-1537
Metabolic activation: Absence and presence of an activating system derived from rat liver (S-9 mix)
Concentrations: 50, 250, 1,250, 2,500, and 5,000 µg/plate
Purity: Not reported
Solvent: DMSO

Method: Procedures stated as complying with OECD Guideline 471 (1983); preliminary toxicity test in strain TA-98. The assay utilized a plate incorporation method. The main study was conducted in duplicate with a negative solvent control, positive controls, and plates devoid of organisms to verify the sterility of the S-9 mix. Incubation at 37°C for 48 hours.
Results: No significant increases in revertant colony numbers over control counts were obtained for trineopentyl alcohol with any of the tester strains, either in the presence or absence of metabolic activation.
Reference: Ameribrom, Inc., 1990

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA-1535, TA-100, TA-1538, TA-98, and TA-1537
Metabolic activation: With and without S-9 mix
Concentrations: 0, 50, 100, 500, and 1,000 µg/plate
Purity: Not reported
Solvent: DMSO
Method: The test was reported as having been performed in accordance with the methods described in detail in the "Principles of the Ames Mutagenicity Test" by M. Green and E. Riklis of 1979. Each compound was tested at least twice and in duplicates. Negative controls. Positive controls, such as methylcholantrene, benzopyrene, and N-methyl-N-nitrosoguanidine (MNNG).
Results: The compound was not mutagenic.
Reference: Ameribrom, Inc., 1982d

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA-1535, TA-1537, and TA-1538
Metabolic activation: With and without mammalian (rabbit, rat, and monkey) metabolic activation
Concentrations: 0.05% (plate tests); 0.025%, 0.050%, and 0.100% (suspension tests)
Purity: >99%, "pure" tribromoneopentyl alcohol
Solvent: DMSO or saline
Method: Cytotoxicity testing performed. Positive and negative controls used. Plate incubation at 37°C for 4 days, with each compound done in duplicate. Suspension tests were conducted with metabolic activation at 37°C for 1 hour in an oxygen atmosphere, or without metabolic activation at 37°C for 1 hour, with all flasks shaken during treatment. Suspension tests were scored after plating and incubation for 48 hours at 37°C.
Results: The test substance did not exhibit genetic activity under any of the testing conditions (plate tests, with and without activation; suspension tests, with and without activation) employed in this study.
Reference: Litton Bionetics, Inc., 1975a

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA-1535, TA-1537, and TA-1538

Metabolic activation: With and without mammalian (rabbit, rat, and monkey) metabolic activation
Concentrations: 0.150% (plate tests); 0.075%, 0.150%, and 0.300% (suspension tests)
Purity: Not reported, "plant" tribromoneopentyl alcohol
Solvent: DMSO or saline
Method: Cytotoxicity testing performed. Positive and negative controls used. Plate incubation at 37°C for 4 days, with each compound done in duplicate. Suspension tests were conducted with metabolic activation at 37°C for 1 hour in an oxygen atmosphere, or without metabolic activation at 37°C for 1 hour, with all flasks shaken during treatment. Suspension tests were scored after plating and incubation for 48 hours at 37°C.
Results: The test substance did not exhibit genetic activity when all test data were considered. The negative assessment was based on combined test results for both rat and rabbit activation assays and non-activation assays, as two sets of original test data with TA-1535 (one with rat tissue, one with rabbit tissue) suggested mutagenic activity, but repeat tests with this strain did not indicate mutagenic activity.
Reference: Litton Bionetics, Inc., 1975b

Additional Information

Results of a 1983 preincubation assay in *Salmonella typhimurium*, listed on the NTP (2004) online database, confirm the negative results of other studies in TA100, TA98, TA1535, and TA1537 without activation or with activation by rat liver S9. Activation using S9 from hamster liver resulted in positive results in TA100 and TA1535, but negative results in the two other strains.

Other

- **Mitotic Gene Conversion in Saccharomyces cerevisiae (OPPTS Harmonized Guideline 870.5575)**

The two available studies, conducted by the same laboratory at about the same time, appear marginally adequate.

Type: Mitotic gene conversion
Species, strain: *Saccharomyces cerevisiae* D4
Metabolic activation: With and without mammalian (rabbit, rat, and monkey) metabolic activation
Concentrations: 0.5%, 1.0%, and 2.0%
Purity: >99%, "pure" tribromoneopentyl alcohol
Solvent: DMSO or saline
Method: Cytotoxicity testing performed. Suspension tests were conducted with metabolic activation at 37°C in an oxygen atmosphere for 4 hours, and without metabolic activation at 30°C for 4 hours, with all flasks shaken during treatment. Scoring was done after plating and

incubation for 3-5 days at 30°C. Concurrent negative controls, positive controls run concurrently with the non-activation assay. Study authors state (without reporting the data) that the positive controls for activation assay were run on a different day, but cell culture was the same. The authors may be referring to the positive control data reported in the appendix of the following report on "plant" tribromoneopentyl alcohol.
Results: The test substance did not exhibit genetic activity either with or without metabolic activation.
Reference: Litton Bionetics, Inc., 1975a

Type: Mitotic gene conversion
Species, strain: *Saccharomyces cerevisiae* D4
Metabolic activation: With and without mammalian (rabbit, rat, and monkey) metabolic activation
Concentrations: 0.375%, 0.750%, and 1.500%
Purity: Not reported, "plant" tribromoneopentyl alcohol
Solvent: DMSO or saline
Method: Cytotoxicity testing performed. Suspension tests were conducted with metabolic activation at 37°C in an oxygen atmosphere for 4 hours, and without metabolic activation at 30°C for 4 hours, with all flasks shaken during treatment. Scoring was done after plating and incubation for 3-5 days at 30°C. Concurrent negative controls. Concurrent positive controls for the activation assays. Positive control data for the non-activation assay were not reported, but may have been those in the above mitotic gene conversion study with pure tribromoneopentyl alcohol.
Results: The test substance did not exhibit significant genetic activity either with or without metabolic activation.
Reference: Litton Bionetics, Inc., 1975b

No studies were available on the genotoxicity of tribromoneopentyl alcohol in the following types of types of tests:

Gene Mutation in Vivo
Chromosomal Aberrations in Vitro
Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

1-Propanol, 2,2-dimethyl-, tribromo derivative

Synonym	Tribromoneopentyl alcohol
CAS	36483-57-5
MF	$C_5H_9Br_3O$
MW	324.84
SMILES	BrC(C(CO)(C)C)(Br)Br

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

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Flame Retardant Alternatives

Tris(1,3-dichloro-2-propyl) Phosphate

Draft Hazard Review

December 2004

Tris(1,3-dichloro-2-propyl) phosphate:
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	✓
Dermal	✓
Inhalation	*
Eye irritation	✓
Dermal irritation	✓
Skin sensitization	*
Subchronic Toxicity	
28-Day oral	
90-Day oral	*
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	*

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	✓
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	✓
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	✓

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✓
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	*
Additional neurotoxicity studies	✘
Immunotoxicity	
Immunotoxicity	*
Genotoxicity	
Gene mutation in vitro	✓
Gene mutation in vivo	✓
Chromosomal aberrations in vitro	✓
Chromosomal aberrations in vivo	*
DNA damage and repair	✓
Other	✓

Tris(1,3-dichloro-2-propyl) phosphate:
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	✓
Octanol/water partition coefficient	✓
Oxidation/reduction	
Melting point	✓
Boiling point	✓
Vapor pressure	*
Odor	✓
Oxidation/reduction chemical incompatibility	
Flammability	✓
Explosivity	
Corrosion characteristics	
pH	✘
UV/visible absorption	✓
Viscosity	✓
Density/relative density/bulk density	✓
Dissociation constant in water	✘
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	✓
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	*
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	✓
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	*
Hydrolysis as a function of pH	✓
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	*
Daphnia acute EC50	*
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	*
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	*

Chemical Identity

2-Propanol, 1,3-dichloro-, phosphate (3:1)

CAS	13674-87-8
MF	$C_9H_{15}Cl_6O_4P$
MW	430.91
SMILES	ClCC(CCl)OP(=O)(OC(CCl)CCl)OC(CCl)CCl
Synonyms	Tris(1,3-dichloro-2-propyl) phosphate, TDCPP, Fyrol FR-2

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401).

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Several acute oral lethality studies were available in a variety of species: rabbits, rats, and mice. These studies were from the older (pre 1980) literature, did not report substance purity, and do not fully conform to OPPTS or OECD guidelines, but given the magnitude of the LD50 values the data are adequate for the evaluation of acute oral toxicity. Acute oral LD50 values generally exceeded the current limit dose of 2,000 mg/kg. Reports that specified a 14-day observation period are presented in detail.

Critical Studies:

Type: Acute oral toxicity
Species, strain, sex, number: Rabbit, Dutch-belted, 5 males/group
Doses: 0, 5,000, 7,500, and 10,000 mg/kg
Purity: Fyrol FR-2; purity not specifically reported
Vehicle: Not reported by Akzo-Nobel
Method: 14-Day post-dosing observation period; observations limited to mortality, clinical signs, and necropsy. LD50 calculated according to Litchfield and Wilcoxon.
Results: Clinical signs shortly after dosing included ataxia, weakness, and diarrhea; survivors normal by day 9. Necropsy revealed no abnormalities. Acute oral male rabbit LD50 = 6,800 mg/kg (95% CI 5,615-8,234 mg/kg).
Reference: Robust summary from Akzo-Nobel, 2001a, unpublished study conducted 1982

Type: Acute oral toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 5 males/group
Dose: 1,000, 2,150, 5,640, or 10,000 mg/kg
Purity: Fyrol FR-2; purity not specifically reported
Vehicle: None
Observation period: 14 days post dosing
Method: 14-Day post-dosing observation period; observations limited to mortality, clinical signs, and necropsy; LD50 calculated according to Litchfield and Wilcoxon; not specified whether fed or fasted at time of dosing.
Results: No effects at 1,000 mg/kg. Dose-related depression at or above 2,160 mg/kg; survivors normal by day 5. No gross lesions in survivors; fatalities had congestion of heart, lung, and liver. Acute rat oral LD50 = 3,160 mg/kg (95% CI 2,050-4,800 mg/kg)
Reference: Stauffer, 1972d; robust summary from Akzo-Nobel, 2001a

Type: Acute oral toxicity
Species, strain, sex, number: Mouse**,** Slc/ddY, 10/sex/dose
Purity: Not reported
Doses: For males: 0, 2,210, 2,380, 2,570, 2,780, 3,000, 3,240, and 3,500 mg/kg. For females: 0, 2,890, 2,040, 2,210, 2,380, 2,570, and 2,780 mg/kg.
Vehicle: Olive oil
Method: Observed for mortality and clinical signs for14 days. No body weight or gross necropsy examination.
Results: Treated animals exhibited ataxic gait, hyperactivity, convulsion and death. No mortality was observed in controls or in males at 2,210 mg/kg or females at 1,890 mg/kg. The LD50 values were 2,670 mg/kg (2,520-2,830 mg/kg) for male mice and 2,250 (2,120-2,380 mg/kg) for female mice.
Reference: Kamata et al., 1989

Additional Studies and Information:

Other studies available only in secondary sources reported similar results. An oral LD50 of >2,000 mg/kg was reported in male and female rats exposed to Tolgard TDCP MK1(Cuthbert, 1989a as reported in WHO, 1998); clinical signs observed during the first 5 days after dosing included hypokinesia, piloerection, soiled coats, ataxia, chromodacryorrhea, rhinorrhea, and salivation.

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged adequate to meet the endpoint.

***Basis for Conclusion*:**

The available studies predate the preferred study guidelines, and did not report purity, but together indicated no mortality at the guideline limit dose of 2,000 mg/kg. The report specifying a 14-day observation period is presented in more detail.

Type: Acute dermal toxicity
Species, strain, sex, number: Rabbit, New Zealand albino, sex not specified, 4
Dose: 4,640 mg/kg
Purity: Fyrol FR-2; Stauffer, no data
Vehicle: None
Exposure period: 24 Hour
Method: 4 Rabbits tested occluded; 14-day observation period. Gross necropsy.
Results: Mortality after 14 days = 0/4. No overt signs of toxicity and no gross necropsy findings. Therefore, dermal acute LD50 >4,640 mg/kg.
Reference: Stauffer, 1973a; additional information from robust summary in Akzo-Nobel, 2001a

Additional Studies and Information:

Other studies available only in secondary sources with minimal detail. A dermal LD50 of >2,000 mg/kg was reported in male and female Sprague-Dawley rats exposed to Tolgard TDCP MK1 (Cuthbert, 1989b as reported in WHO, 1998). No deaths and no clinical signs were noted 24 hours after treatment.

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300; OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available study on TDCPP predates the preferred guidelines. The duration was shorter than currently recommended and no deaths were observed. Analysis of aerosol particle size, however, was not mentioned so it is not known whether the size was respirable. Necropsies were not performed.

Type: Acute inhalation toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 5 males and 5 females
Doses: 9.8 mg/L (9,800 mg/m^3)
Purity: No data
Vehicle: None
Duration: 1 hour

Method: Observation period = 14 days. Observed daily for signs of toxicity and for mortality.
Results: No mortality after 14 days; initial signs of moderate depression
Reference: Stauffer,1973b

Additional Studies and Information:

Other studies available only in secondary sources reported similar results. An acute inhalation LC50 of >5,220 mg/m^3 was reported for Sprague-Dawley rats exposed to aerosol of TDCPP (Amgard TDCP) (Anderson, 1990 as reported in WHO, 1998).

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Two reasonably adequate studies report similar results in rabbits: mild reversible irritation of the conjunctiva. The studies are summarized below.

Type: Acute eye irritation
Species, strain, sex, number: Rabbit, New Zealand White, sex not specified; 6
Doses: 0.1 mL
Purity: No data, Stauffer Fyrol FR-2
Vehicle: None
Method: Cited CFR [U.S. Federal Hazardous Substances Labelling Act] Section 191.12, chapter 1, title 21. Following instillation of TDCPP, eyes were examined at 24, 48, and 72 hours.
Results: Mild conjunctival effects in 3/6 that cleared by 48 hours.
Reference: Stauffer, 1972c

Type: Acute (24-hour) eye irritation
Species, strain, sex, number: Rabbit, New Zealand White, male and female; 9 total
Doses: 0.1 mL
Purity: No data
Vehicle: None
Method: U.S. EPA Hazard Evaluation. 1978. Fed. Reg. 43: 163: pp. 37331-37402. Thirty seconds following instillation of TDCPP, the treated eyes of three rabbits were washed, treated eyes were not washed in 6 rabbits. The untreated eye of each animal served as a control. The cornea, iris and conjunctiva of each eye were examined at 24, 48, and 72 hours, and at 4 and 7 days after instillation of TDCPP using the Draize scoring method.
Results: No signs of eye irritation were observed (average total Draize score of zero).

Reference: Stauffer, 1979; robust summary from Akzo-Nobel, 2001a for study dated 1979

Additional Studies and Information:

One hour following application of Tolgard TDCP MK1 to the eyes of New Zealand White rabbits, slight conjunctival redness and slight discharge were noted (Cuthbert and Jackson, 1990 as reported in WHO, 1998); effects cleared by 24 hours.

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Two reasonably adequate studies, patterned after guidelines in effect at the time, provide similar results, indicating that TDCPP was a non-irritant when applied for 4 hours (consistent with current guidelines) and a mild irritant when applied for 24 hours to rabbit skin. Additional studies provide support. The studies are summarized below.

Critical Studies:

Type: Acute (24-hour) dermal irritation
Species, strain, sex, number: Rabbit, New Zealand, sex not specified, 6
Doses: 0.5 mL
Purity: Not reported; Stauffer Fyrol FR-2
Vehicle: None
Method: Cites "EPA protocol". Back hair was shaved, each rabbit tested on intact and abraded skin, occlusive dressing removed after 24 hours, observations at 24 and 72 hours.
Results: No edema on intact or abraded skin in any of the 6 rabbits. Mild erythema was visible at 24 hours but cleared by 72 hours, resulting in a score of 0.63. The report classified TDCPP as a mild irritant.
Reference: Stauffer, 1979

Type: Acute (4-hour) dermal irritation
Species, strain, sex, number: Rabbit, not specified (but New Zealand white rabbits were used in an eye irritation test conducted at the same time)
Doses: 0.5 mL
Purity: Not reported; Stauffer Fyrol FR-2
Vehicle: None
Method: Back hair shaved, each rabbit tested on intact and abraded skin, occlusive dressing removed after 4 hours, observations at 4, 24 and 48 hours.

Results: No erythema or edema on intact or abraded skin in any of the 6 rabbits.
Reference: Stauffer, 1972c

Additional Studies:

Another study, on Tolgard TDCPP MK1, reported well-defined (score 2) erythema in 2 New Zealand White rabbits and slight erythema in a third rabbit 1 hour after patch removal, but duration of exposure was not specified (Cuthbert, 1989c as reported in WHO, 1998). Effects cleared by 48 hours. The substance was classified as a skin irritant.

Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)

A robust summary in a submission to the HPV Challenge program was located for an unpublished industrial study stated to have been conducted under guideline. The summary probably has not been reviewed by EPA, since this endpoint is not required for the HPV program. Furthermore, the summary omits information necessary to determine study adequacy, such as: the strain, sex, group size, substance purity, and dose levels. The summary claimed that the doses were selected according to guideline, but the exact levels are not stipulated in the guideline. Despite the possibility that the unpublished study might be adequate, without additional information, the skin sensitization endpoint appears not to be satisfied by the available data.

Critical Studies:

Type: Dermal sensitization study
Species, strain, sex, number: Guinea pig, strain and sex not reported
Doses: Stated as according to guideline, but exact doses are not stipulated in guideline.
Purity: Not reported; Fyrol FR-2
Vehicle: Water
Method: Three pairs of intradermal injections into shaved shoulder: 1:1 Freunds Complete Adjuvent (FCA) and saline, the test material, and 1:1 FCA and test material. Controls received water in place of the test material. On day 6, 24 hours before topical induction application, sodium lauryl sulfate was applied to sites to enhance local irritation. On day 7, test substance was applied to sites (water for controls). On day 21, animals received challenge dose by dermal application, occluded for 24 hours. Sites observed for irritation and sensitization (Grade 0-4).
Results: The sensitization score for Fyrol FR-2 was zero, indicating the substance is not a chemical sensitizer.
Reference: Robust summary in Akzo-Nobel, 2001b for unpublished and unidentified study dated 2001

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

Conclusion:

The available subchronic oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A Japanese 90-day dietary study in mice (Kamata et al. 1989) provides limited relevant information in the English abstract and data tables. The study was not adequate to characterize this endpoint because histopathological analysis was apparently limited to the liver. A fertility study by Wilczynski et al. (1983), discussed under the Reproductive Toxicity endpoint, evaluated male rabbits exposed by oral gavage for 12 weeks, but did not involve treated females.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

No study of this type was located.

90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)

Type: 90-Day repeated oral
Species, strain, sex, number: Mouse, Slc/ddY, 12/sex/dose
Doses: TDCPP at dietary concentrations of 0, 0.01, 0.04, 0.13, 0.42, and 1.33% in the diet, resulting in reported average daily doses of 0, 13.2, 47.3, 171.0, 576.0, and 1,792.3 mg/kg/day in males and 0, 15.3, 62.5, 213.6, 598.0, and 1,973.1 mg/kg/day in female mice
Purity: Not reported
Vehicle: None; added to diet
Exposure period, frequency: 90 days, ad lib
Method: Body weight, food consumption measured weekly. At 1 and 3 months in half the animals, hematologic (erythrocyte, hemoglobin, hematocrit, and leukocyte counts) and clinical chemistry parameters (total protein, albumin, albumin/globulin ratio, blood urea nitrogen, glucose, total cholesterol, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase). At 1 and 3 months, half the animals were necropsied and absolute and relative organ weights were determined for brain, heart, lung, liver, kidney, and spleen. The liver was examined for microscopic histopathology; the English text does not mention whether other tissues were examined.
Results: At the highest dietary level, 1.33%, all mice exhibited emaciation, rough hair, and tremor and died within 1 month. At 1.33%, food consumption was reduced and body weight loss occurred in both sexes. Mean body weight gain was reduced by about 10% (estimated from graph) in males at 0.42% throughout the study. The following statistically significant changes occurred in treated groups compared to controls. Slight anemia (reduced hemoglobin; $p<0.05$) in males at 0.42% after 3 months. Anemia (reduced hemoglobin at ≥0.13% after 1 month and at 0.42% at 3 months, erythrocyte and hematocrit at 0.42% at 1 and 3 months) in females (3-month

values $p<0.01$). Albumin/globulin ratios elevated in all treated male groups at 3 months. Alkaline phosphatase elevated in females at 0.42% at 1 month but not later. Dose-related organ weight elevations compared to controls observed at 3 months in males included relative liver weight (+32-51%) at ≥0.13% and relative kidney weight (+39%) at 0.42%. Significant elevations in organ weights in females at 3 months included relative liver weight (+16-51%) at ≥0.04%, absolute (+30%) and relative (+34-40%) kidney weights at ≥0.13%, and absolute liver weight (+40%) at 0.42%. The statistical significance of these organ weight elevations was $p<0.01$ for rats exposed at ≥0.13% and $p<0.05$ for rats exposed at 0.04.%. Histopathology of the liver (slight focal necrosis) was observed in only two females at 0.42%. The dietary level of 0.01% is a NOAEL of 15.3 mg/kg/day and the dietary level of 0.04% is a LOAEL of 62.5 mg/kg/day for liver and kidney weight elevations in female mice.
Reference: Kamata et al., 1989

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

No studies of this type were located.

Subchronic Dermal Toxicity (21/28-day or 90-day)

Conclusion:

The available subchronic dermal toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No data exist for the subchronic dermal toxicity endpoint.

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**

- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

No studies of either type were located.

Subchronic Inhalation Toxicity (90-day)

Conclusion:

The available subchronic inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No repeated-exposure inhalation toxicity studies were located.

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

No studies of this type were located.

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A fertility assay in male rabbits exposed by oral gavage for 12 weeks prior to mating (Wilczynski et al., 1983) partially characterizes this endpoint, but is not sufficient to satisfy the reproductive toxicity endpoint since it was described only in an abstract and females were not tested. Other studies (Hazleton, 1978; Tanaka et al., 1981) described below under Developmental Toxicity reported that in pregnant female rats exposed orally to TDCPP, adverse reproductive effects occurred only at maternally lethal doses. However, no study evaluated reproductive function in females treated prior to mating.

The 2-year feeding bioassay in rats by Freudenthal and Henrich (2000; Bio/Dynamics, 1980, 1981), discussed below under Chronic Toxicity, provides reproductive histopathology data that are, however, insufficient to satisfy the reproductive toxicity endpoint. This study provided histopathology results for the testis, epididymis, seminal vesicle, ovary, and uterus for the control and high-dose groups (0 and 80 mg/kg/day) after 1 year (10 scheduled sacrifices/sex/group) and for survivors in all groups after 2 years; unscheduled sacrifices (rats killed in a moribund state) were also examined. The 2-year exposure is too long to represent reproductive toxicity, because of the confounding effects of aging; the results pointed to dose-related effects in male reproductive organs (at $\geq$5 mg/kg/day, atrophy and decreased secretory product of the seminal vesicles; at $\geq$20 mg/kg/day, testicular germinal atrophy with oligospermia; and at 80 mg/kg/day, oligospermia and luminal accumulation of degenerated seminal products in the epididymis). No significant effect was observed in females. The tested doses, which were considerably lower than the guideline limit dose of 1,000 mg/kg/day, were not high enough to induce significant reproductive histopathology after one year of exposure; 1/10 high-dose males had oligospermia. Thus, a LOAEL for reproductive effects following subchronic (90-day) exposure is not available and cannot be extrapolated from the existing data, but the chronic data indicate a LOAEL of 5 mg/kg/day for atrophy and decreased secretory product of the seminal vesicles.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

No studies were available that met the specific designs of the three protocols listed above.

Additional Studies:

A study described in an abstract by Wilczynski et al. (1983) addresses fertility in male rabbits exposed by oral gavage for 12 weeks prior to mating.

Type: Fertility
Species, strain, sex, number: Rabbit, strain not specified, 10 males/dose
Purity: Not reported
Doses: 0, 2, 20, or 200 mg/kg/day
Vehicle: Not reported
Exposure duration, frequency: 12 weeks, once by oral gavage daily
Method: Males treated for 12 weeks, then mated with untreated females. Body weight, clinical signs, clinical chemistry, hematology, mating behavior, male fertility, sperm quantity and quality, kidney and liver weights, gross and microscopic pathology (range of organs examined not specified).
Results: High-dose animals had significantly increased absolute kidney weight and relative liver weight. TDCPP had no effect on male reproductive parameters; there was no histopathology in kidneys, liver, pituitaries, testes, or epididymides.
Reference: Wilczynski et al., 1983

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Developmental toxicity studies in two strains of rats exposed to Fyrol FR-2 by oral gavage followed methods consistent with OECD Guideline 414 (one study pre-dated the guideline).

Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)

Type: Prenatal developmental toxicity
Species, strain, sex, number: Rat, Wistar, 15 pregnant females at the highest dose, 23-24 pregnant females in controls and other dose groups.
Purity: not reported
Doses: 0, 25, 50, 100, 200, and 400 mg/kg/day
Vehicle: Olive oil
Exposure duration, frequency: Once by oral gavage daily on gestational days (GD) 7-19.
Method: Body weight, food consumption, clinical signs, pregnancy rates, and necropsy of dams, kidney weight; uterine contents (including implants and resorption) at day 20 of gestation, corpora lutea; fetal viability, sex ratio and weight, crown-rump length, and external and skeletal abnormalities.
Seven dams from each of the control and ≤200 mg/kg/day groups were permitted to litter normally and evaluated for implantation sites, delivery index, number of live offspring at birth and survival on PND 4, at 4th week, and at 10th week. Litters were culled to 10 offspring on postnatal day 4 (PND 4) and subjected to behavioral tests (open field, water maze, rota rod, inclined screen, pain reflex and Preyer's reflex). Absolute organ weights of 10 organs plus testis, uterus and ovary were measured in offspring.
Results: Maternal mortality occurred only at 400 mg/kg/day: 11/15 died. Food consumption was suppressed at 400 mg/kg/day and slightly at 200 mg/kg/day. At 400 mg/kg/day, mean body weight loss occurred during GD 7-15, resulting in significantly ($p<0.05$) reduced terminal body weight on GD20: ~17% lower than control group. Absolute and relative kidney weights were significantly increased at 200 and 400 mg/kg/day. TDCPP at ≤200 mg/kg/day had no effect on corpora lutea or mean numbers of implants, fetal body weight, fetal sex ratio, or the number of dead or live fetuses. The numbers of dead fetuses and live fetuses were significantly ($p<0.01$) changed compared to controls by the loss of one whole litter at 400 mg/kg/day. No increase in malformations was observed in treated groups. For maternal toxicity, the NOAEL was 100 mg/kg/day and the LOAEL was 200 mg/kg/day for increased kidney weight. For fetal toxicity, the NOAEL was 200 mg/kg/day and the LOAEL was 400 mg/kg/day for increased fetal death; the highest dose of 400 mg/kg/day was a NOAEL for teratogenicity.
Postnatal observations: TDCPP at ≤200 mg/kg/day had no effect on implantation, delivery, postnatal survival, behavior, functional test results, or absolute organ weights of offspring.
Reference: Tanaka et al., 1981

Type: Prenatal developmental toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 20 pregnant females/dose
Purity: not reported
Doses: 0, 25, 100, and 400 mg/kg/day
Vehicle: Corn oil
Exposure duration, frequency: Once by oral gavage daily on gestational days 6-15

Method: Body weight, food consumption, clinical signs, pregnancy rates, and necropsy of dams; uterine contents (including implants and resorption) at day 19 of gestation, corpora lutea; fetal viability and weight, crown-rump length, external, visceral (1/3 fetuses), and skeletal abnormalities; extensive statistical analyses.
Results: High-dose dams exhibited clinical signs (urine stains, hunched appearance, and alopecia); sporadic signs of urine stains and hunched appearance occurred in a few mid-dose dams, but not at the low-dose. Food consumption was statistically lower in mid-dose dams on days 7-11 and in high-dose group throughout (days 7-15). During Days 6-11, significant ($p<0.05$) reductions in body weight gain in mid-dose dams and mean body weight loss at the high dose; on days 11-15, only high-dose dams showed reduced body weight gain. Overall body weights reduced in high-dose dams. TDCPP had no effect on implantation efficiency or mean number of corpora lutea. Treatment at the high dose significantly ($p<0.05$) increased the number of resorptions (to 14.4% compared to 6.7% in controls) and reduced fetal viability (to 85.6% compared to 93.3% for controls). Decreased skeletal development in the high-dose groups is related to growth retardation and decreased fetal size. The incidence of malformations was not related to treatment. The study indicates a NOAEL of 25 mg/kg/day and a LOAEL of 100 mg/kg/day for maternal toxicity (clinical signs and transient reduction in body weight gain) and a NOAEL of 100 mg/kg/day and a LOAEL of 400 mg/kg/day for developmental toxicity (increased resorptions and fetal mortality).
Reference: Hazleton, 1978

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

No studies with the specific designs of the two tests listed above were available.

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The combined chronic toxicity/carcinogenicity assay in dietarily exposed rats is consistent with the guideline (Freudenthal and Henrich, 2000; Bio/Dynamics, 1980).

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**

No studies of this type were located.

Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)

The protocol of a 2-year feeding bioassay in rats was consistent with this guideline (Freudenthal and Henrich, 2000; Bio/Dynamics, 1980). The published article focused on tumor results rather than non-neoplastic effects.

Type: Combined oral chronic toxicity and carcinogenicity assay
Species, strain, sex, number: Rat, Sprague-Dawley, 60/sex/group
Purity: 95%
Doses: 0, 5, 20, and 80 mg/kg body weight/day
Vehicle: None other than feed
Route: In feed; diets blended weekly to achieve target doses
Exposure duration, frequency: 2 years, ad lib
Method: Examined twice daily for mortality and clinical signs, weekly physical examination. Body weights and food consumption weekly for the first 13 weeks and biweekly thereafter. Ophthalmoscopic examinations every 6 months. Extensive hematology, clinical chemistry and urinalysis parameters at 3, 6, 12, 18, and 24 months. Ten/sex/dose randomly chosen for termination at 12 months; the remainder at 24 months. Gross necropsy including organ weights (8 organs plus gonads); histopathology of more than 30 tissues in control and high-dose rats; at low- and mid-doses, histopathology limited to liver, kidneys, testes, and adrenals. Statistical analyses.
Results: The following changes compared to controls were statistically significant ($p<0.05$). Mortality increased in high-dose males (to 61.7% vs 43.3% for controls). Lower body weights in high-dose males and females. Treatment had no effect on feed consumption. Signs of anemia (lower hemoglobin, hematocrit, erythrocyte counts) in high-dose rats. At the mid-dose, increased absolute and relative kidney weight males and females, absolute liver weight and relative thyroid weight in males, and relative liver weight in females. At the high dose, increased relative liver weight in males and absolute and relative thyroid weights in females.

Increases in the incidences of the following nonneoplastic lesions were statistically significant ($p<0.05$) in treated groups compared to the control groups; changes were not strictly dose-related in that incidences were depressed in high-dose groups. Kidney lesions (convoluted tubule hyperplasia) in males at $\geq$20 mg/kg/day and in females at 80 mg/kg/day. Other systemic lesions at 80 mg/kg/day involved the parathyroid (hyperplasia) in males and the liver (foci) and spleen (erythroid/myeloid hyperplasia) in females. Reproductive system lesions in males involved seminal vesicles (atrophy, decreased secretory product) at $\geq$5 mg/kg/day, testes (eosinophilic material in lumen, periarteritis nodosa) at $\geq$20 mg/kg/day, and epididymis (oligospermia and degenerated seminal product) at 80 mg/kg/day. (Tumor incidences are reported below under

Carcinogenicity.) The authors reported the lowest dose of 5 mg/kg/day as a NOAEL and the mid-dose of 20 mg/kg/day as a LOAEL. However, as evaluated in NRC (2000), the lowest dose of 5 mg/kg/day was a LOAEL for atrophy and decreased secretory product of the seminal vesicle.
Reference: Freudenthal and Henrich, 2000; also Bio/Dynamics (1980), fiche 27 of 32 and Bio/Dynamics (1981) fiche 6 of 6.

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Increased tumor incidences were observed in a combined chronic toxicity/carcinogenicity assay in rats exposed to TDCPP in the diet (Freudenthal and Henrich, 2000).

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**

No studies of this type were located.

Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)

A 2-year feeding bioassay by Freudenthal and Henrich (2000) was consistent with this guideline.

Type: Combined oral chronic toxicity and carcinogenicity assay
Species, strain, sex, number: Rat, Sprague-Dawley, 60/sex/group
Purity: 95%
Doses: 0, 5, 20, and 80 mg/kg body weight/day
Vehicle: None other than feed
Route: In feed; diets blended weekly to achieve target doses
Exposure duration, frequency: 2, ad lib
Method: See description above under Chronic Toxicity
Results: The following neoplastic changes compared to controls were statistically significant ($p<0.05$). Dose-related increased incidences at $\geq$20 mg/kg/day of renal cortical adenomas in both sexes and testicular interstitial tumors in males, and at 80 mg/kg/day, of hepatocellular adenomas and carcinomas combined in both sexes and adrenal cortical adenomas in females. The NRC (2000) concluded that this study provides sufficient evidence of carcinogenicity of TDCPP in rats following chronic oral exposure.
Reference: Freudenthal and Henrich, 2000; also Bio/Dynamics (1980, 1981)

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The delayed neurotoxicity component is satisfied by the existing data, but a developmental toxicity study by Tanaka et al. (1981) that included postnatal behavioral examinations did not fully satisfy the developmental neurotoxicity component. TDCPP gave negative results in single acute and subchronic oral delayed neurotoxicity studies in hens and in limited postnatal testing in rats exposed during gestation. A 2-year feeding bioassay in rats by Freudenthal and Henrich, 2000; Bio/Dynamics, 1980), discussed above under the Chronic Toxicity and Carcinogenicity endpoints, reported no lesions of the cervical spinal cord, but a slight (not statistically significant) increase in the incidence of gliomas of the brain in rats exposed to TDCPP at 80 mg/kg/day. The study authors could not determine whether this effect was related to exposure.

Delayed Neurotoxicity

Conclusion:

The available delayed neurotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Several acute studies and one subchronic study for delayed neurotoxicity in the hen, summarized below, give no evidence of acute cholinergic toxicity, inhibition of neurotoxic esterase (NTE) activity, or delayed neurotoxicity for TDCPP. These studies, performed prior to the existence of the guidelines, do not entirely conform to current guidelines, and may lack detail such as the purity of the TDCPP sample. The lack of significant NTE inhibition following dosing with 10,000 mg/kg suggests that no additional testing for delayed neurotoxicity is needed for TDCPP.

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Unpublished industrial acute (1- or 5-day) and subchronic (90-day) delayed neurotoxicity assays, which pre-date the guideline, are missing some details. One acute study employed a gavage dose 5 times higher than now specified under the guideline. The subchronic assay had a longer duration and a larger group size than specified under the guideline.

Critical Studies

Type: Acute oral delayed neurotoxicity
Species, strain, sex, number: Hen, White Leghorn, 4/dose
Purity: Fyrol FR-2, purity not reported, clear colorless liquid
Doses: 420 mg/kg (highest dose specified in protocol)
Vehicle: test substance diluted 50% in corn oil
Positive control: 90 or 120 mg/kg/day tri-ortho-tylol phosphate (TOCP)
Route: Gavage
Exposure duration, frequency: Once daily on five consecutive days
Method: Navy MIL-H-19457B (SHIPS) protocol. Hens were weighed and graded on days 7, 9, 11, 14, 16, 18, 21, and 23 after the first dose for no signs, doubtful/minor signs, positive paralytic signs, advanced paralytic signs, or death. Scores on the 21st day were compared with results for TOCP. Necropsy not performed.
Results: No overt signs of neurotoxicity in with TDCPP treatment. Positive control caused inability to walk, hypertension, ataxia, and prostration.
Reference: Bullock and Kamienski, 1972 as described in WHO, 1998; Stauffer 1972a

Type: Acute oral delayed neurotoxicity
Species, strain, sex, number: Hen, White Leghorn, 4/dose for TDCPP, 3/dose for controls
Purity: Fyrol FR-2, clear colorless liquid; one part of the report stated that the purity was not reported, whereas another part of the report indicated purity >99%.
Doses: 10,000 mg/kg
Vehicle: None
Positive control: 500 mg/kg tri-ortho-cresyl phosphate (TOCP)
Negative control: 15 mg/kg tetraethyl pyrophosphate (TEPP)
Route: Oral gavage
Exposure duration, frequency: Once
Method: Twenty minutes before dosing, hens received atropine and 2-PAM to protect against cholinergic effects. Hens were observed for toxic signs at 2-hour intervals for the first 8 hours. Mortalities were recorded after 24 hours. Brains were harvested 24 hours after dosing and analyzed for neurotoxic esterase (NTE) activity.
Results: Toxic signs were not reported specifically for TDCPP, but for all compounds tested at the maximum tolerated dose, signs included listlessness and ataxia. Inhibition of NTE activity was 7% for TDCPP and the negative control TEPP, but 85% for the positive control (TOCP). The current guideline specifies that testing is not necessary at doses above 2,000 mg/kg.
Reference: Stauffer, 1978

Type: Subchronic oral delayed neurotoxicity
Species, strain, sex, number: Hen, adult, White Leghorn, 10/dose
Purity: Not reported
Doses: 0, 4, 20, and 100 mg/kg/day
Vehicle: Not reported

Route: Oral Gavage
Exposure duration, frequency: 90 days, daily
Method: Body weight. Daily observations for mortality and behavioral changes; evaluated for signs of motor weakness 3 times per week. At termination, hens were necropsied and brain (multiple sections), sciatic nerve, and spinal cord (cervical, thoracic and lumbar) were examined histopathologically. TOCP was the positive control.
Results: Hens treated with TDCPP at the high dose exhibited mean reductions in body weight during the latter part of the study, but no overt signs of neurotoxicity and no histopathological effects in the nervous tissues. Conversely, the positive control hens exhibited consistently lower body weight gain, clinical signs of toxicity (locomotor impairment and ataxia) that became more severe with time. Histopathology results were not reported for the positive control.
Reference: Robust summary from Akzo-Nobel, 2001a; unpublished, unidentified study dated 1979

Neurotoxicity (Adult)

Conclusion:

The available adult neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The chronic oral bioassay by Freudenthal and Henrich (2000; Bio/Dynamics,1980, 1981) reported no lesions of the brain or spinal cord in rats exposed to TDCPP at doses as high as 80 mg/kg/day for 2 years, but no functional tests of neurotoxicity were performed.

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

No studies of this type were located.

Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)

Conclusion:

The available developmental neurotoxicity data were judged inadequate to meet the endpoint, although the available tests suggest that TDCPP is not a developmental neurotoxin.

Basis for Conclusion:

No studies of this specific design were located. A Japanese-language gavage study by Tanaka et al. (1981), described above under Developmental Toxicity, included postnatal neurobehavioral

tests (open field, water maze, rota rod, inclined screen, pain reflex, and Preyer's reflex) of sensory and motor function in rats. Full descriptions of these tests were not available in the English summary and therefore could not be compared to the guideline protocol. The study reported no adverse effect in these tests for offspring of dams that were exposed on gestational days 7-15 at doses as high as 200 mg/kg/day (the highest tested non-lethal dose that was a LOAEL for increased kidney weight). This study does not fully satisfy the developmental neurotoxicity endpoint because it omitted some parameters specified under the guideline: developmental landmarks for sexual maturity, auditory startle test, and neurohistopathological examinations.

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat)
  - OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent)
  - OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred)
  - OPPTS Harmonized Guideline 870.6855

These studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Conclusion: These endpoints do not appear to be applicable to TDCPP.

Basis for Conclusion: Although there are no studies addressing these endpoints, there are no reliable data for TDCPP, and no structure-activity considerations, that indicate a need for these follow-up studies.

Other Neurotoxicity Data

Cholinesterase inhibition

Fyrol FR-2 administered at 0, 2,000, or 3,980 mg/kg in corn oil was administered to groups of 10 male Sprague-Dawley rats by oral gavage had no effect on plasma or erythrocyte cholinesterase levels measured 4 or 14 hours after dosing (Stauffer, 1972b).

IMMUNOTOXICITY

***Conclusion*:**

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The only study evaluating the potential immunotoxicity of TDCPP (Luster et al., 1981) predates the guideline for immunotoxicity (note that the OPPTS guideline cites other works by this author). There is some uncertainty as the test material, reported as Fyrol FR2, but mis-identified by the authors as tris(**2,3-**dichloropropyl) phosphate. The study methods differed from the guideline in the short exposure period (4 rather than 28 days), parenteral administration (rather than oral or inhalation route), measurement of serum immunoglobulins in non-immunized rather than immunized mice, and the omission of some tests (enumeration of immunological cell subpopulations, test for NK-cell activity). The results do not provide dose–response information as to immunotoxicity of TDCPP following subchronic exposure by oral or inhalation routes of exposure.

Immunotoxicity (OPPTS Harmonized Guideline 870.7800)

Critical study

Type: Immunotoxicity, subcutaneous, acute
Species, strain, sex, number: Mouse, B6C3F$_1$, 6-8 females/dose
Doses: 0, 0.25, 2.5, or 25 mg/kg/day (Total cumulative doses of 0, 1, 10, or 100 mg/kg)
Identity: Stauffer Fyrol FR-2, lot 4670-3-23. This is the same lot as TDCPP tested in the 2-year oral assay by Freudenthal and Henrich (2000)
Purity: Stauffer, purity >95%
Vehicle: Corn oil
Route: Subcutaneous injection
Exposure duration, frequency: 4 days, once daily
Method: Observations included body weight, hematology, clinical chemistry (5 parameters) terminal necropsy, organ weights (liver, spleen and thymus), histopathology of spleen, thymus, and eight other organs, plaque-forming assay response to sheep red blood cells, and serum immunoglobulin quantification (non-immunized mice only). Non-guideline tests included proliferative capacity of granulocyte-macrophage progenitor cells (bone marrow), *in vitro* lymphoproliferative (LP) responses to mitogens, delayed hypersensitivity response to keyhole limpet hemocyanin. Extensive statistical analysis.
Results: Twenty percent of high-dose mice exhibited lymphoid depletion of the thymus. Statistically significant decreases *in vitro* lipopolysaccharide (B-cell antigen) at 2.5 mg/kg/day and concanavalin A (T-cell antigen) at 25 mg/kg/day.
Reference: Luster et al., 1981

GENOTOXICITY

Conclusion: The available genotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

TDCPP has been tested in *in vitro* and *in vivo* genotoxicity assays conducted in prokaryotic and eukaryotic cells under methods similar to guidelines. Results of *in vivo* tests (mutation in *Drosophila*, chromosomal aberration in mice) were negative, but positive results were reported in several *in vitro* assays (mutagenicity in bacterial and mammalian cells, chromosomal aberration).

Gene Mutation in Vitro:

Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA97, TA98, TA100, TA1535, TA1537
Metabolic activation: Tested with and without S9 from livers of Aroclor-induced male Sprague-Dawley rats or male Hamsters
Concentrations: 0, five concentrations between 10 and 10,000 µg/plate.
Purity: 94.4%
Method: Preincubation (20 minutes) and plate incorporation (48 hours) at 37°C. Positive controls were used; DMSO was the solvent. Triplicate plates per concentration. All assays repeated within 1 week.
Results: In three different laboratories, TDCPP tested positive in strains TA97 and TA100 in the presence of S9 from Aroclor-induced hamster liver and in strain TA1535 in the presence of S9 from Aroclor-induced rat or hamster liver. Positive controls gave expected increases. Solvent control and all other test combinations were negative.
Reference: Mortelmans et al., 1986

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538
Metabolic activation: Tested with and without Kanechlor 500 (PCB)-induced liver S9 from male Wistar rats
Concentrations: 0, 10, 30, 100, and 300 µg/plate.
Purity: Assayed as ~94% TDCPP, plus ~6% bis(1-chloromethyl-2-chloroethyl)(2,3-dichloropropyl) phosphate.
Method: Plate incorporation, 48-hour incubation at 37°C. Cited Ames protocol, which presumes the use of replicates and positive controls.
Results: No increase in revertants in any strain without activation or in strains TA98, TA1537, or TA1538 with activation. Weak increases in TA100 and TA1535 at the highest concentrations with S9.
Reference: Nakamura et al., 1979

Additional Studies

Other *S. typhimurium* assays in which S9 was prepared from phenobarbital-induced rat liver reported mutagenicity of TDCPP in strain TA98 by liquid preincubation assay (Abe and Urano, 1994) and in TA100 by plate incorporation assay (Gold et al., 1978; Soederlund et al., 1985). Majeska and Matheson (1983) reported dose-related positive results for TDCPP and its metabolite 1,3-dichloro-2-propanol in TA100 with S9 (phenobarbital-induced) in standard plate assays at concentrations up to 500 μg/plate. In a liquid preincubation quantitative assay, results for TDCPP were essentially negative—only increasing mutation frequencies at cytotoxic concentrations (survival <3%). However, its metabolites increased mutant frequencies with less cytotoxicity: 1,3-dichloro-2-propanone positive at <80% survival and 1,3-dichloro-2-propanol positive at <30% survival.

TDCPP was not mutagenic in *S. typhimurium* strains TA100, TA1535, or TA1538 without activation or when Aroclor-induction was used to prepare the S9 fraction (Prival et al., 1977); the highest exposure level was 10 μL per plate.

In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)

Type: Mammalian Cell Gene Mutation Test: Forward Mutation
Species, strain: Mouse lymphoma L5178Y
Metabolic activation: Tested with and without phenobarbital-induced liver S9 from male mice
Concentrations: 0, and five concentrations up to ~32 nL/mL without S9, and six concentrations up to 70 nL/mL with S9. Test conditions chosen based on preliminary assays so that 50% growth reduction occurred at highest concentration.
Purity: Not reported
Method: Selection of forward mutation from TK+/- to TK-/- genotype. Activity compared to tris(2,3-dibromopropyl)phosphate (TBPP).
Results: TDCPP yielded negative results with or without activation. TBPP was negative without, but positive with activation.
Reference: Brusick et al., 1979; also Litton Bionetics, Inc., 1977

Type: Mammalian Cell Gene Mutation Test: Forward Mutation
Species, strain: V79 Chinese hamster lung cells
Metabolic activation: Tested with phenobarbital-induced liver S9 from male rats
Concentrations: 0, 0.02 mM TDCPP. Test conditions chosen based on preliminary assays.
Purity: Not reported
Method: In two experiments, selection of 6-thioguanine-resistant colonies. Activity compared to tris(2,3-dibromopropyl)phosphate (TBPP).
Results: TDCPP with S9 did not increase mutation frequency. TBPP yielded positive results.
Reference: Soederlund et al., 1985

Gene Mutation in Vivo

Sex-linked Recessive Lethal test in *Drosophila melanogaster* (OPPTS Harmonized Guideline 870.5275)

Type: Sex-linked Recessive Lethal test
Species, strain: *Drosophila melanogaster,* 100 males/concentration
Metabolic activation: None
Concentrations: 2.5 and 25% in feed (1% gum tragacanth in 3% sucrose)
Purity: Technical-grade Fyrol FR-2, purity not reported
Method: TDCPP added to feed of males for 24 hours, subsequently mated with virgin unexposed females
Results: No evidence of toxicity or increase in the percentage of sex-linked recessive lethal mutations.
Reference: Brusick and Jagannath, 1977 as described in WHO, 1998; also Litton Bionetics, Inc., 1976

Chromosomal Aberration in Vitro

In Vitro Mammalian Chromosome Aberration Test (OPPTS Harmonized Guideline 870.5375)

Type: *In vitro* chromosome aberration assay
Species, strain: Mouse lymphoma L5178Y
Metabolic activation: None, phenobarbital-induced or PCB-induced
Concentrations: 0, 0.01 to 0.1 µL/mL for non-induced, phenobarbital-induced or PCB-induced mouse
Purity: Not reported
Method: 4-hour exposure to TDCPP with or without activation. Chromosomal aberrations scored in 50 metaphase spreads per concentration.
Results: TDCPP caused increases chromosomal aberrations (up to 40%) with PCB- or phenobarbital-induction compared to noninduced S9.
Reference: Brusick et al., 1979; also Litton Bionetics, Inc., 1977

Chromosomal Aberration in Vivo

Mammalian Bone Marrow Chromosomal Aberration Test (OPPTS Harmonized Guideline 870.5385)

The available study provides sufficient evidence that TDCPP did not induce chromosomal aberrations in mice exposed at the maximum tolerated dose of 760 mg/kg.

Type: Bone marrow chromosomal aberration *in vivo*

Species, strain: Mouse, CD-1, 4-8 males/group
Metabolic activation: None
Concentrations: 0, 0.05, 0.17, and 0.5 mL/kg; using the specific gravity of 1.52, the doses were 0, 76, 260, or 760 mg/kg. The highest dose was the maximum tolerated dose. Negative control was DMSO
Exposure duration, frequency: By oral gavage in once or daily on 5 consecutive days.
Purity: Technical grade; Not reported
Method: Mice were sacrificed at 6, 24, and 48 hours after single dose or 6 hours after the last of 5 doses. Between 233 and 400 cells were scored, rather than 500/animal. Triethylenemelamine was positive control.
Results: No evidence of increased frequency of chromosomal aberrations with TDCPP. TBPP was also negative at doses up to 1,000 mg/kg. Positive control produce expected large increase in micronucleated polychromatic erythrocytes.
Reference: Brusick et al., 1979; Litton Bionetics, Inc., 1978

Mammalian erythrocyte micronucleus test (OPPTS Harmonized Guideline 870.5395)

TDCPP administered as 2,000 mg/kg by an unspecified route to mice did not induce micronuclei in bone marrow erythrocytes (Thomas and Collier, 1985 as reported in WHO, 1998).

DNA Damage and Repair

Unscheduled DNA synthesis in mammalian cells in culture (OPPTS Harmonized Guideline 870.5550)

Type: Unscheduled DNA synthesis in mammalian cells (hepatocytes) in culture
Species, strain: Rat, Wistar, male
Metabolic activation: With or without phenobarbital-induction
Concentrations: 0, 0.05, and 0.1 mM
Purity: Not reported
Vehicle: DMSO
Method: Cultured hepatocytes exposed to TDCPP or TBPP for 18-19 hours. Incorporation of radiothymidine into DNA.
Results: TDCPP was not genotoxic at 0.05 mM, but at 0.1 mM, a moderate response was observed in hepatocytes from untreated rats, but not phenobarbital-treated rats. TBPP, the positive control, yielded positive results in induced and non-induced hepatocytes.
Reference: Soederlund et al., 1985

Other

In vitro Sister Chromatid Exchange Assay (OPPTS Harmonized Guideline 870.5900)

Type: *In vitro* sister chromatid exchange assay
Species, strain: Mouse lymphoma L5178Y
Metabolic activation: None, phenobarbital-induced or PCB-induced
Concentrations: 0, 0.005-0.03 μL/mL for phenobarbital-induced (4 concentrations), and 6 concentrations up to 0.070 μL/mL for non-induced or PCB-induced mouse
Purity: Not reported
Method: Ten cells per concentration were analyzed.
Results: TDCPP increased the incidence of sister chromatid exchanges in mouse lymphocytes under all three test conditions.
Reference: Brusick et al., 1979; also Litton Bionetics, Inc., 1977

Additional information

Fyrol FR-2 did not induce sister chromatid exchanges when applied to 3- to 4-day-old chicken embryos (Bloom, 1984).

Ecotoxicity

Aquatic Organism Toxicity

Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)

Conclusion:

The available acute toxicity data for freshwater fish (cold- and warm-water species) and saltwater fish were judged inadequate to meet the endpoint. The available acute fish toxicity studies are summarized in Table 1. However, if the results of the SafePharm study (1993a), cited by IPCS (1998) (see below), are confirmed independently, the acute toxicity data for cold freshwater fish species might meet the endpoint given the high degree of agreement of the two available studies in rainbow trout.

Basis for Conclusion:

Freshwater Fish

Ahrens et al. (1979) tested the toxicity to goldfish (*Carassius auratus*) of tris (1,3-dichloro-2-propyl) phosphate (TDCPP) released from fabric treated with the flame retardant. Laundered or unlaundered sections of garment that had been treated with Fyrol FR-2, were placed in tanks with six goldfish. Fish in the tank with the unlaundered section became sluggish and all died within 3 hours. The concentration of Fyrol FR-2 in the test water reached 30 mg/L. Fish exposed for 96 hours to the laundered section of garment did not exhibit signs of toxicity. In another study, TDCPP in water at 1 mg/L was not toxic to goldfish after 168 hours, but 5 mg/L of TDCPP killed all (6/6) goldfish within 24 hours (Eldefrawi et al., 1977). The studies by Ahrens et al. (1979) and Eldefrawi et al. (1977) did not evaluate toxicity using a range of concentrations of TDCPP in water and, thus, cannot be used to derive an LC_{50}.

Sasaki et al. (1981) estimated that the 96-hour LC_{50} values for killifish (*Oryzias latipes*) and goldfish were 3.6 mg/L and 5.1 mg/L, respectively. It appears that mortality was not evaluated in a control group of fish. It is unclear if the TDCPP concentrations in water reported by Sasaki et al. (1981) are measured or nominal values. The latter point is important because a parallel study indicated that the amount of TDCPP added to test water declines rapidly and less than 40% of the original amount of TDCPP remains in the test water after 96 hours (Sasaki et al., 1981). Thus, the lethal concentrations of TDCPP could be lower than the reported LC_{50} values. Sasaki et al. (1981) reported deformation of the spine in 7/10 killifish exposed to 3.5 mg/L TDCPP for 24 hours. However, Sasaki et al. (1981) do not provide sufficient information regarding the spine deformation in killifish to make meaningful use of these observations. It is unclear whether the deformations were observed in the acute toxicity study or in a separate assay

using killifish only. It appears that deformation was tested at only one concentration and a control group of fish was not evaluated.

Another study showed that the 96-hour LC_{50} of TDCPP in rainbow trout (currently classified as *Oncorhynchus mykiss*) was 1.4 mg/L (95% CI: 0.9-1.9 mg/L) (Unpublished study conducted in 1990, summarized in Akzo-Nobel, Inc., 2001a,b). A NOEC was not observed since one fish died at 0.63 mg/L, the lowest concentration tested. Compound purity was not provided in the summary and the reported concentrations of TDCPP in the test water appear to be nominal values. The guideline for acute toxicity in fish (OPPTS 850.1075) indicates that test concentrations must be measured during the test if, as was the case in this study, aeration is used. Thus, the study reported by Akzo-Nobel, Inc. (2001a,b) does not meet the criteria established by the guideline. The studies by Sasaki et al. (1981) and Akzo-Nobel, Inc. (2001a,b) suggest that the 96-hour LC_{50} for TDCPP in fish is in the range of 1 to 5 mg/L, making it moderately toxic to fish. However, the data are inadequate to satisfy the acute toxicity endpoint for freshwater fish. A 96-hour LC_{50} of 1.1 mg/L and a NOEC of 0.56 mg/L for TDCPP in rainbow trout (SafePharm, 1993a) were reported in IPCS (1998). Although the results of the study by SafePharm (1993a) are in agreement with those of Akzo-Nobel, Inc. (2001a,b), the study by SafePharm (1993a), or a study summary, was not available to allow for an independent evaluation of these data. Confirmation of the results of the study by SafePharm (1993a) might allow the acute toxicity endpoint for freshwater fish to be satisfied.

Marine Fish

No acute toxicity studies in saltwater fish species were located.

Table 4-1. Summary of available acute fish toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8)[a]									
			Selected Study Design Parameters[b]						
Study Reference	**Species Tested**	**96-Hour LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Ahrens et al., 1979	Goldfish (*Carassius auratus*)	None	Static	None	6	Yes. The concentration of Fyrol FR-2 in water was determined by gas chromatography.	**pH:** NR **Temp:** 20°C **DO:** NR **Hardness:** NR **Water volume:** 20 L **Electrical conductivity**: 290 micromhos/cm	None	A laundered or unlaundered 38 cm x 64 cm section of garment (0.24 square meter area; 227 g/m^3), which had been treated with Fyrol FR-2, was placed in tanks with six goldfish. Fish in the tank became progressively more sluggish and all died within 3 hours. The measured concentration of Fyrol FR-2 in the test water was 30 mg/L. Fish exposed for 96 hours to the same section of fabric after it had been laundered did not die. Data for mortality in control fish were not presented in the study. Goldfish are not a designated test species, as per OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine).

Table 4-1. Summary of available acute fish toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8)[a]									
			Selected Study Design Parameters[b]						
Study Reference	**Species Tested**	**96-Hour LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Akzo-Nobel, Inc., 2001a,b (Study conducted in 1990)	Rainbow trout (*Salmo gairdneri*)	1.4 mg/L (95% CI: 0.9-1.9 mg/L)	Static	Controls, 0.63, 1.25, 2.5, 5, 10 mg/L	10	No	**pH:** 7.14-7.78 **Temp:** 11.8-14.8 °C. **DO:** 92-100% of air saturation value **Hardness:** 218-228 mg/L as $CaCO_3$.	None reported	All mortalities occurred within the first 24 hours. Mortality was dose related. One fish died in the lowest dose group (0.63 mg/L). All fish died in the 5 and 10 mg/L groups. A NOEC was not observed.

Table 4-1. Summary of available acute fish toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8)[a]									
			Selected Study Design Parameters[b]						
Study Reference	**Species Tested**	**96-Hour LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Eldefrawi et al., 1977	Goldfish (*Carassius auratus*)	None	Static	1 and 5 mg/L in water	6	None reported	**pH:** NR **Temp:** 20°C **DO:** NR **Hardness:** NR **Electrical conductivity*:*** 290 micromhos/cm	Water or acetone	Fish were exposed to 1 or 5 mg/L TDCPP in water or acetone. None of the fish in the 1 mg/L treatment had died after 168 hours. All fish in the 5 mg/L treatment died within 24 hours. The most conspicuous signs of toxicity were sluggishness and disoriented swimming prior to death. Mortality in control fish was not reported. Goldfish are not a designated test species, as per OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine). The study cannot be used to establish an LC_{50} value.

Table 4-1. Summary of available acute fish toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8)[a]									
			Selected Study Design Parameters[b]						
Study Reference	**Species Tested**	**96-Hour LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Sasaki et al., 1981	Killifish (*Oryzias latipes*)	Killifish: 3.6 mg/L	Static	NR	7 to 9	Unclear if conducted	**pH:** NR **Temp:** 25°C. **DO:** NR **Hardness:** NR **Electrical conductivity:** NR	NR	Fish were acclimated at least for 10 days at 25 °C. The test concentrations used were not reported. A control group was not tested. Killifish, but not goldfish, are a designated test species, as per OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine). Deformation of the spine was observed in 7/10 killifish exposed to 3.5 mg/L TDCPP for 24 hours.
	Goldfish (*Carassius auratus*)	Goldfish: 5.1 mg/L							

[a]Studies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.
[b]NR: Not reported

Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD 202)

Conclusion:

The available acute toxicity data for freshwater invertebrates were judged inadequate to meet the endpoint. However, if the results of the study cited by IPCS (1998) (see below) are confirmed independently, the data might meet the endpoint given the high degree of agreement of the two available studies in freshwater invertebrates.

Basis for Conclusion:

The available data are summarized in Table 2. A flow-through study revealed a 48-hour LC_{50} of TDCPP with *Daphnia magna* of 3.8 mg/L (95% CI: 3.5-4.2 mg/L) and a NOEC of 1.6 mg/L (Unpublished study conducted in 1999, summarized in Akzo-Nobel, Inc., 2001a,b). Although some of the conditions of the study design (such as number of organisms, and water temperature and chemistry) appear to meet OPPTS Harmonized Guideline 850.1010, other aspects of the study, including compound purity and condition and fertility of the organisms in culture, were not reported in the summary. The amount of solvent used in the control group and the TDCPP treatments might have exceeded the recommended maximum solvent concentration, as per the OPPTS Guideline (100 mg/L), but this does not appear to have affected the study results. A 48-hour LC_{50} of 4.6 mg/L and a NOEC of 1.8 mg/L were reported for daphnia in a study by SafePharm (1993b), as cited in IPCS (1998). Although the results of the study by SafePharm (1993b) are in agreement with those of Akzo-Nobel, Inc. (2001a,b), the study by SafePharm (1993b), or a study summary, was not available to allow for an independent evaluation of these data. Confirmation of the results of the study by SafePharm (1993b) might allow the acute freshwater invertebrate toxicity endpoint to be satisfied.

Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)

Conclusion:

The available acute marine/estuarine invertebrate toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No acute toxicity studies in marine/estuarine invertebrate species were located.

Table 4-2. Summary of available acute invertebrate toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8)[a]

Study Reference	Species Tested	48-Hour LC_{50}	Selected Study Design Parameters						Comments on the Data
			Study Type	Concentrations Tested	No. of Organisms/ Concentration	Analytical Monitoring	Water Chemistry	Solvent	
Akzo-Nobel, Inc., 2001a,b (Study conducted in 1999)	*Daphnia magna*	3.8 mg/L (95% CI: 3.5-4.2 mg/L)	Flow-through	Negative control, solvent control (dimethyl-formamide), 0.98, 1.6, 2.8, 3.8, 5.1 mg/L	10	Yes	**pH:** 8.3 **Temp:** 20±2°C **DO:** ≥8.5 mg/L (94% of air saturation value) **Hardness:** 126 mg/L as $CaCO_3$.	Dimethyl-formamide	Daphnids in the negative and solvent control groups appeared normal, as did the organisms in the 0.98 and 1.6 mg/L groups. Mortality in the 2.8, 3.8, and 5.1 mg/L groups was 0, 70, and 80%, respectively. Daphnids (15%) in the 2.8 mg/L group were lethargic at study termination. The amount of solvent used in the control group and the TDCPP treatments is estimated to be approximately 300 mg/L. This exceeds the recommended maximum solvent concentration of 100 mg/L. The estimate is based on a reported dimethylformamide volume of 0.1 ml, a test chamber volume of 300 ml and a specific gravity of 0.95.

[a]Studies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.

Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)

***Conclusion**:*

The available chronic toxicity data for freshwater and marine fish data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No chronic toxicity studies in freshwater and marine fish were located.

Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD 211) and Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)

Conclusion:

The available chronic toxicity data for freshwater and marine/estuarine invertebrates were judged inadequate to meet the endpoint.

Basis for Conclusion:

No chronic toxicity studies in freshwater and marine/estuarine invertebrates were located.

Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)

Conclusion:

The available algal toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are summarized in Table 3. The summary of a 96-hour algal toxicity study (Unpublished study conducted in 1992, summarized in Akzo-Nobel, Inc., 2001a,b) indicates that the study does not meet the OPPTS Harmonized Guideline 850.5400. The pH and temperature of the test water during the study were outside of the acceptable ranges for *Selenastrum capricornutum*, as per Guideline 850.5400. Moreover, the two highest concentrations tested exceed the estimated water solubility of TDCPP (42 mg/L) and the concentrations tested were apparently not verified analytically. Additional information, including test substance purity, hardness, DO, TOC, TSS, exposure vessel size and head space, and measured chemical concentrations, were not provided in the summary. Also, there is no evidence that positive controls were used in order to establish that the algae were responding in the expected manner to

a known chemical. The deviations from the OPPTS Guideline indicate that the study is inadequate to satisfy the algal toxicity endpoint. Another study indicates that TDCPP at 10 mg/L had no effect on growth or biomass of the algal species *Scenedesmus subspicatus* exposed for 72 hours (Unpublished study conducted by SafePharm, 1994, cited in IPCS, 1998). The study, or a study summary, was not available for the study by SafePharm (1994) to allow for an independent evaluation of these data.

Table 4-3. Summary of available algal toxicity studies for tris(1,3-dichloro-2-propyl)phosphate [TDCPP] (CASRN: 13674-87-8)[a]								
			Selected Study Design Parameters[b]					
Study Reference	**Species Tested**	**EC_{50}, NOAEC, and LOAEC**	**Study Type**	**Concentration Range Tested**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Akzo-Nobel, Inc., 2001a,b (Study conducted in 1992)	*Selenastrum capricornutum*	96-hour EbC_{50} (biomass) = 12 mg/L (95% CI: 10-15 mg/L). 96-hour ErC_{50} (growth rate) = 39 mg/L (95% CI: 31-50 mg/L). 96-hour NOAEC: 6 mg/L.	Static	0 (negative control), 2, 6, 18, 54, or 162 mg/L	No	**Temp:** 21°C **pH:** 6.7-7.9 **DO:** NR **Hardness:** NR	None reported	A number of problems are evident with this study, namely the pH changed markedly during the study, and the reported pH and water temperature were outside of the recommended values for this algal species.

[a]Studies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.
[b] NR: Not reported.

Terrestrial Organism Toxicity

Acute Oral (OPPTS Harmonized Guideline 850.2100), Dietary (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205), or Reproductive Toxicity (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206) in Birds

Conclusion:

The available acute oral, dietary, and reproductive toxicity data for birds were judged inadequate to meet the endpoints.

Basis for Conclusion:

No acute oral, dietary, or reproductive toxicity studies in birds were located.

Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)

Conclusion:

The available earthworm subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No earthworm subchronic toxicity studies were located. An acute (14-hour) LC_{50} of 130 mg/kg soil and a NOEC of 100 mg/kg soil with the earthworm, *Eisenia fetida* (SafePharm, 1996), were reported in IPCS 1998. However, the study has also been reported to be a 14-day subchronic toxicity study (NICNAS, 2001). The study, or a study summary, was not available for an independent evaluation of the study and the results.

Physical/Chemical Properties

Tris(1,3-dichloro-2-propyl) phosphate
CAS 13674-87-8
MF $C_9H_{15}Cl_6O_4P$
MW 430.91
SMILES ClCC(CCl)OP(=O)(OC(CCl)CCl)OC(CCl)CCl

Physical/Chemical Properties

Water Solubility:
Conclusion: The available water solubility data are adequate.
Basis for Conclusion: The key study (highlighted) was performed according to a reliable method, and is in reasonable agreement with other values reported in the literature.

Solubility (mg/L)	References
42	Akzo Nobel, 2001a,b: Water Solubility determination according to OECD Guideline 105 (shake-flask method)
7	Aston et al., 1996 (24˚C); Hollifield, 1979; SRC, 2004 (PHYSPROP Database, 24˚C); HSDB, 2003 (24˚C)
100	Eldefrawi et al., 1977; WHO, 1998 (30˚C); Budavari, 2001 (The Merck Index); Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)
110	CERI, 1999

Log K_{ow}:
Conclusion: The available log K_{ow} data are adequate.
Basis for Conclusion: The key study (highlighted) was performed according to a reliable method.

Log K_{ow}	Reference
2.4	Akzo Nobel, 2001a,b: Determination of Octanol-Water Partition Coefficient According to OECD Guideline 117 (HPLC Method)
3.8	WHO, 1998
3.65	SRC, 2004 (PHYSPROP Database); HSDB, 2003
3.75	Shake-flask method, Sasaki et al., 1981

Oxidation/Reduction: No data

Melting Point:
Conclusion: The available melting point data for TDCPP are adequate.
Basis for Conclusion: The key study (highlighted) was performed according to a reliable method. It is noted that the other literature data do not agree with the key study; however, the methods used to measure the melting points are not provided in any of the sources. As an OECD-guideline compliant method, the key study is better described and better supported.

Melting Point (˚C)	References
-58	Akzo Nobel, 2001a,b: melting point determination by DSC (compliant with OECD Guideline 102), freezing point was determined to be -40˚C, melting point -58˚C
27	CERI, 1999
26.66	Akzo Nobel, 2003

Boiling Point:
Conclusion: The boiling point data are adequate.
Basis for Conclusion: A variety of literature sources report the same value for the boiling point, although there is some indication that the compound may decompose at or near the boiling point. Since experimental details are not provided in any of the sources, it is not possible to determine whether the temperatures reported are decomposition or boiling temperatures. Nevertheless, given the high boiling point reported for this material, the available data are adequate to characterize its potential volatility.

Boiling Point (˚C/torr)	References
236-237/5	SRC, 2004 (PHYSPROP database); Budavari, 2001 (The Merck Index); Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials); WHO, 1998
200/4	Akzo Nobel, 2003
Dec. >200/4	WHO, 1998
Gradual Dec. >200	HSDB, 2003

Vapor Pressure:
Conclusion*:* The available vapor pressure data are not adequate
Basis for Conclusion: Although this measured vapor pressure is reported in two sources, it appears to be very high relative to the boiling points reported for this chemical. For comparison, an estimated vapor pressure (EPIWIN) is also included in the table below. The vapor pressure remains a data need.

Vapor Pressure (torr/˚C)	Reference
0.01/30	WHO, 1998; Akzo Nobel, 2001a,b
2.98 x10^{-7}	EPIWIN, 2000; v. 3.11 estimate

Odor:
Conclusion: The odor of this compound has been adequately characterized.
Basis for Conclusion: Although no standardized tests are available for characterizing chemical odors, the two descriptions found are similar, and are consistent with the low volatility expected for this chemical.

Odor	Reference
Mild Odor	HSDB, 2003
Bland Odor	Akzo Nobel, 2003

Oxidation/Reduction Chemical Incompatibility: No data

Flammability:
Conclusion: The flammability (as the flash point and autoignition temperature) has been adequately characterized.
Basis for Conclusion: Studies on the flash point and autoingition temperature of this chemical were located and appear reasonable given the other physical/chemical properties available for this compound.

Flash Point	Reference
252˚C (coc)	WHO, 1998; HSDB, 2003
>107.22˚C (Seta closed cup)	Akzo Nobel, 2003

Autoignition Temperature	Reference
512.77˚C	Akzo Nobel, 2003

Explosivity: No data

Corrosion Characteristics: No data

pH:
This chemical does not contain functional groups expected to influence the pH of aqueous solutions. Data for this endpoint are therefore not applicable.

UV/Visible Adsorption: No data

Viscosity:
Conclusion: The viscosity of this chemical at various temperatures has been adequately characterized.
Basis for Conclusion: Studies on the viscosity of this chemical were located and appear reasonable given the other physical/chemical properties available for this compound.

Viscosity (cP)	Reference
1,800 at 25˚C	WHO, 1998; Akzo Nobel, 2003
2,200 at 0˚C	Akzo Nobel, 2003
540 at 40˚C	Akzo Nobel, 2003

Density/Relative Density/Bulk Density:
Conclusion: The density of this compound has been adequately characterized.
Basis for Conclusion: Consistent data are provided in several reputable sources.

Density	Reference
1.52 at 25˚C	Specific gravity. WHO, 1998
1.5022 at 20˚C	Specific gravity. Budavari, 2001 (The Merck Index); Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)
1.48 kg/L at 25˚C	Bulk density. HSDB, 2003

Dissociation Constant in Water:
This compound does not have functional groups that are expected to dissociate in water. This endpoint is therefore not applicable.

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish:
Conclusion: The bioconcentration factor has been adequately characterized.
Basis for Conclusion: The two studies cited in the table below provide consistent information for killifish under both static and flow-through conditions, over a variety of observation times, and with varying initial concentrations of test substance. The BCF was also measured in goldfish; the reported BCFs are independent of study length.

Reference	Species	BCF	Key Design Parameters				Comments
			Exp. type	Range (ppb)	Study length	T (˚C)	
Sasaki et al., 1981	Killifish	113 110 77	Static	1,000 initial	24 hours 55 hours 96 hours	25	Half-life for elimination of the test compound in water + fish = 31 hours.
Sasaki et al., 1981	Goldfish	5 3	Static	1,000 initial	24 hours 96 hours	25	Half-life for elimination of the test compound in water + fish = 42 hours.
Sasaki et al., 1982	Killifish	46±5 32±4 31±6 59±16 49±12	Flow-through (all)	400 300 40 40 80	3 days 4 days 6 days 30 days 32 days	25	BCF is independent of concentration; continuous (flow-through) results correlate to static results (Sasaki et al., 1981).

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism:
Conclusion: The metabolism of TDCPP in fish is not adequately characterized in the literature.
Basis for Conclusion: The depuration rate is adequately described in killifish, however, the metabolite distribution is not addressed.

Species	Rate	Comment	Reference
Killifish	Elimination half-life, 1.65 hours	Depuration rate - elimination of TDCPP when exposed fish are moved to clean water.	Sasaki et al., 1982
Killifish	Apparent metabolism is much faster in killifish than in goldfish. (Quantitative data are not provided.)	~10% of applied TDCPP remains in the water in the presence of killifish after 96 hours. Control (no fish) has no change in TPP concentration.	Sasaki et al., 1981
Goldfish	Apparent metabolism is much slower than in killifish. (Quantitative data are not provided.)	~25% of applied TDCPP remains in the water after 96 hours in presence of goldfish.	Sasaki et al., 1981

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation:
Conclusion: The biodegradation of TDCPP under aerobic conditions has been adequately characterized.
Basis for Conclusion: The key study (highlighted) was performed according to a GLP-compliant OECD guideline test. The other data located in the literature are generally in agreement with the key study.

Study type/ Method	Innoculum	Acclim	Degradation	Time	Comments	Reference
OECD Guideline 301B Modified Sturm Test	Activated sludge		0% by CO_2 evolution. DOC red. not calculated due to solubility issues.	28 days	Initial concentrations 2, 10 mg/L. GLP-compliant. Also reported: 1) Closed bottle test (OECD Guideline 301D) showed no inhibition of bacterial cultures in 10 days. 2) Mean COD 0.85	Akzo Nobel, 2001a,b; Akzo Chemicals Incorporated, 1990

Japanese MITI test	Activated sludge		avg. 1% by BOD	28 days	Initial concentrations 100 mg/L (test substance), 30 mg/L (sludge).	CERI, 1999; HSDB, 2003; Chemicals Inspection and Testing Institute, 1992
OECD 302C			0% by O_2 uptake	28 days		WHO, 1998
River Die-Away	Water from Oh River (Osaka, Japan) Neya River (Osaka, Japan) Seawater (Osaka Bay)		12.5% 18.5% 0% 5.4% 0% 22%	7 days 14 days 7 days 14 days 7 days 14 days	Initial concentrations 20 mg/L in Oh River water and 1 mg/L in Neya River water. Concentration in seawater not reported. Analysis by Molybdenum Blue calorimetric assay for increase in phosphate ion.	WHO, 1998

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis:
Conclusion: The available pyrolysis data are not adequate.
Basis for Conclusion: Although a semi-quantitative description of the pyrolysis products is given in the Choudry and Hutzinger paper, the list of degradates provided accounts for only 60% of the total mass expected and doesn't contain any oxygenated or phosphorus-containing compounds. Therefore, this study does not provide a complete profile of the pyrolysis of TDCPP.

Pyrolysis Products	**Reference**
Relative mol.% degradates, 0.1 mole TDCPP heated at 250-260˚C under reduced pressure (3 mm Hg), overall yield 60 wt%: *trans*-1,3-dichloropropene 26.7%, *cis*-1,3-dichloropropene 36.0%, 1,2,3-trichloropropane 34.4%, 1-chloro-2-propene 2.9%.	Choudhry and Hutzinger, 1982
Thermal oxidative degradation in air at 370˚C: Hydrogen halides, halogenated C2 and C3 species, acrolein	HSDB, 2003

When heated to decomposition, it emits toxic fumes of Cl^+ and PO_x	Lewis, 2000 (Sax's Dangerous Properties of Industrial Materials)

Hydrolysis as a Function of pH:
Conclusion: The hydrolysis rate data are adequate. The hydrolysis products are not described.
Basis for Conclusion: The studies cited below were GLP-compliant tests run according to accepted guidelines.

$T_{1/2}$	pH	Temp.	Comment	Reference
>1 year >1 year 14.7 days	4 7 9	50˚C	OECD 111; EPA Ser. 835 OPPTS No. 835.2110. GLP-compliant. Initial concentration, 10 mg/L. Study length, 5 days. Preliminary study.	Akzo Nobel, 2001a,b
28 days	9	40˚C	OECD 111; EPA Ser. 835 OPPTS No. 835.2110. GLP-compliant. Definitive 30-day study.	Akzo Nobel, 2001a,b
128 days	9	20˚C	OECD 111; EPA Ser. 835 OPPTS No. 835.2110. GLP-compliant. Definitive 30-day study.	Akzo Nobel, 2001a,b

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

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Flame Retardant Alternatives

Proprietary A: Chloroalkyl phosphate (1)

Draft Hazard Review

December 2004

Proprietary A: Chloroalkyl phosphate (1)
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	✓
Dermal	✓
Inhalation	*
Eye irritation	✓
Dermal irritation	✓
Skin sensitization	*
Subchronic Toxicity	
28-Day oral	
90-Day oral	*
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	*

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	✓
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	✓
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	✓

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✓
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	*
Additional neurotoxicity studies	✘
Immunotoxicity	
Immunotoxicity	*
Genotoxicity	
Gene mutation in vitro	✓
Gene mutation in vivo	✓
Chromosomal aberrations in vitro	✓
Chromosomal aberrations in vivo	*
DNA damage and repair	✓
Other	✓

Proprietary A: Chloroalkyl phosphate (1)
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	✓
Octanol/water partition coefficient	✓
Oxidation/reduction	
Melting point	✓
Boiling point	✓
Vapor pressure	*
Odor	✓
Oxidation/reduction chemical incompatibility	
Flammability	✓
Explosivity	
Corrosion characteristics	
pH	✘
UV/visible absorption	✓
Viscosity	✓
Density/relative density/bulk density	✓
Dissociation constant in water	✘
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	✓
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	*
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	✓
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	*
Hydrolysis as a function of pH	✓
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	*
Daphnia acute EC50	*
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	*
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	*

Chemical Identity

Proprietary A: Chloroalkyl phosphate (1)
CAS
MF
MW
SMILES
Synonyms

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401).

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Several acute oral lethality studies were available in a variety of species: rabbits, rats, and mice. These studies were from the older (pre 1980) literature, did not report substance purity, and do not fully conform to OPPTS or OECD guidelines, but given the magnitude of the LD50 values the data are adequate for the evaluation of acute oral toxicity. Acute oral LD50 values generally exceeded the current limit dose of 2,000 mg/kg. Reports that specified a 14-day observation period are presented in detail.

Critical Studies:

Type: Acute oral toxicity
Species, strain, sex, number: Rabbit, Dutch-belted, 5 males/group
Doses: 0, 5,000, 7,500, and 10,000 mg/kg
Purity: [Formulation 2]; purity not specifically reported
Vehicle: Not reported
Method: 14-Day post-dosing observation period; observations limited to mortality, clinical signs, and necropsy. LD50 calculated according to Litchfield and Wilcoxon.
Results: Clinical signs shortly after dosing included ataxia, weakness, and diarrhea; survivors normal by day 9. Necropsy revealed no abnormalities. Acute oral male rabbit LD50 = 6,800 mg/kg (95% CI 5,615-8,234 mg/kg).
Reference: Robust summary from Ref. 4

Type: Acute oral toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 5 males/group
Dose: 1,000, 2,150, 5,640, or 10,000 mg/kg
Purity: [Formulation 2]; purity not specifically reported
Vehicle: None
Observation period: 14 days post dosing
Method: 14-Day post-dosing observation period; observations limited to mortality, clinical signs, and necropsy; LD50 calculated according to Litchfield and Wilcoxon; not specified whether fed or fasted at time of dosing.
Results: No effects at 1,000 mg/kg. Dose-related depression at or above 2,160 mg/kg; survivors normal by day 5. No gross lesions in survivors; fatalities had congestion of heart, lung, and liver. Acute rat oral LD50 = 3,160 mg/kg (95% CI 2,050-4,800 mg/kg)
Reference: Ref. 53; robust summary from Ref. 4

Type: Acute oral toxicity
Species, strain, sex, number: Mouse**,** Slc/ddY, 10/sex/dose
Purity: Not reported
Doses: For males: 0, 2,210, 2,380, 2,570, 2,780, 3,000, 3,240, and 3,500 mg/kg. For females: 0, 2,890, 2,040, 2,210, 2,380, 2,570, and 2,780 mg/kg.
Vehicle: Olive oil
Method: Observed for mortality and clinical signs for14 days. No body weight or gross necropsy examination.
Results: Treated animals exhibited ataxic gait, hyperactivity, convulsion and death. No mortality was observed in controls or in males at 2,210 mg/kg or females at 1,890 mg/kg. The LD50 values were 2,670 mg/kg (2,520-2,830 mg/kg) for male mice and 2,250 (2,120-2,380 mg/kg) for female mice.
Reference: Ref. 30

Additional Studies and Information:

Other studies available only in secondary sources reported similar results. An oral LD50 of >2,000 mg/kg was reported in male and female rats exposed to [Formulation 3] (Ref. 18 as reported in Ref. 61); clinical signs observed during the first 5 days after dosing included hypokinesia, piloerection, soiled coats, ataxia, chromodacryorrhea, rhinorrhea, and salivation.

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged adequate to meet the endpoint.

***Basis for Conclusion*:**

The available studies predate the preferred study guidelines, and did not report purity, but together indicated no mortality at the guideline limit dose of 2,000 mg/kg. The report specifying a 14-day observation period is presented in more detail.

Type: Acute dermal toxicity
Species, strain, sex, number: Rabbit, New Zealand albino, sex not specified, 4
Dose: 4,640 mg/kg
Purity: [Formulation 2], no data
Vehicle: None
Exposure period: 24 Hour
Method: 4 Rabbits tested occluded; 14-day observation period. Gross necropsy.
Results: Mortality after 14 days = 0/4. No overt signs of toxicity and no gross necropsy findings. Therefore, dermal acute LD50 >4,640 mg/kg.
Reference: Ref. 54; additional information from robust summary in Ref. 4

Additional Studies and Information:

Other studies available only in secondary sources with minimal detail. A dermal LD50 of >2,000 mg/kg was reported in male and female Sprague-Dawley rats exposed to [Formulation 3] (Ref. 19 as reported in Ref. 61). No deaths and no clinical signs were noted 24 hours after treatment.

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300; OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available study on Proprietary A predates the preferred guidelines. The duration was shorter than currently recommended and no deaths were observed. Analysis of aerosol particle size, however, was not mentioned so it is not known whether the size was respirable. Necropsies were not performed.

Type: Acute inhalation toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 5 males and 5 females
Doses: 9.8 mg/L (9,800 mg/m^3)
Purity: No data
Vehicle: None
Duration: 1 hour

Method: Observation period = 14 days. Observed daily for signs of toxicity and for mortality.
Results: No mortality after 14 days; initial signs of moderate depression
Reference: Ref. 55

Additional Studies and Information:

Other studies available only in secondary sources reported similar results. An acute inhalation LC50 of >5,220 mg/m^3 was reported for Sprague-Dawley rats exposed to aerosol of Proprietary A [Formulation 1] (Ref. 7 as reported in Ref. 61).

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Two reasonably adequate studies report similar results in rabbits: mild reversible irritation of the conjunctiva. The studies are summarized below.

Type: Acute eye irritation
Species, strain, sex, number: Rabbit, New Zealand White, sex not specified; 6
Doses: 0.1 mL
Purity: No data, [Formulation 2]
Vehicle: None
Method: Cited CFR [U.S. Federal Hazardous Substances Labelling Act] Section 191.12, chapter 1, title 21. Following instillation of Proprietary A, eyes were examined at 24, 48, and 72 hours.
Results: Mild conjunctival effects in 3/6 that cleared by 48 hours.
Reference: Ref. 52

Type: Acute (24-hour) eye irritation
Species, strain, sex, number: Rabbit, New Zealand White, male and female; 9 total
Doses: 0.1 mL
Purity: No data
Vehicle: None
Method: U.S. EPA Hazard Evaluation. 1978. Fed. Reg. 43: 163: pp. 37331-37402. Thirty seconds following instillation of Proprietary A, the treated eyes of three rabbits were washed, treated eyes were not washed in 6 rabbits. The untreated eye of each animal served as a control. The cornea, iris and conjunctiva of each eye were examined at 24, 48, and 72 hours, and at 4 and 7 days after instillation of Proprietary A using the Draize scoring method.
Results: No signs of eye irritation were observed (average total Draize score of zero).

Reference: Ref. 57; robust summary from Ref. 4

Additional Studies and Information:

One hour following application of [Formulation 3] to the eyes of New Zealand White rabbits, slight conjunctival redness and slight discharge were noted (Ref. 21 as reported in Ref. 61); effects cleared by 24 hours.

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Two reasonably adequate studies, patterned after guidelines in effect at the time, provide similar results, indicating that Proprietary A was a non-irritant when applied for 4 hours (consistent with current guidelines) and a mild irritant when applied for 24 hours to rabbit skin. Additional studies provide support. The studies are summarized below.

Critical Studies:

Type: Acute (24-hour) dermal irritation
Species, strain, sex, number: Rabbit, New Zealand, sex not specified, 6
Doses: 0.5 mL
Purity: Not reported; [Formulation 2]
Vehicle: None
Method: Cites "EPA protocol". Back hair was shaved, each rabbit tested on intact and abraded skin, occlusive dressing removed after 24 hours, observations at 24 and 72 hours.
Results: No edema on intact or abraded skin in any of the 6 rabbits. Mild erythema was visible at 24 hours but cleared by 72 hours, resulting in a score of 0.63. The report classified Proprietary A as a mild irritant.
Reference: Ref. 57

Type: Acute (4-hour) dermal irritation
Species, strain, sex, number: Rabbit, not specified (but New Zealand white rabbits were used in an eye irritation test conducted at the same time)
Doses: 0.5 mL
Purity: Not reported; [Formulation 2]
Vehicle: None
Method: Back hair shaved, each rabbit tested on intact and abraded skin, occlusive dressing removed after 4 hours, observations at 4, 24 and 48 hours.

Results: No erythema or edema on intact or abraded skin in any of the 6 rabbits.
Reference: Ref. 52

Additional Studies:

Another study, on [Formulation 3], reported well-defined (score 2) erythema in 2 New Zealand White rabbits and slight erythema in a third rabbit 1 hour after patch removal, but duration of exposure was not specified (Ref. 20 as reported in Ref. 61). Effects cleared by 48 hours. The substance was classified as a skin irritant.

Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)

A robust summary was located for an unpublished industrial study stated to have been conducted under guideline. The summary omits information necessary to determine study adequacy, such as: the strain, sex, group size, substance purity, and dose levels. The summary claimed that the doses were selected according to guideline, but the exact levels are not stipulated in the guideline. Despite the possibility that the unpublished study might be adequate, without additional information, the skin sensitization endpoint appears not to be satisfied by the available data.

Critical Studies:

Type: Dermal sensitization study
Species, strain, sex, number: Guinea pig, strain and sex not reported
Doses: Stated as according to guideline, but exact doses are not stipulated in guideline.
Purity: Not reported; [Formulation 2]
Vehicle: Water
Method: Three pairs of intradermal injections into shaved shoulder: 1:1 Freunds Complete Adjuvent (FCA) and saline, the test material, and 1:1 FCA and test material. Controls received water in place of the test material. On day 6, 24 hours before topical induction application, sodium lauryl sulfate was applied to sites to enhance local irritation. On day 7, test substance was applied to sites (water for controls). On day 21, animals received challenge dose by dermal application, occluded for 24 hours. Sites observed for irritation and sensitization (Grade 0-4).
Results: The sensitization score for [Formulation 2] was zero, indicating the substance is not a chemical sensitizer.
Reference: Robust summary in Ref. 5

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

Conclusion:

The available subchronic oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A Japanese 90-day dietary study in mice (Ref. 30) provides limited relevant information in the English abstract and data tables. The study was not adequate to characterize this endpoint because histopathological analysis was apparently limited to the liver. A fertility study by Ref. 62, discussed under the Reproductive Toxicity endpoint, evaluated male rabbits exposed by oral gavage for 12 weeks, but did not involve treated females.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

No study of this type was located.

90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)

Type: 90-Day repeated oral
Species, strain, sex, number: Mouse, Slc/ddY, 12/sex/dose
Doses: Proprietary A at dietary concentrations of 0, 0.01, 0.04, 0.13, 0.42, and 1.33% in the diet, resulting in reported average daily doses of 0, 13.2, 47.3, 171.0, 576.0, and 1,792.3 mg/kg/day in males and 0, 15.3, 62.5, 213.6, 598.0, and 1,973.1 mg/kg/day in female mice
Purity: Not reported
Vehicle: None; added to diet
Exposure period, frequency: 90 days, ad lib
Method: Body weight, food consumption measured weekly. At 1 and 3 months in half the animals, hematologic (erythrocyte, hemoglobin, hematocrit, and leukocyte counts) and clinical chemistry parameters (total protein, albumin, albumin/globulin ratio, blood urea nitrogen, glucose, total cholesterol, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase). At 1 and 3 months, half the animals were necropsied and absolute and relative organ weights were determined for brain, heart, lung, liver, kidney, and spleen. The liver was examined for microscopic histopathology; the English text does not mention whether other tissues were examined.
Results: At the highest dietary level, 1.33%, all mice exhibited emaciation, rough hair, and tremor and died within 1 month. At 1.33%, food consumption was reduced and body weight loss occurred in both sexes. Mean body weight gain was reduced by about 10% (estimated from graph) in males at 0.42% throughout the study. The following statistically significant changes occurred in treated groups compared to controls. Slight anemia (reduced hemoglobin; $p<0.05$) in males at 0.42% after 3 months. Anemia (reduced hemoglobin at $\geq$0.13% after 1 month and at 0.42% at 3 months, erythrocyte and hematocrit at 0.42% at 1 and 3 months) in females (3-month

values $p<0.01$). Albumin/globulin ratios elevated in all treated male groups at 3 months. Alkaline phosphatase elevated in females at 0.42% at 1 month but not later. Dose-related organ weight elevations compared to controls observed at 3 months in males included relative liver weight (+32-51%) at ≥0.13% and relative kidney weight (+39%) at 0.42%. Significant elevations in organ weights in females at 3 months included relative liver weight (+16-51%) at ≥0.04%, absolute (+30%) and relative (+34-40%) kidney weights at ≥0.13%, and absolute liver weight (+40%) at 0.42%. The statistical significance of these organ weight elevations was $p<0.01$ for rats exposed at ≥0.13% and $p<0.05$ for rats exposed at 0.04.%. Histopathology of the liver (slight focal necrosis) was observed in only two females at 0.42%. The dietary level of 0.01% is a NOAEL of 15.3 mg/kg/day and the dietary level of 0.04% is a LOAEL of 62.5 mg/kg/day for liver and kidney weight elevations in female mice.
Reference: Ref. 30

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

No studies of this type were located.

Subchronic Dermal Toxicity (21/28-day or 90-day)

Conclusion:

The available subchronic dermal toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No data exist for the subchronic dermal toxicity endpoint.

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**

- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

No studies of either type were located.

Subchronic Inhalation Toxicity (90-day)

Conclusion:

The available subchronic inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No repeated-exposure inhalation toxicity studies were located.

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

No studies of this type were located.

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

A fertility assay in male rabbits exposed by oral gavage for 12 weeks prior to mating (Ref. 62) partially characterizes this endpoint, but is not sufficient to satisfy the reproductive toxicity endpoint since it was described only in an abstract and females were not tested. Other studies (Ref. 26, 59) described below under Developmental Toxicity reported that in pregnant female rats exposed orally to Proprietary A, adverse reproductive effects occurred only at maternally lethal doses. However, no study evaluated reproductive function in females treated prior to mating.

The 2-year feeding bioassay in rats by Ref. 24 (Ref. 9, 9a), discussed below under Chronic Toxicity, provides reproductive histopathology data that are, however, insufficient to satisfy the reproductive toxicity endpoint. This study provided histopathology results for the testis, epididymis, seminal vesicle, ovary, and uterus for the control and high-dose groups (0 and 80 mg/kg/day) after 1 year (10 scheduled sacrifices/sex/group) and for survivors in all groups after 2 years; unscheduled sacrifices (rats killed in a moribund state) were also examined. The 2-year exposure is too long to represent reproductive toxicity, because of the confounding effects of aging; the results pointed to dose-related effects in male reproductive organs (at $\geq$5 mg/kg/day, atrophy and decreased secretory product of the seminal vesicles; at $\geq$20 mg/kg/day, testicular germinal atrophy with oligospermia, and at 80 mg/kg/day, atrophy and decreased secretory product of the seminal vesicles and oligospermia and luminal accumulation of degenerated seminal products in the epididymis). No significant effect was observed in females. The tested doses, which were considerably lower than the guideline limit dose of 1,000 mg/kg/day, were not high enough to induce significant reproductive histopathology after one year of exposure; 1/10 high-dose males had oligospermia. Thus, a LOAEL for reproductive effects following subchronic (90-day) exposure is not available and cannot be extrapolated from the existing data, but the chronic data indicate a LOAEL of 5 mg/kg/day for atrophy and decreased secretory product of the seminal vesicles.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

No studies were available that met the specific designs of the three protocols listed above.

Additional Studies:

A study described in an abstract by Ref. 62 addresses fertility in male rabbits exposed by oral gavage for 12 weeks prior to mating.

Type: Fertility
Species, strain, sex, number: Rabbit, strain not specified, 10 males/dose
Purity: Not reported
Doses: 0, 2, 20, or 200 mg/kg/day
Vehicle: Not reported
Exposure duration, frequency: 12 weeks, once by oral gavage daily
Method: Males treated for 12 weeks, then mated with untreated females. Body weight, clinical signs, clinical chemistry, hematology, mating behavior, male fertility, sperm quantity and quality, kidney and liver weights, gross and microscopic pathology (range of organs examined not specified).
Results: High-dose animals had significantly increased absolute kidney weight and relative liver weight. Proprietary A had no effect on male reproductive parameters; there was no histopathology in kidneys, liver, pituitaries, testes, or epididymides.
Reference: Ref. 62

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Developmental toxicity studies in two strains of rats exposed to [Formulation 2] by oral gavage followed methods consistent with OECD Guideline 414 (one study pre-dated the guideline).

Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)

Type: Prenatal developmental toxicity
Species, strain, sex, number: Rat, Wistar, 15 pregnant females at the highest dose, 23-24 pregnant females in controls and other dose groups.
Purity: not reported
Doses: 0, 25, 50, 100, 200, and 400 mg/kg/day
Vehicle: Olive oil
Exposure duration, frequency: Once by oral gavage daily on gestational days (GD) 7-19.
Method: Body weight, food consumption, clinical signs, pregnancy rates, and necropsy of dams, kidney weight; uterine contents (including implants and resorption) at day 20 of gestation, corpora lutea; fetal viability, sex ratio and weight, crown-rump length, and external and skeletal abnormalities.
Seven dams from each of the control and ≤200 mg/kg/day groups were permitted to litter normally and evaluated for implantation sites, delivery index, number of live offspring at birth and survival on PND 4, at 4th week, and at 10th week. Litters were culled to 10 offspring on postnatal day 4 (PND 4) and subjected to behavioral tests (open field, water maze, rota rod, inclined screen, pain reflex and Preyer's reflex). Absolute organ weights of 10 organs plus testis, uterus and ovary were measured in offspring.
Results: Maternal mortality occurred only at 400 mg/kg/day: 11/15 died. Food consumption was suppressed at 400 mg/kg/day and slightly at 200 mg/kg/day. At 400 mg/kg/day, mean body weight loss occurred during GD 7-15, resulting in significantly ($p<0.05$) reduced terminal body weight on GD20: ~17% lower than control group. Absolute and relative kidney weights were significantly increased at 200 and 400 mg/kg/day. Proprietary A at ≤200 mg/kg/day had no effect on corpora lutea or mean numbers of implants, fetal body weight, fetal sex ratio, or the number of dead or live fetuses. The numbers of dead fetuses and live fetuses were significantly ($p<0.01$) changed compared to controls by the loss of one whole litter at 400 mg/kg/day. No increase in malformations was observed in treated groups. For maternal toxicity, the NOAEL was 100 mg/kg/day and the LOAEL was 200 mg/kg/day for increased kidney weight. For fetal toxicity, the NOAEL was 200 mg/kg/day and the LOAEL was 400 mg/kg/day for increased fetal death; the highest dose of 400 mg/kg/day was a NOAEL for teratogenicity.
Postnatal observations: Proprietary A at ≤200 mg/kg/day had no effect on implantation, delivery, postnatal survival, behavior, functional test results, or absolute organ weights of offspring.
Reference: Ref. 59

Type: Prenatal developmental toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 20 pregnant females/dose
Purity: not reported
Doses: 0, 25, 100, and 400 mg/kg/day
Vehicle: Corn oil
Exposure duration, frequency: Once by oral gavage daily on gestational days 6-15

Method: Body weight, food consumption, clinical signs, pregnancy rates, and necropsy of dams; uterine contents (including implants and resorption) at day 19 of gestation, corpora lutea; fetal viability and weight, crown-rump length, external, visceral (1/3 fetuses), and skeletal abnormalities; extensive statistical analyses.
Results: High-dose dams exhibited clinical signs (urine stains, hunched appearance, and alopecia); sporadic signs of urine stains and hunched appearance occurred in a few mid-dose dams, but not at the low-dose. Food consumption was statistically lower in mid-dose dams on days 7-11 and in high-dose group throughout (days 7-15). During Days 6-11, significant ($p<0.05$) reductions in body weight gain in mid-dose dams and mean body weight loss at the high dose; on days 11-15, only high-dose dams showed reduced body weight gain. Overall body weights reduced in high-dose dams. Proprietary A had no effect on implantation efficiency or mean number of corpora lutea. Treatment at the high dose significantly ($p<0.05$) increased the number of resorptions (to 14.4% compared to 6.7% in controls) and reduced fetal viability (to 85.6% compared to 93.3% for controls). Decreased skeletal development in the high-dose groups is related to growth retardation and decreased fetal size. The incidence of malformations was not related to treatment. The study indicates a NOAEL of 25 mg/kg/day and a LOAEL of 100 mg/kg/day for maternal toxicity (clinical signs and transient reduction in body weight gain) and a NOAEL of 100 mg/kg/day and a LOAEL of 400 mg/kg/day for developmental toxicity (increased resorptions and fetal mortality).
Reference: Ref. 26

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

No studies with the specific designs of the two tests listed above were available.

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The combined chronic toxicity/carcinogenicity assay in dietarily exposed rats is consistent with the guideline (Ref. 9, 24).

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**

No studies of this type were located.

Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)

The protocol of a 2-year feeding bioassay in rats was consistent with this guideline (Ref. 9, 24). The published article focused on tumor results rather than non-neoplastic effects.

Type: Combined oral chronic toxicity and carcinogenicity assay
Species, strain, sex, number: Rat, Sprague-Dawley, 60/sex/group
Purity: 95%
Doses: 0, 5, 20, and 80 mg/kg body weight/day
Vehicle: None other than feed
Route: In feed; diets blended weekly to achieve target doses
Exposure duration, frequency: 2 years, ad lib
Method: Examined twice daily for mortality and clinical signs, weekly physical examination. Body weights and food consumption weekly for the first 13 weeks and biweekly thereafter. Ophthalmoscopic examinations every 6 months. Extensive hematology, clinical chemistry and urinalysis parameters at 3, 6, 12, 18, and 24 months. Ten/sex/dose randomly chosen for termination at 12 months; the remainder at 24 months. Gross necropsy including organ weights (8 organs plus gonads); histopathology of more than 30 tissues in control and high-dose rats; at low- and mid-doses, histopathology limited to liver, kidneys, testes, and adrenals. Statistical analyses.
Results: The following changes compared to controls were statistically significant ($p<0.05$). Mortality increased in high-dose males (to 61.7% vs 43.3% for controls). Lower body weights in high-dose males and females. Treatment had no effect on feed consumption. Signs of anemia (lower hemoglobin, hematocrit, erythrocyte counts) in high-dose rats. At the mid-dose, increased absolute and relative kidney weight males and females, absolute liver weight and relative thyroid weight in males, and relative liver weight in females. At the high dose, increased relative liver weight in males and absolute and relative thyroid weights in females.

Increases in the incidences of the following nonneoplastic lesions were statistically significant ($p<0.05$) in treated groups compared to the control groups; changes were not strictly dose-related in that incidences were depressed in high-dose groups. Kidney lesions (convoluted tubule hyperplasia) in males at ≥20 mg/kg/day and in females at 80 mg/kg/day. Other systemic lesions at 80 mg/kg/day involved the parathyroid (hyperplasia) in males and the liver (foci) and spleen (erythroid/myeloid hyperplasia) in females. Reproductive system lesions in males involved seminal vesicles (atrophy, decreased secretory product) at ≥5 mg/kg/day, testes (eosinophilic material in lumen, periarteritis nodosa) at ≥20 mg/kg/day, and epididymis (oligospermia and degenerated seminal product) at 80 mg/kg/day. (Tumor incidences are reported below under Carcinogenicity.) The authors reported the lowest dose of 5 mg/kg/day as a NOAEL and the

mid-dose of 20 mg/kg/day as a LOAEL. However, as evaluated in NRC (2000), the lowest dose of 5 mg/kg/day was a LOAEL for atrophy and decreased secretory product of the seminal vesicle.
Reference: Ref. 24; also Ref. 9 and 9a.

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Increased tumor incidences were observed in a combined chronic toxicity/carcinogenicity assay in rats exposed to Proprietary A in the diet (Ref. 24).

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**

No studies of this type were located.

Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)

A 2-year feeding bioassay by Ref. 24 was consistent with this guideline.

Type: Combined oral chronic toxicity and carcinogenicity assay
Species, strain, sex, number: Rat, Sprague-Dawley, 60/sex/group
Purity: 95%
Doses: 0, 5, 20, and 80 mg/kg body weight/day
Vehicle: None other than feed
Route: In feed; diets blended weekly to achieve target doses
Exposure duration, frequency: 2, ad lib
Method: See description above under Chronic Toxicity
Results: The following neoplastic changes compared to controls were statistically significant ($p<0.05$). Dose-related increased incidences at $\geq$20 mg/kg/day of renal cortical adenomas in both sexes and testicular interstitial tumors in males, and at 80 mg/kg/day, of hepatocellular adenomas and carcinomas combined in both sexes and adrenal cortical adenomas in females. Ref. 40 concluded that this study provides sufficient evidence of carcinogenicity of Proprietary A in rats following chronic oral exposure.
Reference: Ref. 24; also Ref. 9, 9a

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The delayed neurotoxicity component is satisfied by the existing data, but a developmental toxicity study by Ref. 59 that included postnatal behavioral examinations did not fully satisfy the developmental neurotoxicity component. Proprietary A gave negative results in single acute and subchronic oral delayed neurotoxicity studies in hens and in limited postnatal testing in rats exposed during gestation. A 2-year feeding bioassay in rats by Ref. 24, discussed above under the Chronic Toxicity and Carcinogenicity endpoints, reported no lesions of the cervical spinal cord, but a slight (not statistically significant) increase in the incidence of gliomas of the brain in rats exposed to Proprietary A at 80 mg/kg/day. The study authors could not determine whether this effect was related to exposure.

Delayed Neurotoxicity

Conclusion:

The available delayed neurotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Several acute studies and one subchronic study for delayed neurotoxicity in the hen, summarized below, give no evidence of acute cholinergic toxicity, inhibition of neurotoxic esterase (NTE) activity, or delayed neurotoxicity for Proprietary A. These studies, performed prior to the existence of the guidelines, do not entirely conform to current guidelines, and may lack detail such as the purity of the Proprietary A sample. The lack of significant NTE inhibition following dosing with 10,000 mg/kg suggests that no additional testing for delayed neurotoxicity is needed for Proprietary A.

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Unpublished industrial acute (1- or 5-day) and subchronic (90-day) delayed neurotoxicity assays, which pre-date the guideline, are missing some details. One acute study employed a gavage dose 5 times higher than now specified under the guideline. The subchronic assay had a longer duration and a larger group size than specified under the guideline.

Critical Studies

Type: Acute oral delayed neurotoxicity
Species, strain, sex, number: Hen, White Leghorn, 4/dose
Purity: [Formulation 2], purity not reported, clear colorless liquid
Doses: 420 mg/kg (highest dose specified in protocol)
Vehicle: test substance diluted 50% in corn oil
Positive control: 90 or 120 mg/kg/day tri-ortho-tylol phosphate (TOCP)
Route: Gavage
Exposure duration, frequency: Once daily on five consecutive days
Method: Navy MIL-H-19457B (SHIPS) protocol. Hens were weighed and graded on days 7, 9, 11, 14, 16, 18, 21, and 23 after the first dose for no signs, doubtful/minor signs, positive paralytic signs, advanced paralytic signs, or death. Scores on the 21st day were compared with results for TOCP. Necropsy not performed.
Results: No overt signs of neurotoxicity in with Proprietary A treatment. Positive control caused inability to walk, hypertension, ataxia, and prostration.
Reference: Ref. 14 as described in Ref. 61; Ref. 50

Type: Acute oral delayed neurotoxicity
Species, strain, sex, number: Hen, White Leghorn, 4/dose for Proprietary A, 3/dose for controls
Purity: [Formulation 2], clear colorless liquid; one part of the report stated that the purity was not reported, whereas another part of the report indicated purity >99%.
Doses: 10,000 mg/kg
Vehicle: None
Positive control: 500 mg/kg tri-ortho-cresyl phosphate (TOCP)
Negative control: 15 mg/kg tetraethyl pyrophosphate (TEPP)
Route: Oral gavage
Exposure duration, frequency: Once
Method: Twenty minutes before dosing, hens received atropine and 2-PAM to protect against cholinergic effects. Hens were observed for toxic signs at 2-hour intervals for the first 8 hours. Mortalities were recorded after 24 hours. Brains were harvested 24 hours after dosing and analyzed for neurotoxic esterase (NTE) activity.
Results: Toxic signs were not reported specifically for Proprietary A, but for all compounds tested at the maximum tolerated dose, signs included listlessness and ataxia. Inhibition of NTE activity was 7% for Proprietary A and the negative control tetraethyl pyrophosphate, but 85% for the positive control (TOCP). The current guideline specifies that testing is not necessary at doses above 2,000 mg/kg.
Reference: Ref. 56

Type: Subchronic oral delayed neurotoxicity
Species, strain, sex, number: Hen, adult, White Leghorn, 10/dose
Purity: Not reported
Doses: 0, 4, 20, and 100 mg/kg/day

Vehicle: Not reported
Route: Oral Gavage
Exposure duration, frequency: 90 days, daily
Method: Body weight. Daily observations for mortality and behavioral changes; evaluated for signs of motor weakness 3 times per week. At termination, hens were necropsied and brain (multiple sections), sciatic nerve, and spinal cord (cervical, thoracic and lumbar) were examined histopathologically. TOCP was the positive control.
Results: Hens treated with Proprietary A at the high dose exhibited mean reductions in body weight during the latter part of the study, but no overt signs of neurotoxicity and no histopathological effects in the nervous tissues. Conversely, the positive control hens exhibited consistently lower body weight gain, clinical signs of toxicity (locomotor impairment and ataxia) that became more severe with time. Histopathology results were not reported for the positive control.
Reference: Robust summary from Ref. 4

Neurotoxicity (Adult)

Conclusion:

The available adult neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The chronic oral bioassay by (Ref. 9, 9a, 24) reported no lesions of the brain or spinal cord in rats exposed to TDCPP at doses as high as 80 mg/kg/day for 2 years, but no functional tests of neurotoxicity were performed.

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

No studies of this type were located.

Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)

Conclusion:

The available developmental neurotoxicity data were judged inadequate to meet the endpoint, although the available tests suggest that Proprietary A is not a developmental neurotoxin.

Basis for Conclusion:

No studies of this specific design were located. A Japanese-language gavage study by Ref. 59, described above under Developmental Toxicity, included postnatal neurobehavioral tests (open field, water maze, rota rod, inclined screen, pain reflex, and Preyer's reflex) of sensory and motor function in rats. Full descriptions of these tests were not available in the English summary and therefore could not be compared to the guideline protocol. The study reported no adverse effect in these tests for offspring of dams that were exposed on gestational days 7-15 at doses as high as 200 mg/kg/day (the highest tested non-lethal dose that was a LOAEL for increased kidney weight). This study does not fully satisfy the developmental neurotoxicity endpoint because it omitted some parameters specified under the guideline: developmental landmarks for sexual maturity, auditory startle test, and neurohistopathological examinations.

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat)
  - OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent)
  - OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred)
  - OPPTS Harmonized Guideline 870.6855

These studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Conclusion: These endpoints do not appear to be applicable to Proprietary A.

Basis for Conclusion: Although there are no studies addressing these endpoints, there are no reliable data for Proprietary A, and no structure-activity considerations, that indicate a need for these follow-up studies.

Other Neurotoxicity Data

Cholinesterase inhibition

[Formulation 2] administered at 0, 2,000, or 3,980 mg/kg in corn oil was administered to groups of 10 male Sprague-Dawley rats by oral gavage had no effect on plasma or erythrocyte cholinesterase levels measured 4 or 14 hours after dosing (Ref. 51).

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The only study evaluating the potential immunotoxicity of Proprietary A (Ref. 35) predates the guideline for immunotoxicity (note that the OPPTS guideline cites other works by this author). There is some uncertainty as the test material, reported as [Formulation 2], but mis-identified by the authors as [Chemical 1]. The study methods differed from the guideline in the short exposure period (4 rather than 28 days), parenteral administration (rather than oral or inhalation route), measurement of serum immunoglobulins in non-immunized rather than immunized mice, and the omission of some tests (enumeration of immunological cell subpopulations, test for NK-cell activity). The results do not provide dose–response information as to immunotoxicity of Proprietary A following subchronic exposure by oral or inhalation routes of exposure.

Immunotoxicity (OPPTS Harmonized Guideline 870.7800)

Critical study

Type: Immunotoxicity, subcutaneous, acute
Species, strain, sex, number: Mouse, B6C3F$_1$, 6-8 females/dose
Doses: 0, 0.25, 2.5, or 25 mg/kg/day (Total cumulative doses of 0, 1, 10, or 100 mg/kg)
Identity: [Formulation 2]; this is the same as Proprietary A tested in the 2-year oral assay by Ref. 24
Purity: purity >95%
Vehicle: Corn oil
Route: Subcutaneous injection
Exposure duration, frequency: 4 days, once daily
Method: Observations included body weight, hematology, clinical chemistry (5 parameters) terminal necropsy, organ weights (liver, spleen and thymus), histopathology of spleen, thymus, and eight other organs, plaque-forming assay response to sheep red blood cells, and serum immunoglobulin quantification (non-immunized mice only). Non-guideline tests included proliferative capacity of granulocyte-macrophage progenitor cells (bone marrow), *in vitro* lymphoproliferative (LP) responses to mitogens, delayed hypersensitivity response to keyhole limpet hemocyanin. Extensive statistical analysis.
Results: Twenty percent of high-dose mice exhibited lymphoid depletion of the thymus. Statistically significant decreases *in vitro* lipopolysaccharide (B-cell antigen) at 2.5 mg/kg/day and concanavalin A (T-cell antigen) at 25 mg/kg/day.
Reference: Ref. 35

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Proprietary A has been tested in *in vitro* and *in vivo* genotoxicity assays conducted in prokaryotic and eukaryotic cells under methods similar to guidelines. Results of *in vivo* tests (mutation in *Drosophila*, chromosomal aberration in mice) were negative, but positive results were reported in several *in vitro* assays (mutagenicity in bacterial and mammalian cells, chromosomal aberration).

Gene Mutation in Vitro:

Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA97, TA98, TA100, TA1535, TA1537
Metabolic activation: Tested with and without S9 from livers of Aroclor-induced male Sprague-Dawley rats or male Hamsters
Concentrations: 0, five concentrations between 10 and 10,000 µg/plate.
Purity: 94.4%
Method: Preincubation (20 minutes) and plate incorporation (48 hours) at 37°C. Positive controls were used; DMSO was the solvent. Triplicate plates per concentration. All assays repeated within 1 week.
Results: In three different laboratories, Proprietary A tested positive in strains TA97 and TA100 in the presence of S9 from Aroclor-induced hamster liver and in strain TA1535 in the presence of S9 from Aroclor-induced rat or hamster liver. Positive controls gave expected increases. Solvent control and all other test combinations were negative.
Reference: Ref. 37

Type: Bacterial reverse mutation
Species, strain: *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538
Metabolic activation: Tested with and without Kanechlor 500 (PCB)-induced liver S9 from male Wistar rats
Concentrations: 0, 10, 30, 100, and 300 µg/plate.
Purity: Assayed as ~94% Proprietary A, plus ~6% [Chemical 7]
Method: Plate incorporation, 48-hour incubation at 37°C. Cited Ames protocol, which presumes the use of replicates and positive controls.

Results: No increase in revertants in any strain without activation or in strains TA98, TA1537, or TA1538 with activation. Weak increases in TA100 and TA1535 at the highest concentrations with S9.
Reference: Ref. 38

Additional Studies

Other *S. typhimurium* assays in which S9 was prepared from phenobarbital-induced rat liver reported mutagenicity of Proprietary A in strain TA98 by liquid preincubation assay (Ref. 1) and in TA100 by plate incorporation assay (Ref. 25, 48). Ref. 36 reported dose-related positive results for Proprietary A and its metabolite [Chemical 8] in TA100 with S9 (phenobarbital-induced) in standard plate assays at concentrations up to 500 μg/plate. In a liquid preincubation quantitative assay, results for Proprietary A were essentially negative—only increasing mutation frequencies at cytotoxic concentrations (survival <3%). However, its metabolites increased mutant frequencies with less cytotoxicity: [Chemical 9] positive at <80% survival and [Chemical 8] positive at <30% survival.

Proprietary A was not mutagenic in *S. typhimurium* strains TA100, TA1535, or TA1538 without activation or when Aroclor-induction was used to prepare the S9 fraction (Ref. 41); the highest exposure level was 10 μL per plate.

In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)

Type: Mammalian Cell Gene Mutation Test: Forward Mutation
Species, strain: Mouse lymphoma L5178Y
Metabolic activation: Tested with and without phenobarbital-induced liver S9 from male mice
Concentrations: 0, and five concentrations up to ~32 nL/mL without S9, and six concentrations up to 70 nL/mL with S9. Test conditions chosen based on preliminary assays so that 50% growth reduction occurred at highest concentration.
Purity: Not reported
Method: Selection of forward mutation from TK+/- to TK-/- genotype. Activity compared to [Chemical 2].
Results: Proprietary A yielded negative results with or without activation. [Chemical 2] was negative without, but positive with activation.
Reference: Ref. 12; also Ref. 33

Type: Mammalian Cell Gene Mutation Test: Forward Mutation
Species, strain: V79 Chinese hamster lung cells
Metabolic activation: Tested with phenobarbital-induced liver S9 from male rats
Concentrations: 0, 0.02 mM Proprietary A. Test conditions chosen based on preliminary assays.
Purity: Not reported

Method: In two experiments, selection of 6-thioguanine-resistant colonies. Activity compared to [Chemical 2].
Results: Proprietary A with S9 did not increase mutation frequency. [Chemical 2] yielded positive results.
Reference: Ref. 48

Gene Mutation in Vivo

Sex-linked Recessive Lethal test in *Drosophila melanogaster* (OPPTS Harmonized Guideline 870.5275)

Type: Sex-linked Recessive Lethal test
Species, strain: *Drosophila melanogaster,* 100 males/concentration
Metabolic activation: None
Concentrations: 2.5 and 25% in feed (1% gum tragacanth in 3% sucrose)
Purity: Technical-grade [Formulation 2], purity not reported
Method: Proprietary A added to feed of males for 24 hours, subsequently mated with virgin unexposed females
Results: No evidence of toxicity or increase in the percentage of sex-linked recessive lethal mutations.
Reference: Ref. 11 as described in Ref. 61; also Ref. 32

Chromosomal Aberration in Vitro

In Vitro Mammalian Chromosome Aberration Test (OPPTS Harmonized Guideline 870.5375)

Type: *In vitro* chromosome aberration assay
Species, strain: Mouse lymphoma L5178Y
Metabolic activation: None, phenobarbital-induced or PCB-induced
Concentrations: 0, 0.01 to 0.1 µL/mL for non-induced, phenobarbital-induced or PCB-induced mouse
Purity: Not reported
Method: 4-hour exposure to Proprietary A with or without activation. Chromosomal aberrations scored in 50 metaphase spreads per concentration.
Results: Proprietary A caused increases chromosomal aberrations (up to 40%) with PCB- or phenobarbital-induction compared to noninduced S9.
Reference: Ref. 12; also Ref. 33

Chromosomal Aberration in Vivo

Mammalian Bone Marrow Chromosomal Aberration Test (OPPTS Harmonized Guideline 870.5385)

The available study provides sufficient evidence that Proprietary A did not induce chromosomal aberrations in mice exposed at the maximum tolerated dose of 760 mg/kg.

Type: Bone marrow chromosomal aberration *in vivo*
Species, strain: Mouse, CD-1, 4-8 males/group
Metabolic activation: None
Concentrations: 0, 0.05, 0.17, and 0.5 mL/kg; using the specific gravity of 1.52, the doses were 0, 76, 260, or 760 mg/kg. The highest dose was the maximum tolerated dose. Negative control was DMSO
Exposure duration, frequency: By oral gavage in once or daily on 5 consecutive days.
Purity: Technical grade; Not reported
Method: Mice were sacrificed at 6, 24, and 48 hours after single dose or 6 hours after the last of 5 doses. Between 233 and 400 cells were scored, rather than 500/animal. Triethylenemelamine was positive control.
Results: No evidence of increased frequency of chromosomal aberrations with Proprietary A. [Chemical 2] was also negative at doses up to 1,000 mg/kg. Positive control produce expected large increase in micronucleated polychromatic erythrocytes.
Reference: Ref. 12; Ref. 34

Mammalian erythrocyte micronucleus test (OPPTS Harmonized Guideline 870.5395)

Proprietary A administered as 2,000 mg/kg by an unspecified route to mice did not induce micronuclei in bone marrow erythrocytes (Ref. 60 as reported in Ref. 61).

DNA Damage and Repair

Unscheduled DNA synthesis in mammalian cells in culture (OPPTS Harmonized Guideline 870.5550)

Type: Unscheduled DNA synthesis in mammalian cells (hepatocytes) in culture
Species, strain: Rat, Wistar, male
Metabolic activation: With or without phenobarbital-induction
Concentrations: 0, 0.05, and 0.1 mM
Purity: Not reported
Vehicle: DMSO
Method: Cultured hepatocytes exposed to Proprietary A or [Chemical 2] for 18-19 hours. Incorporation of radiothymidine into DNA.

Results: Proprietary A was not genotoxic at 0.05 mM, but at 0.1 mM, a moderate response was observed in hepatocytes from untreated rats, but not phenobarbital-treated rats. [Chemical 2], the positive control, yielded positive results in induced and non-induced hepatocytes.
Reference: Ref. 48

Other

In vitro Sister Chromatid Exchange Assay (OPPTS Harmonized Guideline 870.5900)

Type: *In vitro* sister chromatid exchange assay
Species, strain: Mouse lymphoma L5178Y
Metabolic activation: None, phenobarbital-induced or PCB-induced
Concentrations: 0, 0.005-0.03 μL/mL for phenobarbital-induced (4 concentrations), and 6 concentrations up to 0.070 μL/mL for non-induced or PCB-induced mouse
Purity: Not reported
Method: Ten cells per concentration were analyzed.
Results: Proprietary A increased the incidence of sister chromatid exchanges in mouse lymphocytes under all three test conditions.
Reference: Ref. 12; also Ref. 33

Additional information

[Formulation 2] did not induce sister chromatid exchanges when applied to 3- to 4-day-old chicken embryos (Ref. 10).

Ecotoxicity

Aquatic Organism Toxicity

Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)

Conclusion:

The available acute toxicity data for freshwater fish (cold- and warm-water species) and saltwater fish were judged inadequate to meet the endpoints. The available acute fish toxicity studies are summarized in Table 1. However, if the results of Ref. 42, cited by Ref. 29 (see below), are confirmed independently, the acute toxicity endpoint for cold freshwater fish species might be satisfied given the high degree of agreement of the two available studies in rainbow trout.

Basis for Conclusion:

Freshwater Fish

Ref. 2 tested the toxicity to goldfish (*Carassius auratus*) of Proprietary A released from fabric treated with the flame retardant. Laundered or unlaundered sections of garment that had been treated with [Formulation 2], were placed in tanks with six goldfish. Fish in the tank with the unlaundered section became sluggish and all died within 3 hours. The concentration of [Formulation 2] in the test water reached 30 mg/L. Fish exposed for 96 hours to the laundered section of garment did not exhibit signs of toxicity. In another study, Proprietary A in water at 1 mg/L was not toxic to goldfish after 168 hours, but 5 mg/L of Proprietary A killed all (6/6) goldfish within 24 hours (Ref. 22). Ref. 2 and 21 did not evaluate toxicity using a range of concentrations of Proprietary A in water and, thus, cannot be used to derive an LC_{50}.

Ref. 46 estimated that the 96-hour LC_{50} values for killifish (*Oryzias latipes*) and goldfish were 3.6 mg/L and 5.1 mg/L, respectively. It appears that mortality was not evaluated in a control group of fish. It is unclear if the Proprietary A concentrations in water reported by Ref. 46 are measured or nominal values. The latter point is important because a parallel study indicated that the amount of Proprietary A added to test water declines rapidly and less than 40% of the original amount of Proprietary A remains in the test water after 96 hours (Ref. 46). Thus, the lethal concentrations of Proprietary A could be lower than the reported LC_{50} values.

Ref. 46 reported deformation of the spine in 7/10 killifish exposed to 3.5 mg/L Proprietary A for 24 hours. However, Ref. 46 does not provide sufficient information regarding the spine deformation in killifish to make meaningful use of these observations. It is unclear whether the deformations were observed in the acute toxicity study or in a separate assay using killifish only.

It appears that deformation was tested at only one concentration and a control group of fish was not evaluated.

Another study showed that the 96-hour LC_{50} of Proprietary A in rainbow trout (currently classified as *Oncorhynchus mykiss*) was 1.4 mg/L (95% CI: 0.9-1.9 mg/L) (Unpublished study conducted in 1990, summarized in Ref. 4, 5). A NOEC was not observed since one fish died at 0.63 mg/L, the lowest concentration tested. Compound purity was not provided in the summary and the reported concentrations of Proprietary A in the test water appear to be nominal values. The guideline for acute toxicity in fish (OPPTS 850.1075) indicates that test concentrations must be measured during the test if, as was the case in this study, aeration is used. Thus, the study reported by Ref. 4, 5 does not meet the criteria established by the guideline. The studies by Ref. 46 and Ref. 4, 5 suggest that the 96-hour LC_{50} for Proprietary A in fish is in the range of 1 to 5 mg/L, making it moderately toxic to fish. However, the data are inadequate to satisfy the acute toxicity endpoint for freshwater fish. A 96-hour LC_{50} of 1.1 mg/L and a NOEC of 0.56 mg/L for Proprietary A in rainbow trout (Ref. 42) were reported in Ref. 29. Although the results of the study by Ref. 42 are in agreement with those of Ref. 4, 5, the study by Ref. 42, or a study summary, was not available to allow for an independent evaluation of these data. Confirmation of the results of the study by Ref. 42 might allow the acute toxicity endpoint for freshwater fish to be satisfied.

Marine Fish

No acute toxicity studies in saltwater fish species were located.

Table 5-1. Summary of available acute fish toxicity studies for Proprietary A[a]									
			Selected Study Design Parameters[b]						
Study Reference	**Species Tested**	**96-Hour LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Ref. 2	Goldfish (*Carassius auratus*)	None	Static	None	6	Yes. The concentration of [Formulation 2] in water was determined by gas chromatography.	**pH:** NR **Temp:** 20°C **DO:** NR **Hardness:** NR **Water volume:** 20 L **Electrical conductivity**: 290 micromhos/cm	None	A laundered or unlaundered 38 cm x 64 cm section of garment (0.24 square meter area; 227 g/m^3), which had been treated with [Formulation 2], was placed in tanks with six goldfish. Fish in the tank became progressively more sluggish and all died within 3 hours. The measured concentration of [Formulation 2] in the test water was 30 mg/L. Fish exposed for 96 hours to the same section of fabric after it had been laundered did not die. Data for mortality in control fish were not presented in the study. Goldfish are not a designated test species, as per OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine).

Table 5-1. Summary of available acute fish toxicity studies for Proprietary A[a]									
			Selected Study Design Parameters[b]						
Study Reference	**Species Tested**	**96-Hour LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Ref. 4, 5	Rainbow trout (*Salmo gairdneri*)	1.4 mg/L (95% CI: 0.9-1.9 mg/L)	Static	Controls, 0.63, 1.25, 2.5, 5, 10 mg/L	10	No	**pH:** 7.14-7.78 **Temp:** 11.8-14.8 °C. **DO:** 92-100% of air saturation value **Hardness:** 218-228 mg/L as $CaCO_3$.	None reported	All mortalities occurred within the first 24 hours. Mortality was dose related. One fish died in the lowest dose group (0.63 mg/L). All fish died in the 5 and 10 mg/L groups. A NOEC was not observed.

Table 5-1. Summary of available acute fish toxicity studies for Proprietary A[a]									
			Selected Study Design Parameters[b]						
Study Reference	**Species Tested**	**96-Hour LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Ref. 22	Goldfish (*Carassius auratus*)	None	Static	1 and 5 mg/L in water	6	None reported	**pH:** NR **Temp:** 20°C **DO:** NR **Hardness:** NR **Electrical conductivity:** 290 micromhos/cm	Water or acetone	Fish were exposed to 1 or 5 mg/L Proprietary A in water or acetone. None of the fish in the 1 mg/L treatment had died after 168 hours. All fish in the 5 mg/L treatment died within 24 hours. The most conspicuous signs of toxicity were sluggishness and disoriented swimming prior to death. Mortality in control fish was not reported. Goldfish are not a designated test species, as per OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine). The study cannot be used to establish an LC_{50} value.

Table 5-1. Summary of available acute fish toxicity studies for Proprietary A[a]									
			Selected Study Design Parameters[b]						
Study Reference	**Species Tested**	**96-Hour LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Fish/ Conc**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Ref. 46	Killifish (*Oryzias latipes*)	Killifish: 3.6 mg/L	Static	NR	7 to 9	Unclear if conducted	**pH:** NR **Temp:** 25°C. **DO:** NR **Hardness:** NR **Electrical conductivity:** NR	NR	Fish were acclimated at least for 10 days at 25 °C. The test concentrations used were not reported. A control group was not tested. Killifish, but not goldfish, are a designated test species, as per OPPTS 850.1075 (Fish Acute Toxicity Test, Freshwater and Marine). Deformation of the spine was observed in 7/10 killifish exposed to 3.5 mg/L Proprietary A for 24 hours.
	Goldfish (*Carassius auratus*)	Goldfish: 5.1 mg/L							

[a]Studies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.
[b]NR: Not reported

Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD 202)

Conclusion:

The acute toxicity data for freshwater invertebrates were judged inadequate to meet the endpoint. However, if the results of the study cited by Ref. 29 (see below) are confirmed independently, the endpoint might be satisfied given the high degree of agreement of the two available studies in freshwater invertebrates.

Basis for Conclusion:

The available data are summarized in Table 2. A flow-through study revealed a 48-hour LC_{50} of Proprietary A with *Daphnia magna* of 3.8 mg/L (95% CI: 3.5-4.2 mg/L) and a NOEC of 1.6 mg/L (Unpublished study conducted in 1999, summarized in Ref. 4, 5). Although some of the conditions of the study design (such as number of organisms, and water temperature and chemistry) appear to meet OPPTS Harmonized Guideline 850.1010, other aspects of the study, including compound purity and condition and fertility of the organisms in culture, were not reported in the summary. The amount of solvent used in the control group and the Proprietary A treatments might have exceeded the recommended maximum solvent concentration, as per the OPPTS Guideline (100 mg/L), but this does not appear to have affected the study results. A 48-hour LC_{50} of 4.6 mg/L and a NOEC of 1.8 mg/L were reported for daphnia in a study by Ref. 43, as cited in Ref. 29. Although the results of the study by Ref. 43 are in agreement with those of Ref. 4, 5, the study by Ref. 43, or a study summary, was not available to allow for an independent evaluation of these data. Confirmation of the results of the study by Ref. 43 might allow the acute freshwater invertebrate toxicity endpoint to be satisfied.

Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)

Conclusion:

The available acute marine/estuarine invertebrate toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No acute toxicity studies in marine/estuarine invertebrate species were located.

Table 5-2. Summary of available acute invertebrate toxicity studies for Proprietary A[a]									
			Selected Study Design Parameters						
Study Reference	**Species Tested**	**48-Hour LC_{50}**	**Study Type**	**Concentrations Tested**	**No. of Organisms/ Concentration**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Ref. 4, 5	*Daphnia magna*	3.8 mg/L (95% CI: 3.5-4.2 mg/L)	Flow-through	Negative control, solvent control (dimethyl-formamide), 0.98, 1.6, 2.8, 3.8, 5.1 mg/L	10	Yes	**pH:** 8.3 **Temp:** 20±2°C **DO:** ≥8.5 mg/L (94% of air saturation value) **Hardness:** 126 mg/L as $CaCO_3$.	Dimethyl-formamide	Daphnids in the negative and solvent control groups appeared normal, as did the organisms in the 0.98 and 1.6 mg/L groups. Mortality in the 2.8, 3.8, and 5.1 mg/L groups was 0, 70, and 80%, respectively. Daphnids (15%) in the 2.8 mg/L group were lethargic at study termination. The amount of solvent used in the control group and the Proprietary A treatments is estimated to be approximately 300 mg/L. This exceeds the recommended maximum solvent concentration of 100 mg/L. The estimate is based on a reported dimethylformamide volume of 0.1 ml, a test chamber volume of 300 ml and a specific gravity of 0.95.

[a]Studies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.

Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)

Conclusion:

The available chronic toxicity data for freshwater and marine fish were judged inadequate to meet the endpoint.

Basis for Conclusion:

No chronic toxicity studies in freshwater and marine fish were located.

Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD 211) and Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)

Conclusion:

The available chronic toxicity data for freshwater and marine/estuarine invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No chronic toxicity studies in freshwater and marine/estuarine invertebrates were located.

Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)

Conclusion:

The available algal toxicity data were judged inadequate to satisfy the endpoint.

Basis for Conclusion:

The available data are summarized in Table 3. The summary of a 96-hour algal toxicity study (Unpublished study conducted in 1992, summarized in Ref. 4, 5) indicates that the study does not meet the OPPTS Harmonized Guideline 850.5400. The pH and temperature of the test water during the study were outside of the acceptable ranges for *Selenastrum capricornutum*, as per Guideline 850.5400. Moreover, the two highest concentrations tested exceed the estimated water solubility of Proprietary A (42 mg/L) and the concentrations tested were apparently not verified analytically. Additional information, including test substance purity, hardness, DO, TOC, TSS, exposure vessel size and head space, and measured chemical concentrations, were not provided in the summary. Also, there is no evidence that positive controls were used in order to establish that the algae were responding in the expected manner to a known chemical.

The deviations from the OPPTS Guideline indicate that the study is inadequate to satisfy the algal toxicity endpoint. Another study indicates that Proprietary A at 10 mg/L had no effect on growth or biomass of the algal species *Scenedesmus subspicatus* exposed for 72 hours (Unpublished study conducted by Ref. 44, cited in Ref. 29). The study, or a study summary, was not available for the study by Ref. 44 to allow for an independent evaluation of these data.

Table 5-3. Summary of available algal toxicity studies for Proprietary A[a]								
			Selected Study Design Parameters[b]					
Study Reference	**Species Tested**	**EC_{50}, NOAEC, and LOAEC**	**Study Type**	**Concentration Range Tested**	**Analytical Monitoring**	**Water Chemistry**	**Solvent**	**Comments on the Data**
Ref. 4, 5	*Selenastrum capricornutum*	96-hour EbC_{50} (biomass) = 12 mg/L (95% CI: 10-15 mg/L). 96-hour ErC_{50} (growth rate) = 39 mg/L (95% CI: 31-50 mg/L). 96-hour NOAEC: 6 mg/L.	Static	0 (negative control), 2, 6, 18, 54, or 162 mg/L	No	**Temp:** 21°C **pH:** 6.7-7.9 **DO:** NR **Hardness:** NR	None reported	A number of problems are evident with this study, namely the pH changed markedly during the study, and the reported pH and water temperature were outside of the recommended values for this algal species.

[a]Studies that were either published in a foreign language or that were not readily and that were not critical to the hazard assessment were not retrieved.
[b] NR: Not reported.

Terrestrial Organism Toxicity

Acute Oral (OPPTS Harmonized Guideline 850.2100), Dietary (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205), or Reproductive Toxicity (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206) in Birds

Conclusion:

The available acute oral, dietary, and reproductive toxicity data for birds were judged inadequate to meet the endpoints.

Basis for Conclusion:

No acute oral, dietary, or reproductive toxicity studies in birds were located.

Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)

Conclusion:

The available earthworm subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No earthworm subchronic toxicity studies were located. An acute (14-hour) LC_{50} of 130 mg/kg soil and a NOEC of 100 mg/kg soil with the earthworm, *Eisenia fetida* (Ref. 45), were reported in Ref. 29. However, the study has also been reported to be a 14-day subchronic toxicity study (Ref. 39). The study, or a study summary, was not available for an independent evaluation of the study and the results.

Physical/Chemical Properties

CAS
MF
MW
SMILES

Physical/Chemical Properties

Water Solubility:
Conclusion: The available water solubility data are adequate.
Basis for Conclusion: The key study (highlighted) was performed according to a reliable method, and is in reasonable agreement with other values reported in the literature.

Solubility (mg/L)	References
42	Ref. 4, 5; water solubility determination according to OECD Guideline 105 (shake-flask method)
7	Ref. 8 (24˚C); Ref. 27; Ref. 49 (24˚C); Ref. 28 (24˚C)
100	Ref. 13, 21, 31, 61 (30˚C)
110	Ref. 15

Log K_{ow}:
Conclusion: The available log K_{ow} data are adequate.
Basis for Conclusion: The key study was performed according to a reliable method.

Log K_{ow}	Reference
2.4	4, 5; determination of Octanol-Water Partition Coefficient According to OECD Guideline 117 (HPLC Method)
3.8	Ref. 61
3.65	Ref. 28, 49
3.75	Shake-flask method, Ref. 46

Oxidation/Reduction: No data

Melting Point:
Conclusion: The available melting point data for Proprietary A are adequate.

Basis for Conclusion: The key study was performed according to a reliable method. It is noted that the other literature data do not agree with the key study; however, the methods used to measure the melting points are not provided in any of the sources. As an OECD-guideline compliant method, the key study is better described and better supported.

Melting Point (˚C)	**References**
-58	Ref. 4, 5: melting point determination by DSC (compliant with OECD Guideline 102), freezing point was determined to be -40˚C, melting point -58˚C
27	Ref. 15
26.66	Ref. 6

Boiling Point:
Conclusion: The boiling point data are adequate.
Basis for Conclusion: A variety of literature sources report the same value for the boiling point, although there is some indication that the compound may decompose at or near the boiling point. Since experimental details are not provided in any of the sources, it is not possible to determine whether the temperatures reported are decomposition or boiling temperatures. Nevertheless, given the high boiling point reported for this material, the available data are adequate to characterize its potential volatility.

Boiling Point (˚C/torr)	**References**
236-237/5	Ref. 13, 31, 49, 61
200/4	Ref. 6
Dec. >200/4	Ref. 61
Gradual Dec. >200	Ref. 28

Vapor Pressure:
Conclusion*:* The available vapor pressure data are not adequate
Basis for Conclusion: Although this measured vapor pressure is reported in two sources, it appears to be very high relative to the boiling points reported for this chemical. For comparison, an estimated vapor pressure (Ref. 23) is also included in the table below. The vapor pressure remains a data need.

Vapor Pressure (torr/˚C)	Reference
0.01/30	Ref. 4, 5, 61
2.98 x10^{-7}	Ref. 23 estimate

Odor:
Conclusion: The odor of this compound has been adequately characterized.
Basis for Conclusion: Although no standardized tests are available for characterizing chemical odors, the two descriptions found are similar, and are consistent with the low volatility expected for this chemical.

Odor	Reference
Mild Odor	Ref. 28
Bland Odor	6

Oxidation/Reduction Chemical Incompatibility: No data

Flammability:
Conclusion: The flammability (as the flash point and autoignition temperature) has been adequately characterized.
Basis for Conclusion: Studies on the flash point and autoingition temperature of this chemical were located and appear reasonable given the other physical/chemical properties available for this compound.

Flash Point	Reference
252˚C (coc)	Ref. 28, 61
>107.22˚C (Seta closed cup)	Ref. 6

Autoignition Temperature	Reference
512.77˚C	Ref. 6

Explosivity: No data

Corrosion Characteristics: No data

pH:
This chemical does not contain functional groups expected to influence the pH of aqueous solutions. Data for this endpoint are therefore not applicable.

UV/Visible Adsorption: No data

Viscosity:
Conclusion: The viscosity of this chemical at various temperatures has been adequately characterized.
Basis for Conclusion: Studies on the viscosity of this chemical were located and appear reasonable given the other physical/chemical properties available for this compound.

Viscosity (cP)	Reference
1,800 at 25˚C	Ref. 6, 61
2,200 at 0˚C	Ref. 6
540 at 40˚C	Ref. 6

Density/Relative Density/Bulk Density:
Conclusion: The density of this compound has been adequately characterized.
Basis for Conclusion: Consistent data are provided in several reputable sources.

Density	Reference
1.52 at 25˚C	Specific gravity. Ref. 61
1.5022 at 20˚C	Specific gravity. Ref. 13, 31
1.48 kg/L at 25˚C	Bulk density. Ref. 28

Dissociation Constant in Water:
This compound does not have functional groups that are expected to dissociate in water. This endpoint is therefore not applicable.

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish:
Conclusion: The bioconcentration factor has been adequately characterized.
Basis for Conclusion: The two studies cited in the table below provide consistent information for killifish under both static and flow-through conditions, over a variety of observation times, and with varying initial concentrations of test substance. The BCF was also measured in goldfish; the reported BCFs are independent of study length.

Reference	Species	BCF	Key Design Parameters				Comments
			Exp. type	Range (ppb)	Study length	T (˚C)	
Ref. 46	Killifish	113 110 77	Static	1,000 initial	24 hours 55 hours 96 hours	25	Half-life for elimination of the test compound in water + fish = 31 hours.
Ref. 46	Goldfish	5 3	Static	1,000 initial	24 hours 96 hours	25	Half-life for elimination of the test compound in water + fish = 42 hours.
Ref. 47	Killifish	46±5 32±4 31±6 59±16 49±12	Flow-through (all)	400 300 40 40 80	3 days 4 days 6 days 30 days 32 days	25	BCF is independent of concentration; continuous (flow-through) results correlate to static results (Ref. 46).

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism:
Conclusion: The metabolism of Proprietary A in fish is not adequately characterized in the literature.

Basis for Conclusion: The depuration rate is adequately described in killifish, however, the metabolite distribution is not addressed.

Species	Rate	Comment	Reference
Killifish	Elimination half-life, 1.65 hours	Depuration rate - elimination of Proprietary A when exposed fish are moved to clean water.	Ref. 47
Killifish	Apparent metabolism is much faster in killifish than in goldfish. (Quantitative data are not provided.)	~10% of applied Proprietary A remains in the water in the presence of killifish after 96 hours. Control (no fish) has no change in TPP concentration.	Ref. 46
Goldfish	Apparent metabolism is much slower than in killifish. (Quantitative data are not provided.)	~25% of applied Proprietary A remains in the water after 96 hours in presence of goldfish.	Ref. 46

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation:
Conclusion: The biodegradation of Proprietary A under aerobic conditions has been adequately characterized.
Basis for Conclusion: The key study (highlighted) was performed according to a GLP-compliant OECD guideline test. The other data located in the literature are generally in agreement with the key study.

Study type/ Method	Innoculum	Acclim	Degradation	Time	Comments	Reference
OECD Guideline 301B Modified Sturm Test	Activated sludge		0% by CO_2 evolution. DOC red. not calculated	28 days	Initial concentrations 2, 10 mg/L. GLP-compliant. Also reported: 1) Closed bottle test	Ref. 3, 4, 5

Japanese MITI test	Activated sludge		avg. 1% by BOD	28 days	Initial concentrations 100 mg/L (test substance), 30 mg/L (sludge).	Ref. 15, 16, 28
OECD 302C			0% by O_2 uptake	28 days		Ref. 61
River Die-Away	Water from Oh River (Osaka, Japan) Neya River (Osaka, Japan) Seawater (Osaka Bay)		12.5% 18.5% 0% 5.4% 0% 22%	7 days 14 days 7 days 14 days 7 days 14 days	Initial concentrations 20 mg/L in Oh River water and 1 mg/L in Neya River water. Concentration in seawater not reported. Analysis by Molybdenum Blue calorimetric assay for increase in phosphate ion.	Ref. 61

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis:
Conclusion: The available pyrolysis data are not adequate.
Basis for Conclusion: Although a semi-quantitative description of the pyrolysis products is given in Ref. 18, the list of degradates provided accounts for only 60% of the total mass expected and doesn't contain any oxygenated or phosphorus-containing compounds. Therefore, this study does not provide a complete profile of the pyrolysis of Proprietary A.

Pyrolysis Products	**Reference**
Relative mol.% degradates, 0.1 mole Proprietary A heated at 250-260˚C under reduced pressure (3 mm Hg), overall yield 60 wt%: [Chemical 3] 26.7%, [Chemical 4] 36.0%, [Chemical 5] 34.4%, [Chemical 6] 2.9%.	Ref. 18
Thermal oxidative degradation in air at 370˚C: Hydrogen halides, halogenated C2 and C3 species, acrolein	Ref. 28
When heated to decomposition, it emits toxic fumes of Cl^+ and PO_x	Ref. 31

Hydrolysis as a Function of pH:
Conclusion: The hydrolysis rate data are adequate. The hydrolysis products are not described.
Basis for Conclusion: The studies cited below were GLP-compliant tests run according to accepted guidelines.

$T_{1/2}$	pH	Temp.	Comment	Reference
>1 year >1 year 14.7 days	4 7 9	50˚C	OECD 111; EPA Ser. 835 OPPTS No. 835.2110. GLP-compliant. Initial concentration, 10 mg/L. Study length, 5 days. Preliminary study.	Ref. 4, 5
28 days	9	40˚C	OECD 111; EPA Ser. 835 OPPTS No. 835.2110. GLP-compliant. Definitive 30-day study.	Ref. 4, 5
128 days	9	20˚C	OECD 111; EPA Ser. 835 OPPTS No. 835.2110. GLP-compliant. Definitive 30-day study.	Ref. 4, 5

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary B: Aryl phosphate

Draft Hazard Review

December 2004

Proprietary B: Aryl phosphate
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	*
Dermal	*
Inhalation	
Eye irritation	*
Dermal irritation	*
Skin sensitization	
Subchronic Toxicity	
28-Day oral	*
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✓
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	*
Gene mutation in vivo	*
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	*
DNA damage and repair	*
Other	*

Proprietary B: Aryl phosphate
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	*
Daphnia acute EC50	*
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary B: Aryl phosphate
Synonym
CAS
MF
MW
SMILES

Many of the available health effects studies were conducted with commercial mixtures that commonly contained triphenyl phosphate as well as Proprietary B. The available information regarding the composition of these mixtures is presented below, but the composition of the actual samples tested in the health effects studies usually was not reported.

[Formulation 1] is reported to contain 60-100% Proprietary B and 15-40% triphenyl phosphate (Ref. 24) and [Formulation 2] is reported to contain 60-100% Proprietary B and 4-7% triphenyl phosphate (Ref. 25).

Major Components of [Formulation 3] and [Formulation 4] as reported in Ref. 34		
Component	**[Formulation 3]**	**[Formulation 4]**
Total Proprietary B	**49**	**61**
[Chemical 1]	8	11
[Chemical 2]	6	7
[Chemical 3]	2	5
[Chemical 4]	21	27
[Chemical 5]	12	11
Triphenyl Phosphate	33	18

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)

Conclusion:

The available acute oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for limit tests on undefined flame retardants for which compositional information was not provided. The authors of the studies referred to them as "non-definitive", possibly because of the small group sizes (which, however, are consistent with current guidelines); in other respects the studies follow current guidelines.

Additional Studies and Information:

No deaths were observed in Sprague-Dawley rats (3/sex) given [Formulation 1] (mixture of Proprietary B and triphenyl phosphate) as a single oral dose of 5,000 mg/kg (Ref. 13). Clinical signs, which included tremors (0/3 males, 1/3 females), oral discharge, ataxia (0/3 males, 1/3 females), decreased locomotion (1/3 males, 1/3 females), chromorhinorrhea, chromodacryorrhea, and abdominogenital staining, subsided by day 11. No effects on body weight gain and no gross internal lesions were observed.

A parallel acute oral study on Sprague-Dawley rats (3/sex) given [Formulation 2] at a dose of 5,000 mg/kg, reported clinical signs (abdominogenital staining and chromorhinorrhea) on the first 2 days post dosing, but no mortality, body weight gain effects, or gross internal lesions were reported (Ref. 17).

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged inadequate to meet the endpoint.

***Basis for Conclusion*:**

The available data are for limit tests on undefined flame retardants for which compositional information was not provided. The authors of the studies referred to them as "non-definitive",

possibly because of the small group sizes (which, however, are consistent with current guidelines); in other respects, the studies follow current guidelines.

Additional Studies and Information:

No deaths were observed among Sprague-Dawley rats (3/sex) that were dermally exposed to [Formulation 1] (mixture of Proprietary B and triphenyl phosphate) at a dose of 2,000 mg/kg for 24 hours under an occlusive covering (Ref. 14). There were no effects on body weight gain, no signs of irritation on the test site, and no gross internal lesions observed.

In a parallel study in Sprague-Dawley rats (3/sex) dermally treated with 2,000 mg/kg [Formulation 2], all but one female gained weight, but there were no deaths, signs of irritation, or gross internal lesions (Ref, 18).

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300; OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies were located that followed or were similar to the guideline. A non-guideline study evaluated neurotoxicity of combustion products of an Proprietary B/triphenyl phosphate mixture in the presence of cyclic phosphonate compounds.

Additional Studies and Information:

Preliminary results of a study were reported (Ref. 38) investigating whether toxic compounds were formed when cyclic phosphonate compounds were thermally decomposed in the presence of other phosphate compounds in trimethylol polyol-based urethane foam. When rats were exposed (head only) for 20 minutes to smoke and decomposition gases from foam containing equal proportions of the cyclic phosphonate compounds and a mixture of Proprietary B and triphenyl phosphate, no convulsive seizures, characteristic of exposure to toxic bicyclic phosphites or phosphates, were observed.

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for undefined flame retardants for which compositional information was not provided. The authors of the studies referred to them as "non-definitive", although they were consistent with current guidelines.

Additional Studies and Information:

Slight conjunctival erythema was observed in the eyes of 1/1 male and 1/2 female New Zealand White rabbits 24 hours after instillation with 0.01 mL of [Formulation 1] (mixture of Proprietary B and triphenyl phosphate) but was resolved by 48 hours (Ref. 15). No conjunctival discharge or effects on the cornea or iris were observed. The material was tentatively characterized as "practically non-irritating", based on a maximum irritation score of 1.3/110 at 24 hours.

In a parallel study in New Zealand White rabbits (1 male and 2 females) instilled with 0.01 mL [Formulation 2], there were no signs of eye irritation observed at 1, 24, 48, or 72 hours (Ref. 19). The material was tentatively characterized as non-irritating to the eyes based on a primary irritation index of 0/110 at all timepoints.

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for undefined flame retardants for which compositional information was not provided. The authors of the studies on the Durad materials referred to them as "non-definitive", although they were consistent with current guidelines.

Additional Studies:

No dermal irritation (erythema or edema) was observed in one male and two female New Zealand White rabbits that were dermally exposed for 4 hours to [Formulation 1] (mixture of Proprietary B and triphenyl phosphate) on two occluded test sites (0.5 mL per site) and examined at 4.5, 24, 48, or 72 hours (Ref. 16). The material was tentatively rated as non-irritating to intact rabbit skin, based on scores of 0/8.0 at all timepoints.

In a parallel dermal irritation study in one male and two female New Zealand White rabbits exposed for 4 hours to [Formulation 2] on two occluded test sites (0.5 mL per site), no irritation was observed at times between 4.5 and 72 hours (Ref. 20). The material was tentatively rated as non-irritating to intact rabbit skin, based on scores of 0/8.0 at all timepoints.

In skin irritation assays in male New Zealand White rabbits (6/group), 24-hour topical administration (0.5 mL/site) of [Formulation 4] or [Formulation 10] did not elicit erythema or edema to intact or abraded skin (examined at 24 and 72 hours) (Ref. 6). The mean primary dermal irritation indices were 0/2.0 for both materials, which were characterized as non-irritating to skin.

- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

No studies of this type were located.

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

Conclusion:

The available subchronic oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No verifiable data were available for defined substances tested under guideline methods. A study on undefined [Formulation 4] appeared to follow the guideline for a 28-day oral study, but was only available as an incomplete robust summary. The unexplained mortality in this study indicates that it may not be an adequate study.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

As described in an incomplete robust summary (results were not presented quantitatively) for an HPV submission, Sprague-Dawley rats (10/sex) received [Formulation 4] in the diet at concentrations of 0, 0.1, 0.5, or 1.0% for 28 days (Ref. 5). Treatment had no effect on survival (but 12 rats died: 1 control, 4 low-dose, 4 mid-dose, and 3 high-dose rats). Treatment also had no effect on urinalysis results, incidence of gross lesions at necropsy, or histology of the liver and kidney (histology examined only in high dose animals and controls). It was not specified whether animals that died during the study were necropsied or examined histologically. Reduced feed consumption was observed in the mid-dose group in both sexes and reduced body weight gain was noted in high-dose females. Abnormalities (not specified) were observed in clinical chemistry measurements in mid- and high-dose groups and in hematology parameters at the high dose. Relative liver weights were elevated in all treated groups. The unexplained mortality during this short term study raises concern for study adequacy.

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

Subchronic Dermal Toxicity (21/28-day or 90-day)

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90-day)

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

Additional information

As described in an unvalidated robust summary, 3 days of exposure to [Formulation 7], tested without metabolic activation at concentrations between 0.04 and 5.0 µg/mL, did not induce cell transformation in cultured Balb/c-3T3 cells (Ref. 36).

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

Available acute and 28-day studies indicate that there is a risk of delayed neurotoxicity from exposure to Proprietary B. Most studies either were conducted on undefined substances or were not described in sufficient detail. A summary of a study on purified components of [Formulated] flame retardants suggests that [Chemical 4] or [Chemical 2] are the neurotoxic components of these mixtures; however, details of the *in vivo* study in hens were not located. The neurotoxicity of Proprietary B preparations would be dependent on the relative content of [Formulation 11] isomers. No data are available for the full battery of tests for functional neurotoxicity or for developmental neurotoxicity.

Delayed Neurotoxicity

Conclusion:

The available delayed neurotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The acute study (experiment A) on a defined Proprietary B mixture departed from guideline in that enzyme inhibition was assayed 24 hours after dosing rather than 48 hours, but reported significant suppression of both brain neurotoxic esterase and plasma cholinesterase levels. The longer study did not conduct a complete battery of neurobehavioral tests as stipulated under the guideline, but reported adverse effects on motor coordination at all doses on the day of treatment. The highest dose (11,700 mg/kg) exceeded that recommended under the guideline, but that deviation does not affect the conclusion of the study. Studies on purified components of [Formulated] flame retardants identified the neurotoxic components, but were not adequately described. The majority of studies suggest that delayed neurotoxicity may result from exposure to oral doses in excess of 1,000 mg//kg.

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Critical Studies

Type: Acute oral delayed neurotoxicity

Species, strain, sex, number: Hen, 12-14 months old, White Leghorn, 4/dose for experiment A; 10-12/dose for experiment B.
Purity: Proprietary B with the composition as in the following table.

Composition of Proprietary B assayed by Ref. 37	
Component	**Percent**
Total Proprietary B	**<75**
[Chemical 4]	24
[Chemical 6]	18
[Chemical 2]	10
[Chemical 7]	10
[Chemical 5]	6
[Chemical 8]	7
[Chemical 9]	<1
Triphenyl Phosphate	24

Doses: Experiment A. Six doses between 12 and 11,700 mg/kg;
Experiment B. 0, 12, or 370 mg/kg in corn oil or 11,700 mg/kg undiluted
Vehicle: Corn oil
Positive control: Tri-*ortho*-cresyl phosphate (TOCP**)**
Route: Oral (not specified)
Exposure duration, frequency: Experiment A, single treatment followed 24 hours later by biochemical assay; Experiment B, 6 weeks, single treatments 3 weeks apart; study terminated 3 weeks after second dose.
Method: Experiment A. Brain neurotoxic esterase (NTE) and plasma cholinesterase (PChE) measurements recorded 24 hours after single treatment with Proprietary B, corn oil or TOCP.
Experiment B. Doses were chosen based on results of experiment A to represent minimal, 50%, and maximal inhibition of brain NTE. Body weight and food consumption measured every 3-4 days, walking behavior evaluated weekly. Neurohistopathology evaluated at termination.
Results: Experiment A. The NOAELs for inhibition of NTE or PChE were 12 and 180 mg/kg, respectively. Doses about 1,000 mg/kg and higher caused ~70% inhibition of NTE and ~80% inhibition of PChE. The positive control (500 mg/kg of TOCP) inhibited brain NTE by 85.2% and PChE by 70%.
Experiment B. Proprietary B had no effect on mortality. Few adverse signs visible at or below 370 mg/kg. All treated at 11,700 mg/kg showed motor incoordination beginning day 1, with feather loss 7-11 days later. Body weights not affected at lowest dose. Body weight effects at mid- and high-dose are uncertain because text and graph do not match; one dose caused transient weight loss on days 22-38 and the other persistent weight loss from day 22 to the end of the

study. TOCP caused persistent weight loss beginning day 5. Food consumption was transiently reduced in all groups (including positive and negative controls) on day 2 and 23, also on day 18 for TOCP. Significant transient, dose-dependent impairment of gait was observed on day 1 and 22 for hens treated with Proprietary B at all doses. Hens treated with TOCP showed significant impairment on day 1 and 15, with gradual worsening to the end of the study. Neurohistopathological examinations revealed no significant difference between Proprietary B treatment and corn oil controls, whereas TOCP caused a significant increase in axonal degeneration in brain, spinal cord (cervical, thoracic and sacro-lumbar), and bilateral degeneration of the sciatic nerve.
Reference: Ref. 37

Additional Studies:

As described in Ref. 44, a series of acute delayed neurotoxicity assays were conducted on [Formulated] flame retardants. No ataxia was observed in groups of 4 hens treated with [Formulation 5] at doses of 2,000, 4,000, or 8,000 mg/kg; 3/30 hens treated with 16,000 mg/kg showed ataxia (Ref. 7). Only 1/10 hens treated with [Formulation 6] at 20,000 mg/kg exhibited ataxia (Ref. 8). In one study on [Formulation 4], no ataxia was observed at doses of 500, 1,000, or 2,000 mg/kg, whereas 2/10 treated at 4,000 mg/kg showed ataxia (Ref. 9); inhibition of brain NTE was 79.5% at the highest dose. In a second study on [Formulation 4], incidences of ataxia (0/10, 3/10, 1/10 and 1/10) and neurohistopathological lesions (1/10, 0/10, 1/10, and 2/10) were not precisely related to the respective doses of 3,000, 5,000, 7,000, and 9,000 mg/kg (Ref. 10). For [Formulation 3], incidences of ataxia (1/9, 4/10, 6/10 and 3/10) and neurohistopathology (0/10, 4/10, 7/10 and 1/10) were observed in the 2,000, 4,000, 6,000, and 8,000 mg/kg groups, respectively (Ref. 11).

A subchronic (91-day) oral neurotoxicity assay is summarized briefly in a TSCA 8e submission (Ref. 12), and in more detail by Ref. 44 and in a robust summary in an HPV submission (Ref. 23; U.S. EPA comments not available). In this study, hens (20/group) were administered [Formulation 3] (mixture of Proprietary B and triphenyl phosphate) daily at doses of 0, 10, 20, 90, and 270 mg/kg/day. Deaths occurred in all dose groups as follows: 2/20 vehicle controls, 4/20 positive controls, 3/20 at 10 mg/kg/day, 5/20 at 90 mg/kg/day, and 6/20 at 270 mg/kg/day. Ataxia was observed in 4/20 at 90 mg/kg/day and 9/20 at 270 mg/kg/day. Histopathological examination of nervous tissue of 10 hens/group revealed the following: significant degeneration at 3 levels of the spinal cord in 3 vehicle controls, significant degeneration of the spinal cord in TOCP hens, degeneration of the spinal cord and peripheral nerves in hens of the 90 and 270 mg/kg/day groups, with a dose-response relationship for severity and incidence (further details not reported). No ataxia or brain histopathology was observed at 10 or 20 mg/kg/day.

[Formulation 4] and [Formulation 6] were given in two 2,000 mg/kg doses 21 days apart to hens (4/group) (Ref. 22). Neither compound caused body weight effects, clinical signs of neurotoxicity or an increase in gross internal lesions at necropsy (21 days after the second dose).

There was no evidence of neurohistopathology in hens treated with [Formulation 4], but one out of four hens treated with [Formulation 6] had unilateral brain lesions at two histological levels.

Proprietary B at tested positive for neurotoxicity in hens treated at three 21-day intervals with 10,000 mg/kg (Ref. 33). Effects included gross paralysis with demyelination confirmed histopathologically.

Several components of the [Formulated] series of flame retardants were isolated to >99% purity and tested at doses as high as 1,000 mg/kg in hens for neurotoxicity and suppression of neurotoxic esterase (Ref. 29). Details of these studies were not located. Three isomers of [Chemical 1] and [Chemical 5] elicited no signs of neurotoxicity and no suppression of NTE levels. [Chemical 5] was also judged to be non-neurotoxic, eliciting no ataxia or other signs of neurotoxicity and insignificant suppression of NTE (-4% or -15%) in two tests. Both [Chemical 2] and [Chemical 4] were positive, eliciting ataxia and neurotoxicity at 1,000 mg/kg, but not at lower doses; [Chemical 2] suppressed NTE by 85% and [Chemical 4] suppressed NTE by 79 and 90% in two assays. The author suggested that neurotoxicity was associated with triaryl phosphates containing a 2-alkyl substituent with an oxidizable alpha-hydrogen.

In a two-hen screening test, a single 1,000 mg/kg dose of [Formulation 3] administered in gelatin capsules to two hens resulted in a 53.1% inhibition of neurotoxic esterase activity in the brain (Ref. 42). The report was not clear as to the day on which the hens were sacrificed.

No neurotoxicity studies were located that followed or were similar to the guidelines listed below.

Neurotoxicity (Adult)

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity

- **Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat) OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent) OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred) OPPTS Harmonized Guideline 870.6855

These studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Other Neurotoxicity Data

Cholinesterase inhibition

[Formulation 3] at doses of 15, 20, or 25 mL/kg did not inhibit blood cholinesterase activity, but neither species of animal (3/group) nor the specific biological material assayed were reported (Ref. 4).

IMMUNOTOXICITY

***Conclusion*:**

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No immunotoxicity study was located that followed or was similar to the guideline listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No verifiable genotoxicity data were located. The available studies were only accessible as robust summaries in a IUCLID Dataset that had not undergone review by the European Commission (Ref. 3). Furthermore, the data were unpublished industry-sponsored studies on commercial products for which no contemporaneous component analyses were provided. Current compositional information taken from MSDS documents are presented in the following table. The results of these studies are summarized below despite their uncertain validity. In general, not enough details were provided to ascertain whether protocols met the standards of OPPT or OECD guidelines.

Percentage of Proprietary B and triphenyl phosphate in Currently Available Commercial Products			
Product	**Proprietary B (%)**	**triphenyl phosphate (%)**	**Reference**
[Formulation 7]	60-100	15-40	Ref. 26
[Formulation 8]	60-100	10-30	Ref. 27
[Formulation 9]	60-100	7-13	Ref. 28
[Formulation 2]	60-100	4-7	Ref. 25

Gene Mutation in Vitro:

- **Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)**

As described in unvalidated robust summaries, negative results were reported for mutagenicity assays in *Salmonella typhimurium* with or without metabolic activation. [Formulation 7] and [Formulation 9] were tested in strains TA98, TA100, and TA1537 at concentrations as high as 1.62 mg/mL (Ref. 1, 2). [Formulation 9] and [Formulation 2] were tested in strains TA98, TA100, TA1535, TA1537, and TA1538 at concentrations as high as 0.1 mL per plate (Ref. 31, 32).

- **In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)**

As described in an unvalidated robust summary, [Formulation 7] at concentrations of 0.0013-0.1 µL/mL was not mutagenic to cultured mouse lymphoma L5178Y $TK^{+/-}$ cells without metabolic activation (Ref. 30). Results in the presence of metabolic activation were equivocal in that a dose-response was observed, but none of the cultures exhibiting >10% total growth had mutant frequencies 2-fold greater than background.

Gene Mutation in Vivo

- **Sex-linked Recessive Lethal test in *Drosophila melanogaster* (OPPTS Harmonized Guideline 870.5275**)

As described in an unvalidated robust summary, [Formulation 7] (32.5, 75, or 150 mg/mL) fed to adult male fruit flies for 3 days did not induce heritable mutations (Ref. 43).

Chromosomal Aberration in Vitro

No pertinent studies were located.

Chromosomal Aberration in Vivo

- **Mammalian Bone Marrow Chromosomal Aberration Test (OPPTS Harmonized Guideline 870.5385)**

As described in an unvalidated robust summary no increase in chromosomal aberrations was observed in the bone marrow of Chinese hamsters (8/sex/group), 16, 24, or 48 hours after receiving a single oral dose of 5,000 mg/kg [Formulation 7] by gavage (Ref. 41). The summary indicated that the study was conducted under OECD Guideline 475 and GLP. Another unvalidated robust summary reported that a significant increase (compared to controls) in the incidence of bone marrow cells with chromosomal anomalies was observed in Chinese hamsters (6/sex/group) 24 hours after receiving the second of two consecutive daily doses of 2,500 or 5,000 mg/kg/day [Formulation 7] by oral gavage (Ref. 40); no increase was observed in animals receiving 1,250 mg/kg/day.

DNA Damage and Repair

- **Unscheduled DNA synthesis in mammalian cells in culture (OPPTS Harmonized Guideline 870.5550)**

As described in an unvalidated robust summary, [Formulation 7] tested without metabolic activation at concentrations between 0.6 and 75 nL/mL did not cause unscheduled DNA synthesis in cultured rat hepatocytes (Ref. 35).

Other

- **In vivo Sister Chromatid Exchange Assay (OPPTS Harmonized Guideline 870.5915)**

As described in an unvalidated robust summary, there was no increase in the frequency of sister chromatid exchanges in bone marrow cells of Chinese hamsters (4/sex/group) 24 hours after receiving a single oral dose of 1250, 2,500, or 5,000 mg/kg [Formulation 7] by gavage in carboxymethylcellulose (Ref. 39).

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

Summaries were located for several acute toxicity studies of Proprietary B in an HPV test plan submission and accompanying robust summaries (Ref. 23); however, EPA comments on this submission were not available. The summaries included two 96-hour studies in fathead minnows (*Pimephales promelas*), three 96-hour studies in rainbow trout (*Oncorhynchus mykiss*), and three 48-hour studies in *Daphnia magna*. According to Ref. 21, all of the studies were conducted with 100% Proprietary B; however, other reports have identified the tested material in some of these studies as [Formulation 1] (Ref. 24) or [Formulation 4] (Ref. 21). [Formulation 1] is a mixture containing 60-100% Proprietary B and 15-40% triphenyl phosphate (Ref. 24). [Formulation 4] has been reported to contain 61% Proprietary B and 18% triphenyl phosphate (Ref. 34; see table at beginning of Human Health Effects for details). The available study summaries and Material Safety Data Sheets are insufficient to precisely establish the composition of the materials tested in the acute toxicity studies. Without precise knowledge of the composition of the tested materials, it is not possible to use these studies to make a definitive statement regarding the acute toxicity of Proprietary B. The available information regarding the acute toxicity of Proprietary B to freshwater fish or aquatic invertebrates is insufficient to satisfy the endpoints in the guideline protocols listed below.

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish or aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary B
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary C: Chloroalkyl phosphate (2)

Draft Hazard Review

December 2004

Proprietary C: Chloroalkyl phosphate (2)
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	✓
Dermal	✓
Inhalation	*
Eye irritation	✓
Dermal irritation	✓
Skin sensitization	✓
Subchronic Toxicity	
28-Day oral	
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	*
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	*
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	✓
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	

Proprietary C: Chloroalkyl phosphate (2)
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	
Daphnia acute EC50	
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary C: Chloroalkyl phosphate (2)
Synonym
CAS
MF
MW
SMILES

Test materials used in health effects studies included two formulations, [Formulation 1] and [Formulation 2]. Analysis of [Formulation 1] indicated an approximate ~85% content of Proprietary C, 6.7% [Chemical 1], and 5-10% related compounds. The following table shows a comparison of properties and of impurities in [Formulation 1] and a sample of [Formulation 2] (Ref. 11). [Chemical 2] was an additive to prevent scorching during foam preparation; it is a neuroleptic agent. Results for [Formulation 2]and [Formulation 3] are provided as supplemental information only, as current products do not contain [Chemical 2].

A Comparison of [Formulation 1] with [Formulation 2] (Ref. 11)		
	[Formulation 1]	**[Formulation 2]**
Acidity (mg KOH/g)	0.1-1.0	1.6
Color (APHA)	100-200	500+
Viscosity (corrected to 25°C)	2,000-3,500 cp	3,950
[Chemical Group 1]	100-500 ppm	less than detectable
[Chemical 1] (%)	4-9%	9.0%
[Chemical 2]	absent	1.5-2.0%

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Acute oral toxicity studies on undiluted [Formulation 1] (~85% Proprietary C) conformed to OPPTS or OECD guidelines except that survivors were not necropsied. The LD50 exceeded the current limit dose of 5,000 mg/kg for acute oral toxicity.

Critical Study:

Type: Acute oral toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 5/sex/group
Doses: Two tests performed, the first at 5,000 mg/kg (sample 83341) and the second at 2,000 mg/kg (sample 83365)
Purity: ~85% Proprietary C in [Formulation 1]; also contains ~6.7% [Chemical 1] and 5-10% "related compounds"
Vehicle: None
Observation period: 14 days
Method: Rats observed for clinical signs frequently on the first day and daily for 14 days. Animals dying prematurely were given a gross necropsy examination.
Results: Rats were fasted prior to dosing. Clinical signs included decreased activity, respiratory distress, lacrimation, oral discharge, soft stool, decreased feces, and perianal discharge. There were no specific signs of cholinesterase inhibition (myosis or fasciculations). After day 2, all low-dose survivors showed no clinical signs of toxicity. Necropsy findings included effects in the gastrointestinal system (stomach containing air and reddish-yellow material, small intestine containing mucoid material, injected blood vessels of stomach and small intestines), kidney (dark coloration and congestion), thymus (dark coloration and mottling), lungs (redness), lymph nodes (darkened), and liver (pale). Mortality, all within 48 hours of dosing, was 1/10 at the low dose and 8/10 at the high dose. Acute oral LD50 (not calculated) was between 2,000 and 5,000 mg/kg.
Comment: The doses used in this study were equivalent to limit doses under OPPT guidelines
Reference: Ref. 6

Additional information:

An acute oral toxicity study conducted by Ref. 21 that reported an LD50 of 160 mg/kg in Sprague-Dawley rats exposed to [Formulation 3] in 10% aqueous solution was not considered, since compositional data were not available. Analysis of a similar material ([Formulation 2]) indicated that the [Chemical 1] content was twice that of [Formulation 1], and also indicated the presence of 1.5-2% [Chemical 2], a neuroleptic agent that may have contributed to the higher relative toxicity compared to [Formulation 1] (Ref. 11).

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged adequate to meet the endpoint.

***Basis for Conclusion*:**

Despite not fully conforming to OPPTS or OECD guidelines, the available study on [Formulation 1] appears to be adequate since neither clinical signs nor mortality were observed at the limit dose of 2,000 mg/kg. A similar LD50 was reported for [Formulation 3].

Critical Study:

Type: Acute dermal toxicity
Species, strain, sex, number: Rabbit, New Zealand albino, 3/sex
Dose: 2,000 mg/kg
Purity: ~85% Proprietary C in [Formulation 1]
Vehicle: None
Exposure period: 24 hours
Method: Hair was clipped from entire trunk of each rabbit. Skin of 1 male and 2 females was left intact; skin of 2 males and 1 female was abraded. Test material applied under occlusive bandage. Animals examined for clinical signs "frequently" during first day and daily for 14 days. Test sites were washed with saline after 24 hours; irritation assessed at 26 hours, 72 hours, and 7 days. No gross necropsy was performed.
Results: No deaths occurred; therefore, the acute dermal LD50 exceeded 2,000 mg/kg in rabbits. There were no clinical signs of toxicity and no body weight effects.
Reference: Ref. 7

Additional information:

An acute dermal LD50 exceeding 5,010 mg/kg in rabbits was reported for [Formulation 3] (Ref. 21). No compositional information was available for this material, but analysis of [Formulation 2] indicated that the [Chemical 1] content was twice that of [Formulation 1], and also indicated the presence of 1.5-2% [Chemical 2], a neuroleptic agent (Ref. 11).

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300; OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No verifiable acute inhalation toxicity data were located, but an incomplete robust summary for a study apparently conducted under the guideline was available in an unevaluated IUCLID Dataset (Ref. 3).

According to a robust summary for a GLP-compliant study (Ref. 3), the acute (4-hour) inhalation LC50 for Proprietary C (as [Formulation 4] or [Formulation 5]) exceeded 1.65 mg/L.

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

An acute eye irritation study on [Formulation 1] was essentially consistent with OPPTS and OECD guidelines. The only effect was conjunctival irritation that was resolved by 24 hours.

Critical Study:

Type: Acute eye irritation
Species, strain, sex, number: Rabbit, New Zealand White, sex not reported, 6
Doses: 0.1 mL
Purity: ~85% Proprietary C in [Formulation 1]
Vehicle: None
Method: 0.1 mL of the neat test material was instilled into one eye and not washed. The eyes were scored for irritation at 1, 24, 48, and 72 hours.
Results: The average scores (maximal possible 110) were 5.0, 0, 0, and 0 at 1, 24, 48, and 72 hours, respectively, based on conjunctival effects. No irritation of the cornea or iris was observed.
Reference: Ref. 8

Additional information:

An acute eye irritation study on [Formulation 3] reported conjunctival effects persisting to 24 hours, but resolved by 42 hours (Ref. 21). Compositional information was not available for this material, but analysis of a related substance ([Formulation 2]) indicated that its greater irritation properties, relative to [Formulation 1], might be attributed to its greater acidity: titration with 1.6 mg KOH/g, compared to 0.1-1.0 mg KOH/g, respectively (Ref. 11).

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

An acute (24-hour) dermal irritation study for [Formulation 1] was consistent with OPPTS and OECD guidelines. The test material was characterized as non-irritating.

Critical Study:

Type: Acute (24-hour) dermal irritation
Species, strain, sex, number: Rabbit, New Zealand White, 3/sex
Doses: 0.5 mL to each test site (abraded, non-abraded) on each animal
Purity: ~85% Proprietary C in [Formulation 1]
Vehicle: None
Method: Hair was clipped from sides and backs of 6 rabbits; on one side, skin was abraded with point of 22 gauge needle. The test material was applied occluded; after 1 hour, Elizabethan collars were used to prevent disturbance of test sites. Sites were cleaned after 24 hours. Sites were examined for irritation at 26 hours and 72 hours after application.
Results: Males showed no signs of irritation (erythema or edema). No edema was observed in females. Barely perceptible irritation (erythema) was detected in 2/3 females at 26 hours (mean scores of 0.3 on intact and 0.2 on abraded skin), but in none at 72 hours; the primary irritation index was 0.1/8.0. The study authors characterized the material as a "non irritant" to skin following occlusive exposure for 24 hours.
Reference: Ref. 9

Additional information:

A 4-hour dermal irritation study in rabbits exposed to [Formulation 3] also reported erythema but no edema, with effects resolving by 48 hours (Ref. 21). No compositional information was available for this material, but analysis of [Formulation 1] indicated that the [Chemical 1] content was twice that of [Formulation 1] and its acidity was greater: titration with 1.6 mg KOH/g, compared to 0.1-1.0 mg KOH/g, respectively (Ref. 11).

Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)

Conclusion:

The available dermal sensitization data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available studies, both of which indicate no evidence of dermal sensitization, appear to have been consistent with OPPTS and OECD guidelines. Few details were available for the Buehler test on [Formulation 1] (~85% Proprietary C), but this method is one considered preferable under OPPTS guideline 870.2600. No sensitization was reported for [Formulation 2], although analyses suggest that it is less pure than [Formulation 1], having double the content of [Chemical 1] and slightly greater acidity than the latter, and containing 1.5-20% [Chemical 2] as a scorch inhibitor (Ref. 11).

Critical Studies:

Type: Dermal sensitization (Buehler) study
Species, strain, sex, number: Guinea pig, Hartley albino, 5/sex/group
Doses: Not reported, but probably 0.5 mL, since Buehler method is cited.
Purity: ~85% Proprietary C in [Formulation 1]
Vehicle: None
Method: Cited as Ritz and Buehler. The test material was applied dermally once per week for 3 weeks. Fourteen and 21 days after the third application, challenge and rechallenge doses were applied to treated animals and to a set of previously untreated controls (5/sex). Skin responses were evaluated at 24 and 48 hours after the initial challenge and rechallenge.
Result: No sensitization reactions were observed.
Reference: Ref. 19

Type: Dermal sensitization study
Species, strain, sex, number: Guinea pig, albino, 10 males/group
Doses: 0.05 mL of 10% or 25% (v/v)
Purity: Not reported; [Formulation 2]
Vehicle: 13% guinea pig fat dissolved in 50/50 acetone/dioxane (FAD)
Method: The test material was applied to shaved intact shoulder skin and gently rubbed in with a Teflon rod. Sensitization by 4 sacral intradermal injections of 0.1 mL of 1% solution in DMSO. Challenge after 2 weeks by 0.05 mL of 10 or 25% (v/v) in FAD applied to shaved intact shoulder skin. Groups of previously exposed animals (10/dose) were also given the challenge doses.
Result: Reactions after 1 day were negative for all groups. The authors conclude that the material is not a dermal sensitizer.
Reference: Ref. 4

Additional information:

One-inch squares of acetate fiber with 5.0% [Formulation 2] did not elicit skin reactions when applied for 6 days to the skin of 211 human subjects (Ref. 4). Two weeks later, no sensitization reactions were observed following a 48-hour challenge application.

SUBCHRONIC TOXICITY

Conclusion:

The available subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**
- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

Subchronic Dermal Toxicity (21/28-day or 90-day)

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90-day)

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

Although [Formulation 2] apparently has a similar if lower Proprietary C content compared to [Formulation 1] (~85% Proprietary C), it also contains 1.5-2.0% [Chemical 2] as an anti-scorching additive (Ref. 11). The presence of [Chemical 2], a neuroleptic, could confound the identification of the maternal NOAEL/LOAEL values. The small group size prevents the identification of fetal NOAEL/LOAEL values.

Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)

Type: Prenatal developmental toxicity
Species, strain, sex, number: Rat, CD, 5 pregnant females/group
Purity: Not reported; [Formulation 2]
Doses: 0 (distilled water at volume of high-dose), 100, 200, 400, 800, and 1,600 mg/kg/day
Vehicle: none
Exposure duration, frequency: gestational days (GD) 6-19
Method: Pregnant rats were treated once daily on GD 6-17 by oral gavage and were observed once daily on GD 6-20 for mortality and clinical signs. Maternal body weights were measured on GD 0, 6, 9, 12, 16, and 20. Dams dying prematurely were necropsied to determine cause of death. Examinations of thoracic and abdominal cavities for gross lesions, ovaries, and uterine contents were conducted on all surviving dams on GD 20. Endpoints included fetal viability, early and late resorptions, post- implantation loss, total implantations, and corpora lutea.
Results: Maternal mortality was observed in 5/5 at 1,600 mg/kg/day (GD 7 and 8) and 1/5 at 800 mg/kg/day (GD 9); causes of death were not determined. Treatment-related clinical signs were not observed at ≤200 mg/kg/day. Clinical signs included dry red matter around the nose and forepaws (in 1 rat at 400 mg/kg/day and 2 rats at 800 mg/kg/day), and staining of the anogenital area (in 4/5 rats at 800 mg/kg/day). Maternal body weight gain was reduced by 32% at 800 mg/kg/day (largely because of weight loss during GD6-9), but not affected at lower doses. A slight increase in mean postimplantation losses (1.0 per dam) at 800 mg/kg/day (compared to 0.6 per dam in concurrent controls) was similar to the mean historical control value of 0.9 per dam.

No other significant treatment-related effects were observed. The maternal NOAEL was 400 mg/kg/day and the LOAEL was 800 mg/kg/day for clinical signs (anogenital staining) and increased mortality (1/5). [Formulation 2] was not a specific developmental toxicant as the only effect in offspring (marginally increased postimplantation loss) occurred at a maternally toxic dose (800 mg/kg/day). The small group size (four surviving dams) does not permit accurate identification of fetal NOAEL/LOAEL values.
Reference: Ref. 5

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

No studies were located that followed or were similar to the two tests listed above.

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**

- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No neurotoxicity studies were available that followed guideline methods. However, inhibition of cholinesterase activity, an optional parameter for delayed neurotoxicity in hens under OPPTS Guideline 870.6100, was noted in rats orally exposed to [Formulation 1] (~85% Proprietary C) (Ref. 10, 14).

No studies were located that followed or were similar to the guidelines listed below.

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**
- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**
- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**
- **Additional neurotoxicity studies:**
    - Schedule-Controlled Operant Behavior (mouse or rat) (OPPTS Harmonized Guideline 870.6500)
    - Peripheral Nerve Function (rodent) (OPPTS Harmonized Guideline 870.6850)
    - Sensory Evoked Potentials (rat, pigmented strain preferred) (OPPTS Harmonized Guideline 870.6855)

These studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Additional Neurotoxicity Studies:

Cholineserase Inhibition

Depression of serum cholinesterase activity was observed in male and female Sprague-Dawley rats given 500 or 1,500 mg/kg [Formulation 1] (~85% Proprietary C) by gavage (Ref. 10); females were more sensitive than males. Suppression was by ~33% in males and ~78% in females after 1 hour and was maximal at 8 hours by ~62% in males and ~93% in females.

In a study comparing three different [Formulation 1] samples (from two different manufacturing protocols), female Sprague-Dawley rats (4/group) were treated with 0 or 250 mg/kg by oral gavage in 50% aqueous polyethylene glycol 200 (Ref. 14). Four hours later, serum cholinesterase activity was suppressed by 60-70% for [Sample 1] and [Sample 2] and by ~30% for [Sample 3].

Groups of four female Sprague-Dawley rats were administered [Formulation 1] at 0, 15, 50, 150, 500, or 1,500 mg/kg by oral gavage in 50% aqueous polyethylene glycol 200 (Ref. 12). After 4 hours, depression of serum cholinesterase activity was statistically significant and dose-related, compared to controls in groups treated at ≥50 mg/kg. In this study, brain cholinesterase levels were not significantly affected four hours after treatment at doses as high as 1,500 mg/kg.

Groups of three female New Zealand white rabbits were untreated (controls) or dermally administered 2,000 mg/kg [Formulation 1] (Ref. 13). Dermal treatment caused no significant suppression of cholinesterase activity measured in serum and whole blood at 7 or 24 hours or in brain at 24 hours.

IMMUNOTOXICITY

***Conclusion*:**

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the endpoints in the guidelines listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The only available data are negative results for the mutagenicity of [Formulation 1] (~85%Proprietary C) in mammalian cells *in vitro* assayed under methods equivalent to OPPTS and OECD guidelines. Similar assays on formulations with added propylene oxide also gave negative results. No testing for chromosomal aberrations has been performed on Proprietary C.

Gene Mutation in Vitro:

Conclusion:

The available *in vitro* gene mutation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Studies on the mutagenicity of [Formulation 1] (~85% Proprietary C) in cultured mouse lymphoma cells were conducted according to methods equivalent to OPPTS and OECD guidelines and yielded negative results. Negative results were also observed for [Formulation 1] with added propylene oxide.

- **Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)**

No verifiable studies were located for bacterial mutagenicity assays following or similar to the guideline listed above, but a robust summary for a GLP-compliant study was included in an unevaluated IUCLID Dataset (Ref. 3).

As described in an incomplete robust summary Ref. 2 conducted a mutagenicity (Ames) assay in *Salmonella typhimurium* strains TA98 and TA100 for Proprietary C (Formulation 4 or Formulation 5) (Ref. 3). Results were negative with or without metabolic activation at concentrations as high as 5 mg/plate. This study would not completely satisfy the guideline, since only two strains were tested.

- **In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)**

Critical Study:

Type: Mammalian Cell Gene Mutation Test: Forward Mutation
Species, strain: Mouse lymphoma L5178Y
Metabolic activation: Tested with and without Aroclor-1242-induced liver S9 from Sprague-Dawley rat
Concentrations: 0.01-0.8 µL/mL without S9 and 0.06-0.15 µL/mL with S9
Purity: ~85% Proprietary C as [Formulation 1]; also contains 6.7% [Chemical 1], and 5-10% related compounds
Method: Selection of forward mutation from $TK^{+/-}$ to $TK^{-/-}$ genotype. Activity compared to positive controls (ethylmethylsulfonate and dimethylbenzanthracene) and vehicle (DMSO).
Results: No increase in forward mutations was observed.
Reference: Ref. 15

Additional information:

Similar mouse lymphoma mutagenicity assays conducted on [Formulation 1] containing 0.05-0.25% [Chemical 3] also yielded negative results (Ref. 16, 17, 18).

No genotoxicity studies relevant to the below categories or to other types of genotoxic effects were located.

Gene Mutation in Vivo
Chromosomal Aberrations in Vitro
Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

A study exists of the acute toxicity to mysid shrimp of wastewater generated during the manufacture of the flame-retardant compound [Formulation 1] (Ref. 20). A handwritten correction on the title page of the study indicates that the wastewater samples were from the production of [Formulation 1], not [Formulation 4]. [Formulation 1] contains Proprietary C; however, the wastewater samples used in the study contained a mixture of compounds, none of which appeared to be Proprietary C.

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**

- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

<u>Acute and Subchronic Toxicity to Terrestrial Organisms</u>

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms data were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary C
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary D: Reactive brominated flame retardant

Draft Hazard Review

December 2004

Proprietary D: Reactive brominated flame retardant
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	*
Dermal	*
Inhalation	*
Eye irritation	*
Dermal irritation	*
Skin sensitization	
Subchronic Toxicity	
28-Day oral	
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✘
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	*
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	

Proprietary D: Reactive brominated flame retardant
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	*
Daphnia acute EC50	
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary D: Reactive brominated flame retardant
Synonyms
CAS
MF
MW
SMILES

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)

Conclusion:

The available acute oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

An acute oral study to determine the LD_{50} of Proprietary D was conducted on rats, but was available only as an incomplete robust summary.

As described in an incomplete robust summary, Sprague-Dawley rats (5/sex) were administered a single dose of 10,000 mg/kg of Proprietary D orally in corn oil, and observed for 4 hours and then daily for 14 days. No deaths occurred, and no gross lesions were seen at necropsy. Therefore, the LD50 was >10,000 mg/kg (Ref. 2).

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged inadequate to meet the endpoint.

***Basis for Conclusion*:**

An acute dermal study was conducted in rabbits, but was available only as an incomplete robust summary.

As described in an incomplete robust summary, New Zealand white rabbits (2/sex) were exposed to a single application of 20,000 mg/kg of Proprietary D applied dermally to intact and abraded

skin of the back and flank under an occlusive dressing for 24 hours. The dressings were then removed and the application sites were washed. There were no animal deaths. Therefore, the dermal LD50 was >20,000 mg/kg. Very slight to slight erythema, edema, and atonia were noted during the 14-day observation period (Ref. 2).

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300 (OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

An acute inhalation study in rats was available only as an incomplete robust summary.

As described in an incomplete robust summary, Charles River CD rats (5/sex) were exposed to 0.008 mg/L of Proprietary D as a saturated vapor for 1 hour. There were no animal deaths and no signs of toxicity during the exposure or the 14-day observation period, and no gross lesions were observed at necropsy. Thus, the LC50 was >0.008 mg/L (Ref. 5).

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available acute eye irritation data were judged inadequate to meet the endpoint.

Basis for Conclusion:
Two acute eye irritation studies in rabbits were available only as an incomplete data summaries in an HPV submission.

As described in the data summary, Proprietary D (dose not reported) was instilled into the right eye of 6 rabbits. Observations recorded at 1, 24, 48, and 72 hours after treatment reported no positive ocular scores, and found the test material was not irritating to the eyes. The study was conducted according to Good Laboratory Practices (Ref. 6).

An additional study described in the data summary, instilled 0.1 mL of Proprietary D in the right sacs of the right eyes of 6 New Zealand albino rabbits (3/sex). In the 72-hour observation period, redness and chemosis of the conjuctiva were reported. Discharge was also noted in 1 rabbit at 24 hours.

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available acute dermal irritation data were judged inadequate to meet the endpoint.

Basis for Conclusion:

An acute dermal irritation study in rabbits was available only as an incomplete data summary in an HPV submission.

As described in the data summary, a single application of 0.5 mL Proprietary D was made to the clipped backs of 6 New Zealand albino rabbits (3/sex) under a gauze patch and wrapped with an air-tight occlusive wrap (duration not reported). The skin of 3 rabbits was abraded. Observations recorded at 24, 48, and 72 hours after treatment reported no irritation on the intact skin, and erythema and edema on the abraded skin. The primary irritation index, according to the method of Draize, was 0.7, and the chemical was not considered to be a primary skin irritant (Ref. 3).

No pertinent acute toxicity studies were located that addressed the endpoint in the guideline listed below.

- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

SUBCHRONIC TOXICITY

Conclusion:

The available subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**
- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**,

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422), respectively**.

Subchronic Dermal Toxicity (21/28-day or 90-day).

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90 day)

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent neurotoxicity studies were located that addressed the endpoints in the guidelines listed below.

Delayed Neurotoxicity

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**
- Note this guideline is not relevant for Proprietary D, which is not an organophosphorus substance.

Neurotoxicity (Adult)

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity

- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies of immunotoxicity were located that addressed the endpoints in the guideline listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available gene mutation data were judged inadequate to meet the endpoint.

Basis for Conclusion:

Two *in vitro* gene mutation studies were conducted, but were only available as incomplete robust summaries. Studies of chromosomal aberrations were not available, however, and are needed for adequate characterization of the genotoxicity endpoint.

Gene Mutation *in vitro*: Bacterial Reverse Mutation Test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)

An *in vitro* gene mutation study reported negative results in *Salmonella typhimurium* bacteria (strains not specified) and in *Saccharomyces cerevisiae* (D4) at concentrations up to 1.0 µg/plate of Proprietary D, with and without metabolic activation (Ref. 3).

An additional *in vitro* gene mutation study, reported negative results in *Salmonella typhimurium* bacteria (TA 1535, TA 1537, TA 98, and TA 100) at concentrations up to 5,000 µg/plate (which was cytotoxic) of [Formulation 1] (a trade name for Proprietary D), with and without metabolic activation. Negative and positive controls were used (Ref. 4).

No genotoxicity studies relevant to the below categories or to other types of genotoxic effects were located.

Gene Mutation in Vivo
Chromosomal Aberrations in Vitro
Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

A data summary was located for a 96-hour acute toxicity study in bluegill sunfish (*Lepomis macrochirus*) exposed to Proprietary D (Ref. 1). Fish were exposed to aqueous dilutions of the test material at 0, 10, 18, 32, 56, and 100 mg/L. Acetone was used as a carrier solvent. The test waters were completely opaque at the two highest concentrations. The calculated 96-hour LC50 was 12 mg/L (95% CI: 1-18 mg/L). Study details were unavailable to conduct a thorough, independent review of the study. The concentrations in the test waters were not analytically verified; however, the opacity of the water at the two highest concentrations suggest that the test material was not well dissolved. The available data are not adequate to satisfy the acute toxicity endpoint for freshwater fish.

No pertinent acute toxicity studies with marine fish, aquatic invertebrates, or algae were located that followed or were similar to the guideline protocols listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that followed or were similar to the guideline protocols listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

<u>Acute and Subchronic Toxicity to Terrestrial Organisms</u>

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that followed or were similar to the guideline protocols listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary D: Reactive brominated flame retardant
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary E: Tetrabromophthalate diol diester

Draft Hazard Review

December 2004

Proprietary E: Tetrabromophthalate diol diester
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	
Dermal	
Inhalation	
Eye irritation	
Dermal irritation	
Skin sensitization	
Subchronic Toxicity	
28-Day oral	
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	

Proprietary E: Tetrabromophthalate diol diester
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	
Daphnia acute EC50	
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary E: Tetrabromophthalate diol diester
CAS
MF
MW
SMILES

Human Health Endpoints

ACUTE TOXICITY

Conclusion:

The available acute toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No acute toxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)**
- **Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)**
- **Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300 (OECD Guideline 403)**
- **Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)**
- **Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)**
- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

SUBCHRONIC TOXICITY

Conclusion:

The available subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**
- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**,
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422), respectively**.

Subchronic Dermal Toxicity (21/28-day or 90-day).

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90 day)

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No neurotoxicity studies were located that addressed the endpoints in the guidelines listed below.

Delayed Neurotoxicity
- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Neurotoxicity (Adult)
- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity
- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No immunotoxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No genotoxicity studies relevant to the below categories or to other types of genotoxic effects were located.

Gene Mutation in Vitro
Gene Mutation in Vivo
Chromosomal Aberrations in Vitro
Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary E: Tetrabromophthalate diol diester
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary F: Halogenated aryl ester

Draft Hazard Review

December 2004

Proprietary F: Halogenated aryl ester
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	✓
Dermal	
Inhalation	
Eye irritation	
Dermal irritation	
Skin sensitization	
Subchronic Toxicity	
28-Day oral	
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	

Proprietary F: Halogenated aryl ester
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	
Daphnia acute EC50	
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary F: Halogenated aryl ester
CAS
MF
MW
SMILES

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available acute oral lethality study was conducted according to EEC acute toxicity methods for fixed-dose studies. Methodological procedures appear consistent with OECD methods for acute oral toxicity testing (i.e., OECD Guideline 401). The study appears adequate.

Type: Acute oral LD50
Species, strain, sex, number: Rat, Sprague-Dawley, 5 males and 5 females
Dose: 2000 mg/kg
Purity: 99.7%
Vehicle: Not indicated
Observation period: 14 days post dosing
Method: Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B.1 bis. Acute toxicity (oral), fixed-dose method.
Results: No deaths; therefore, LD50 >2000 mg/kg. Piloerection and hunched posture in 10/10 rats; recovery by post-exposure day 4.
Reference: Ref. 1

- **Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)**
- **Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300 (OECD Guideline 403)**
- **Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)**

- **Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)**
- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

No studies that followed these or similar guideline protocols were located.

SUBCHRONIC TOXICITY

Conclusion:

The available subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)
- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**
- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**,
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422), respectively**.

Subchronic Dermal Toxicity (21/28-day or 90-day).
- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90 day)
- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No neurotoxicity studies were located that addressed the endpoints in the guidelines listed below.

Delayed Neurotoxicity
- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Neurotoxicity (Adult)
- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity
- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No immunotoxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No genotoxicity studies relevant to the below categories or to other types of genotoxic effects were located.

Gene Mutation in Vitro
Gene Mutation in Vivo
Chromosomal Aberrations in Vitro
Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary F: Halogenated aryl ester
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability:

Conclusion: The flammability (as the flash point) has been adequately characterized.

Basis for Conclusion: The key study was performed according to EEC Methods, Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part A, Method A9, flash point.

Flash Point: 215°C (Ref. 2)

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary G: Triaryl phosphate, isopropylated

Draft Hazard Review

December 2004

Proprietary G: Triaryl phosphate, isopropylated
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	*
Dermal	*
Inhalation	
Eye irritation	*
Dermal irritation	*
Skin sensitization	
Subchronic Toxicity	
28-Day oral	*
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✓
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	*
Gene mutation in vivo	*
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	*
DNA damage and repair	*
Other	*

Proprietary G: Triaryl phosphate, isopropylated
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	*
Daphnia acute EC50	*
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary G: Triaryl phosphate, isopropylated
Synonym:
CAS
MF
MW
SMILES

Many of the available health effects studies were conducted with commercial mixtures that commonly contained triphenyl phosphate as well as Proprietary G. The available information regarding the composition of these mixtures is presented below, but the composition of the actual samples tested in the health effects studies usually was not reported.

[Formulation 1] is reported to contain 60-100% Proprietary G and 15-40% triphenyl phosphate (Ref. 24) and [Formulation 2] is reported to contain 60-100% Proprietary G and 4-7% triphenyl phosphate (Ref. 25).

Major Components of [Formulation 3] and [Formulation 4] as reported in Ref. 34		
Component	**[Formulation 3]**	**[Formulation 4]**
Total Proprietary G	**49**	**61**
[Chemical 1]	8	11
[Chemical 2]	6	7
[Chemical 3]	2	5
[Chemical 4]	21	27
[Chemical 5]	12	11
Triphenyl Phosphate	33	18

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)

Conclusion:

The available acute oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for limit tests on undefined flame retardants for which compositional information was not provided. The authors of the studies referred to them as "non-definitive", possibly because of the small group sizes (which, however, are consistent with current guidelines); in other respects the studies follow current guidelines.

Additional Studies and Information:

No deaths were observed in Sprague-Dawley rats (3/sex) given [Formulation 1] (mixture of Proprietary G and triphenyl phosphate) as a single oral dose of 5,000 mg/kg (Ref. 13). Clinical signs, which included tremors (0/3 males, 1/3 females), oral discharge, ataxia (0/3 males, 1/3 females), decreased locomotion (1/3 males, 1/3 females), chromorhinorrhea, chromodacryorrhea, and abdominogenital staining, subsided by day 11. No effects on body weight gain and no gross internal lesions were observed.

A parallel acute oral study on Sprague-Dawley rats (3/sex) given [Formulation 2] at a dose of 5,000 mg/kg, reported clinical signs (abdominogenital staining and chromorhinorrhea) on the first 2 days post dosing, but no mortality, body weight gain effects, or gross internal lesions were reported (Ref. 17).

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged inadequate to meet the endpoint.

***Basis for Conclusion*:**

The available data are for limit tests on undefined flame retardants for which compositional information was not provided. The authors of the studies referred to them as "non-definitive", possibly because of the small group sizes (which, however, are consistent with current guidelines); in other respects, the studies follow current guidelines.

Additional Studies and Information:

No deaths were observed among Sprague-Dawley rats (3/sex) that were dermally exposed to [Formulation 1] (mixture of Proprietary G and triphenyl phosphate) at a dose of 2,000 mg/kg for 24 hours under an occlusive covering (Ref. 14). There were no effects on body weight gain, no signs of irritation on the test site, and no gross internal lesions observed.

In a parallel study in Sprague-Dawley rats (3/sex) dermally treated with 2,000 mg/kg

[Formulation 2], all but one female gained weight, but there were no deaths, signs of irritation, or gross internal lesions (Ref, 18).

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300; OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies were located that followed or were similar to the guideline. A non-guideline study evaluated neurotoxicity of combustion products of an Proprietary G/triphenyl phosphate mixture in the presence of cyclic phosphonate compounds.

Additional Studies and Information:

Preliminary results of a study were reported (Ref. 38) investigating whether toxic compounds were formed when cyclic phosphonate compounds were thermally decomposed in the presence of other phosphate compounds in trimethylol polyol-based urethane foam. When rats were exposed (head only) for 20 minutes to smoke and decomposition gases from foam containing equal proportions of the cyclic phosphonate compounds and a mixture of Proprietary G and triphenyl phosphate, no convulsive seizures, characteristic of exposure to toxic bicyclic phosphites or phosphates, were observed.

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for undefined flame retardants for which compositional information was not provided. The authors of the studies referred to them as “non-definitive”, although they were consistent with current guidelines.

Additional Studies and Information:

Slight conjunctival erythema was observed in the eyes of 1/1 male and 1/2 female New Zealand White rabbits 24 hours after instillation with 0.01 mL of [Formulation 1] (mixture of Proprietary G and triphenyl phosphate) but was resolved by 48 hours (Ref. 15). No conjunctival discharge

or effects on the cornea or iris were observed. The material was tentatively characterized as "practically non-irritating", based on a maximum irritation score of 1.3/110 at 24 hours.

In a parallel study in New Zealand White rabbits (1 male and 2 females) instilled with 0.01 mL [Formulation 2], there were no signs of eye irritation observed at 1, 24, 48, or 72 hours (Ref. 19). The material was tentatively characterized as non-irritating to the eyes based on a primary irritation index of 0/110 at all timepoints.

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available data are for undefined flame retardants for which compositional information was not provided. The authors of the studies on the Durad materials referred to them as "non-definitive", although they were consistent with current guidelines.

Additional Studies:

No dermal irritation (erythema or edema) was observed in one male and two female New Zealand White rabbits that were dermally exposed for 4 hours to [Formulation 1] (mixture of Proprietary G and triphenyl phosphate) on two occluded test sites (0.5 mL per site) and examined at 4.5, 24, 48, or 72 hours (Ref. 16). The material was tentatively rated as non-irritating to intact rabbit skin, based on scores of 0/8.0 at all timepoints.

In a parallel dermal irritation study in one male and two female New Zealand White rabbits exposed for 4 hours to [Formulation 2] on two occluded test sites (0.5 mL per site), no irritation was observed at times between 4.5 and 72 hours (Ref. 20). The material was tentatively rated as non-irritating to intact rabbit skin, based on scores of 0/8.0 at all timepoints.

In skin irritation assays in male New Zealand White rabbits (6/group), 24-hour topical administration (0.5 mL/site) of [Formulation 4] or [Formulation 10] did not elicit erythema or edema to intact or abraded skin (examined at 24 and 72 hours) (Ref. 6). The mean primary dermal irritation indices were 0/2.0 for both materials, which were characterized as non-irritating to skin.

- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

No studies of this type were located.

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

Conclusion:

The available subchronic oral toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No verifiable data were available for defined substances tested under guideline methods. A study on undefined [Formulation 4] appeared to follow the guideline for a 28-day oral study, but was only available as an incomplete robust summary. The unexplained mortality in this study indicates that it may not be an adequate study.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

As described in an incomplete robust summary (results were not presented quantitatively) for an HPV submission, Sprague-Dawley rats (10/sex) received [Formulation 4] in the diet at concentrations of 0, 0.1, 0.5, or 1.0% for 28 days (Ref. 5). Treatment had no effect on survival (but 12 rats died: 1 control, 4 low-dose, 4 mid-dose, and 3 high-dose rats). Treatment also had no effect on urinalysis results, incidence of gross lesions at necropsy, or histology of the liver and kidney (histology examined only in high dose animals and controls). It was not specified whether animals that died during the study were necropsied or examined histologically. Reduced feed consumption was observed in the mid-dose group in both sexes and reduced body weight gain was noted in high-dose females. Abnormalities (not specified) were observed in clinical chemistry measurements in mid- and high-dose groups and in hematology parameters at the high dose. Relative liver weights were elevated in all treated groups. The unexplained mortality during this short term study raises concern for study adequacy.

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

Subchronic Dermal Toxicity (21/28-day or 90-day)

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**

- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90-day)

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

Additional information

As described in an unvalidated robust summary, 3 days of exposure to [Formulation 7], tested without metabolic activation at concentrations between 0.04 and 5.0 µg/mL, did not induce cell transformation in cultured Balb/c-3T3 cells (Ref. 36).

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

Available acute and 28-day studies indicate that there is a risk of delayed neurotoxicity from exposure to Proprietary G. Most studies either were conducted on undefined substances or were not described in sufficient detail. A summary of a study on purified components of [Formulated] flame retardants suggests that [Chemical 4] or [Chemical 2] are the neurotoxic components of these mixtures; however, details of the *in vivo* study in hens were not located. The neurotoxicity of Proprietary G preparations would be dependent on the relative content of [Formulation 11] isomers. No data are available for the full battery of tests for functional neurotoxicity or for developmental neurotoxicity.

Delayed Neurotoxicity

Conclusion:

The available delayed neurotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The acute study (experiment A) on a defined Proprietary G mixture departed from guideline in that enzyme inhibition was assayed 24 hours after dosing rather than 48 hours, but reported significant suppression of both brain neurotoxic esterase and plasma cholinesterase levels. The longer study did not conduct a complete battery of neurobehavioral tests as stipulated under the guideline, but reported adverse effects on motor coordination at all doses on the day of treatment. The highest dose (11,700 mg/kg) exceeded that recommended under the guideline, but that deviation does not affect the conclusion of the study. Studies on purified components of [Formulated] flame retardants identified the neurotoxic components, but were not adequately described. The majority of studies suggest that delayed neurotoxicity may result from exposure to oral doses in excess of 1,000 mg//kg.

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Critical Studies

Type: Acute oral delayed neurotoxicity
Species, strain, sex, number: Hen, 12-14 months old, White Leghorn, 4/dose for experiment A; 10-12/dose for experiment B.
Purity: Proprietary G with the composition as in the following table.

Composition of Proprietary G assayed by Ref. 37	
Component	**Percent**
Total Proprietary G	**<75**
[Chemical 4]	24
[Chemical 6]	18
[Chemical 2]	10
[Chemical 7]	10
[Chemical 5]	6
[Chemical 8]	7
[Chemical 9]	<1
Triphenyl Phosphate	24

Doses: Experiment A. Six doses between 12 and 11,700 mg/kg;
Experiment B. 0, 12, or 370 mg/kg in corn oil or 11,700 mg/kg undiluted
Vehicle: Corn oil
Positive control: Tri-*ortho*-cresyl phosphate (TOCP**)**
Route: Oral (not specified)
Exposure duration, frequency: Experiment A, single treatment followed 24 hours later by biochemical assay; Experiment B, 6 weeks, single treatments 3 weeks apart; study terminated 3 weeks after second dose.
Method: Experiment A. Brain neurotoxic esterase (NTE) and plasma cholinesterase (PChE) measurements recorded 24 hours after single treatment with Proprietary G, corn oil or TOCP.
Experiment B. Doses were chosen based on results of experiment A to represent minimal, 50%, and maximal inhibition of brain NTE. Body weight and food consumption measured every 3-4 days, walking behavior evaluated weekly. Neurohistopathology evaluated at termination.
Results: Experiment A. The NOAELs for inhibition of NTE or PChE were 12 and 180 mg/kg, respectively. Doses about 1,000 mg/kg and higher caused ~70% inhibition of NTE and ~80% inhibition of PChE. The positive control (500 mg/kg of TOCP) inhibited brain NTE by 85.2% and PChE by 70%.
Experiment B. Proprietary G had no effect on mortality. Few adverse signs visible at or below 370 mg/kg. All treated at 11,700 mg/kg showed motor incoordination beginning day 1, with feather loss 7-11 days later. Body weights not affected at lowest dose. Body weight effects at mid- and high-dose are uncertain because text and graph do not match; one dose caused transient weight loss on days 22-38 and the other persistent weight loss from day 22 to the end of the study. TOCP caused persistent weight loss beginning day 5. Food consumption was transiently reduced in all groups (including positive and negative controls) on day 2 and 23, also on day 18 for TOCP. Significant transient, dose-dependent impairment of gait was observed on day 1 and 22 for hens treated with Proprietary G at all doses. Hens treated with TOCP showed significant

impairment on day 1 and 15, with gradual worsening to the end of the study. Neurohistopathological examinations revealed no significant difference between Proprietary G treatment and corn oil controls, whereas TOCP caused a significant increase in axonal degeneration in brain, spinal cord (cervical, thoracic and sacro-lumbar), and bilateral degeneration of the sciatic nerve.
Reference: Ref. 37

Additional Studies:

As described in Ref. 44, a series of acute delayed neurotoxicity assays were conducted on [Formulated] flame retardants. No ataxia was observed in groups of 4 hens treated with [Formulation 5] at doses of 2,000, 4,000, or 8,000 mg/kg; 3/30 hens treated with 16,000 mg/kg showed ataxia (Ref. 7). Only 1/10 hens treated with [Formulation 6] at 20,000 mg/kg exhibited ataxia (Ref. 8). In one study on [Formulation 4], no ataxia was observed at doses of 500, 1,000, or 2,000 mg/kg, whereas 2/10 treated at 4,000 mg/kg showed ataxia (Ref. 9); inhibition of brain NTE was 79.5% at the highest dose. In a second study on [Formulation 4], incidences of ataxia (0/10, 3/10, 1/10 and 1/10) and neurohistopathological lesions (1/10, 0/10, 1/10, and 2/10) were not precisely related to the respective doses of 3,000, 5,000, 7,000, and 9,000 mg/kg (Ref. 10). For [Formulation 3], incidences of ataxia (1/9, 4/10, 6/10 and 3/10) and neurohistopathology (0/10, 4/10, 7/10 and 1/10) were observed in the 2,000, 4,000, 6,000, and 8,000 mg/kg groups, respectively (Ref. 11).

A subchronic (91-day) oral neurotoxicity assay is summarized briefly in a TSCA 8e submission (Ref. 12), and in more detail by Ref. 44 and in a robust summary in an HPV submission (Ref. 23; U.S. EPA comments not available). In this study, hens (20/group) were administered [Formulation 3] (mixture of Proprietary G and triphenyl phosphate) daily at doses of 0, 10, 20, 90, and 270 mg/kg/day. Deaths occurred in all dose groups as follows: 2/20 vehicle controls, 4/20 positive controls, 3/20 at 10 mg/kg/day, 5/20 at 90 mg/kg/day, and 6/20 at 270 mg/kg/day. Ataxia was observed in 4/20 at 90 mg/kg/day and 9/20 at 270 mg/kg/day. Histopathological examination of nervous tissue of 10 hens/group revealed the following: significant degeneration at 3 levels of the spinal cord in 3 vehicle controls, significant degeneration of the spinal cord in TOCP hens, degeneration of the spinal cord and peripheral nerves in hens of the 90 and 270 mg/kg/day groups, with a dose-response relationship for severity and incidence (further details not reported). No ataxia or brain histopathology was observed at 10 or 20 mg/kg/day.

[Formulation 4] and [Formulation 6] were given in two 2,000 mg/kg doses 21 days apart to hens (4/group) (Ref. 22). Neither compound caused body weight effects, clinical signs of neurotoxicity or an increase in gross internal lesions at necropsy (21 days after the second dose). There was no evidence of neurohistopathology in hens treated with [Formulation 4], but one out of four hens treated with [Formulation 6] had unilateral brain lesions at two histological levels.

Proprietary G at tested positive for neurotoxicity in hens treated at three 21-day intervals with 10,000 mg/kg (Ref. 33). Effects included gross paralysis with demyelination confirmed histopathologically.

Several components of the [Formulated] series of flame retardants were isolated to >99% purity and tested at doses as high as 1,000 mg/kg in hens for neurotoxicity and suppression of neurotoxic esterase (Ref. 29). Details of these studies were not located. Three isomers of [Chemical 1] and [Chemical 5] elicited no signs of neurotoxicity and no suppression of NTE levels. [Chemical 5] was also judged to be non-neurotoxic, eliciting no ataxia or other signs of neurotoxicity and insignificant suppression of NTE (-4% or -15%) in two tests. Both [Chemical 2] and [Chemical 4] were positive, eliciting ataxia and neurotoxicity at 1,000 mg/kg, but not at lower doses; [Chemical 2] suppressed NTE by 85% and [Chemical 4] suppressed NTE by 79 and 90% in two assays. The author suggested that neurotoxicity was associated with triaryl phosphates containing a 2-alkyl substituent with an oxidizable alpha-hydrogen.

In a two-hen screening test, a single 1,000 mg/kg dose of [Formulation 3] administered in gelatin capsules to two hens resulted in a 53.1% inhibition of neurotoxic esterase activity in the brain (Ref. 42). The report was not clear as to the day on which the hens were sacrificed.

No neurotoxicity studies were located that followed or were similar to the guidelines listed below.

Neurotoxicity (Adult)

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity

- **Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat) OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent) OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred) OPPTS Harmonized Guideline 870.6855

These studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Other Neurotoxicity Data

Cholinesterase inhibition

[Formulation 3] at doses of 15, 20, or 25 mL/kg did not inhibit blood cholinesterase activity, but neither species of animal (3/group) nor the specific biological material assayed were reported (Ref. 4).

IMMUNOTOXICITY

***Conclusion*:**

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No immunotoxicity study was located that followed or was similar to the guideline listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No verifiable genotoxicity data were located. The available studies were only accessible as robust summaries in a IUCLID Dataset that had not undergone review by the European Commission (Ref. 3). Furthermore, the data were unpublished industry-sponsored studies on commercial products for which no contemporaneous component analyses were provided. Current compositional information taken from MSDS documents are presented in the following table. The results of these studies are summarized below despite their uncertain validity. In general, not enough details were provided to ascertain whether protocols met the standards of OPPT or OECD guidelines.

Percentage of Proprietary G and triphenyl phosphate in Currently Available Commercial Products			
Product	**Proprietary G (%)**	**triphenyl phosphate (%)**	**Reference**
[Formulation 7]	60-100	15-40	Ref. 26
[Formulation 8]	60-100	10-30	Ref. 27
[Formulation 9]	60-100	7-13	Ref. 28
[Formulation 2]	60-100	4-7	Ref. 25

Gene Mutation in Vitro:

- **Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)**

As described in unvalidated robust summaries, negative results were reported for mutagenicity assays in *Salmonella typhimurium* with or without metabolic activation. [Formulation 7] and [Formulation 9] were tested in strains TA98, TA100, and TA1537 at concentrations as high as 1.62 mg/mL (Ref. 1, 2). [Formulation 9] and [Formulation 2] were tested in strains TA98, TA100, TA1535, TA1537, and TA1538 at concentrations as high as 0.1 mL per plate (Ref. 31, 32).

- **In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)**

As described in an unvalidated robust summary, [Formulation 7] at concentrations of 0.0013-0.1 µL/mL was not mutagenic to cultured mouse lymphoma L5178Y $TK^{+/-}$ cells without metabolic activation (Ref. 30). Results in the presence of metabolic activation were equivocal in that a dose-response was observed, but none of the cultures exhibiting >10% total growth had mutant frequencies 2-fold greater than background.

Gene Mutation in Vivo

- **Sex-linked Recessive Lethal test in *Drosophila melanogaster* (OPPTS Harmonized Guideline 870.5275**)

As described in an unvalidated robust summary, [Formulation 7] (32.5, 75, or 150 mg/mL) fed to adult male fruit flies for 3 days did not induce heritable mutations (Ref. 43).

Chromosomal Aberration in Vitro

No pertinent studies were located.

Chromosomal Aberration in Vivo

- **Mammalian Bone Marrow Chromosomal Aberration Test (OPPTS Harmonized Guideline 870.5385)**

As described in an unvalidated robust summary no increase in chromosomal aberrations was observed in the bone marrow of Chinese hamsters (8/sex/group), 16, 24, or 48 hours after receiving a single oral dose of 5,000 mg/kg [Formulation 7] by gavage (Ref. 41). The summary indicated that the study was conducted under OECD Guideline 475 and GLP. Another unvalidated robust summary reported that a significant increase (compared to controls) in the incidence of bone marrow cells with chromosomal anomalies was observed in Chinese hamsters (6/sex/group) 24 hours after receiving the second of two consecutive daily doses of 2,500 or 5,000 mg/kg/day [Formulation 7] by oral gavage (Ref. 40); no increase was observed in animals receiving 1,250 mg/kg/day.

DNA Damage and Repair

- **Unscheduled DNA synthesis in mammalian cells in culture (OPPTS Harmonized Guideline 870.5550)**

As described in an unvalidated robust summary, [Formulation 7] tested without metabolic activation at concentrations between 0.6 and 75 nL/mL did not cause unscheduled DNA synthesis in cultured rat hepatocytes (Ref. 35).

Other

- **In vivo Sister Chromatid Exchange Assay (OPPTS Harmonized Guideline 870.5915)**

As described in an unvalidated robust summary, there was no increase in the frequency of sister chromatid exchanges in bone marrow cells of Chinese hamsters (4/sex/group) 24 hours after receiving a single oral dose of 1250, 2,500, or 5,000 mg/kg [Formulation 7] by gavage in carboxymethylcellulose (Ref. 39).

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

Summaries were located for several acute toxicity studies of Proprietary G in an HPV test plan submission and accompanying robust summaries (Ref. 23); however, EPA comments on this submission were not available. The summaries included two 96-hour studies in fathead minnows (*Pimephales promelas*), three 96-hour studies in rainbow trout (*Oncorhynchus mykiss*), and three 48-hour studies in *Daphnia magna*. According to Ref. 21, all of the studies were conducted with 100% Proprietary G; however, other reports have identified the tested material in some of these studies as [Formulation 1] (Ref. 24) or [Formulation 4] (Ref. 21). [Formulation 1] is a mixture containing 60-100% Proprietary G and 15-40% triphenyl phosphate (Ref. 24). [Formulation 4] has been reported to contain 61% Proprietary G and 18% triphenyl phosphate (Ref. 34; see table at beginning of Human Health Effects for details). The available study summaries and Material Safety Data Sheets are insufficient to precisely establish the composition of the materials tested in the acute toxicity studies. Without precise knowledge of the composition of the tested materials, it is not possible to use these studies to make a definitive statement regarding the acute toxicity of Proprietary G. The available information regarding the acute toxicity of Proprietary G to freshwater fish or aquatic invertebrates is insufficient to satisfy the endpoints in the guideline protocols listed below.

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary G: Triaryl phosphate, isopropylated
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary H: Halogenated aryl ester

Draft Hazard Review

December 2004

Proprietary H: Halogenated aryl ester
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	✓
Dermal	
Inhalation	
Eye irritation	
Dermal irritation	
Skin sensitization	
Subchronic Toxicity	
28-Day oral	
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	

Proprietary H: Halogenated aryl ester
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	
Daphnia acute EC50	
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary H: Halogenated aryl ester
CAS
MF
MW
SMILES

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available acute oral lethality study was conducted according to EEC acute toxicity methods for fixed-dose studies. Methodological procedures appear consistent with OECD methods for acute oral toxicity testing (i.e., OECD Guideline 401). The study appears adequate.

Type: Acute oral LD50
Species, strain, sex, number: Rat, Sprague-Dawley, 5 males and 5 females
Dose: 2000 mg/kg
Purity: 99.7%
Vehicle: Not indicated
Observation period: 14 days post dosing
Method: Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part B, Method B.1 bis. Acute toxicity (oral), fixed-dose method.
Results: No deaths; therefore, LD50 >2000 mg/kg. Piloerection and hunched posture in 10/10 rats; recovery by post-exposure day 4.
Reference: Ref. 1

- **Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)**
- **Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300 (OECD Guideline 403)**
- **Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)**

- **Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)**
- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

No studies that followed these or similar guideline protocols were located.

SUBCHRONIC TOXICITY

Conclusion:

The available subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)
- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**
- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**,
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422), respectively**.

Subchronic Dermal Toxicity (21/28-day or 90-day).
- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90 day)
- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No neurotoxicity studies were located that addressed the endpoints in the guidelines listed below.

Delayed Neurotoxicity
- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Neurotoxicity (Adult)
- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity
- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No immunotoxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No genotoxicity studies relevant to the below categories or to other types of genotoxic effects were located.

Gene Mutation in Vitro
Gene Mutation in Vivo
Chromosomal Aberrations in Vitro
Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary H: Halogenated aryl ester
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability:

Conclusion: The flammability (as the flash point) has been adequately characterized.

Basis for Conclusion: The key study was performed according to EEC Methods, Directive 92/69/EEC (OJ No. L383A, 29.12.92), Part A, Method A9, flash point.

Flash Point: 215°C (Ref. 2)

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary I: Organic phosphate ester

Draft Hazard Review

December 2004

Proprietary I: Organic phosphate ester
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	
Dermal	
Inhalation	
Eye irritation	
Dermal irritation	
Skin sensitization	
Subchronic Toxicity	
28-Day oral	
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	

Proprietary I: Organic phosphate ester
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	✘
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	✘
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	
Daphnia acute EC50	
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary I: Organic phosphate ester
CAS
MF
MW
SMILES

Human Health Endpoints

ACUTE TOXICITY

Conclusion:

The available acute toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No acute toxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)**
- **Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)**
- **Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300 (OECD Guideline 403)**
- **Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)**
- **Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)**
- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

SUBCHRONIC TOXICITY

Conclusion:

The available subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**
- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**,
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422), respectively**.

Subchronic Dermal Toxicity (21/28-day or 90-day).

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90 day)

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No neurotoxicity studies were located that addressed the endpoints in the guidelines listed below.

Delayed Neurotoxicity
- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Neurotoxicity (Adult)
- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity
- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No immunotoxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No genotoxicity studies relevant to the below categories or to other types of genotoxic effects were located.

Gene Mutation in Vitro
Gene Mutation in Vivo
Chromosomal Aberrations in Vitro
Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary I: Organic phosphate ester
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: It is anticipated that the pH for this compound will be not applicable because the functional groups present are not expected to affect the pH of an aqueous solution.

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: It is anticipated that the dissociation constant for this compound will be not applicable because the functional groups present are not expected to dissociate.

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary J: Aryl phosphate

Draft Hazard Review

December 2004

Proprietary J: Aryl phosphate
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	✓
Dermal	✓
Inhalation	*
Eye irritation	✓
Dermal irritation	✓
Skin sensitization	
Subchronic Toxicity	
28-Day oral	*
90-Day oral	✓
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	*
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	*
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	✓
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	*
Gene mutation in vivo	
Chromosomal aberrations in vitro	*
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	*

Proprietary J: Aryl phosphate
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	✓
Octanol/water partition coefficient	✓
Oxidation/reduction	
Melting point	✓
Boiling point	✓
Vapor pressure	✓
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	✓
Density/relative density/bulk density	✓
Dissociation constant in water	
Henry's Law constant	✓

Environmental Fate	
Bioconcentration	
Fish	*
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	✓
Photolysis in soil	
Aerobic biodegradation	*
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	✓
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	*

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	*
Daphnia acute EC50	*
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary J: Aryl phosphate
Synonyms
CAS
MF
MW
SMILES

Omitted from this report are a number of studies conducted on [Formulation 2] (~43% Proprietary J). The omitted studies included 21-day dermal toxicity, 90-day aerosol inhalation toxicity, and 90-day oral (feeding) toxicity in rats and neurotoxicity studies in hens. Replacement studies subsequently commissioned by the contracting company are reviewed here.

Many health effects studies have been conducted on commercial products that are mixtures of Proprietary J and closely related compounds: [Chemical 1], [Chemical 2], and [Chemical 3]. Typical composition data for these products are given in Table 1 below.

Table 17-1. Composition data (%) for selected t-butylated aryl phosphate products

Component	[Formulation 1][a]	[Formulation 2][b]	[Formulation 3][c]	[Formulation 4][d]	[Formulation 5][e]
Proprietary J	43	43	>99	30-35	73
[Chemical Class 1]	23				
[Chemical 1]		14		30-35	
[Chemical 2]		2		10-15	
[Chemical 3]	34	40		15-25	27
stabilizers			<1		

[a]Ref. 15
[b]Ref. 42
[c]Ref. 7
[d]Ref. 22
[e]Ref. 63. Ref. 58 reported that [Formulation 5] was [Chemical Class 1], but did not report the precise concentration of Proprietary J. After saponification, the isomer distribution of the [Chemical Class 2] portion was 39.2% [Chemical 4] and [Chemical 5] and 59.7% [Chemical 6].

Human Health Endpoints

ACUTE TOXICITY

Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401).

Conclusion:

The available acute oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

Despite reporting deficiencies in some studies (lack of precise information on substance purity, group size), the available data indicate acute oral LD50 values exceeding 5,000 mg/kg for [Chemical Class 1] tested by methods equivalent to guidelines.

Critical Studies:

Type: Acute oral toxicity
Species, strain, sex, number: Rat, CD Sprague-Dawley, 5/sex
Doses: 5,000 mg/kg
Purity: isomeric mixture of [Chemical Class 1] as [Formulation 7] (Ref. 7)
Vehicle: None
Method: Based on OECD Guideline 401. Rats examined for mortality and clinical signs frequently on day 1, twice daily thereafter to day 14. Body weights recorded on days 1, 8, and 15. Gross necropsy on all rats.
Results: No deaths. Clinical signs in all rats after dosing included pilo-erection, hunched posture, and abnormal gait (waddling). Half of the animals had diarrhea. Clinical signs resolved by day 8. There were no effects on body weight gain or terminal necropsy findings. Acute oral LD50 was greater than 5,000 mg/kg in rats.
Reference: Ref. 25

Type: Acute oral toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 3/sex
Dose: 5,000 mg/kg
Purity: Not reported; isomeric mixture of Proprietary J as [Formulation 10]. Ref. 20 reports composition of 60-100% [Chemical Class 1] and 7-13% [Chemical 3].
Vehicle: None
Observation period: 14 days
Method: Rats observed 14 days after single dose, gross necropsy on all rats. Body weights recorded days 0, 7, and 14.

Results: No deaths. Clinical signs included abdominogenital staining, chromorhinorrhea, and decreased locomotion, all subsiding by day 10. All rats gained weight. No gross lesions. The LD50 exceeded 5,000 mg/kg.
Comment: This study was equivalent to a limit test under OPPTS 870.1100 except that the group size was 3/sex rather than 5/sex.
Reference: Ref. 16

Type: Acute oral toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, males and females, numbers not reported
Dose: 15,800 mg/kg
Purity: Near pure Proprietary J
Vehicle: None
Observation period: 14 days
Method: Rats observed 14 days after single dose.
Results: The LD50 exceeded 15,800 mg/kg in rats (specific mortality results were not reported).
Reference: Ref. 34

Additional Studies and Information:

Ref. 10 evaluated the oral toxicity of [Chemical Class 1] administered to rabbits by oral gavage in 8% gum acacia; rabbits were observed "several days" for clinical signs of toxicity. There were no effects in single rabbits receiving 1,000 or 3,000 mg/kg of Proprietary J or [Chemical 1], or 1,000 mg/kg of [Chemical 2].

In another study, male rabbits were administered [Chemical Class 1] by oral gavage in 5% gum acacia and observed for varying amounts of time (Ref. 11). One rabbit received 2,000 mg/kg of Proprietary J and was observed for 5 days and two rabbits received 5,000 mg/kg and were observed for 4 or 16 days. All showed hepatic degeneration and two had kidney effects (tubular degeneration and congestion or swelling); necrosis of the stomach (high dose) and moderate lung congestion (low dose) were seen in single animals. A parallel experiment with rabbits treated with [Chemical 1] had similar results: liver effects in 1/1 at 2,000 mg/kg (killed day 5) and 2/2 at 5,000 mg/kg (killed day 4 or 17), and lung congestion and cloudy swelling of the kidneys in one high- and one low-dose animal. No deaths and no overt clinical signs were seen in rabbits treated with either compound.

A related compound, [Chemical 2] (containing 1-2% [Chemical 5]), was administered at doses of 3,000 or 10,000 mg/kg by oral gavage in olive oil to rats (Ref. 12). Mortality was 1/5 at the low dose and 1/3 at the high dose, but the length of the observation period was not reported.

As described in a robust summary, there were no deaths and no gross lesions in Sprague-Dawley rats (5/sex) orally exposed to 5,000 mg/kg [Formulation 5] (see Note e in Table 1) and observed for 14 days (Ref. 53 cited in Ref. 1). Clinical signs (depression, diarrhea, and stains on fur and

around the nose) resolved by day 6. A letter from Ref. 52 to EPA suggests that this study was conducted under the 1978 EPA proposed test guidelines.

Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)

Conclusion:

The available acute dermal toxicity data were judged adequate to meet the endpoint.

***Basis for Conclusion*:**

Despite reporting deficiencies in some studies (lack of precise information on substance purity, group size), the available data indicate acute dermal LD50 values exceeding 2,000 mg/kg for Proprietary J tested by methods equivalent to guidelines.

Critical Studies

Type: Acute (24-hour) dermal toxicity
Species, strain, sex, number: Rat, Sprague-Dawley, 3/sex
Dose: 2,000 mg/kg
Purity: Not reported; isomeric mixture of Proprietary J as [Formulation 10]
Vehicle: None
Exposure period: 24 hours
Method: Undiluted test material applied to intact clipped dorsal skin. Treated areas occluded, washed after 24 hours with methanol and then water. Animals observed for 3 hours after dosing and daily thereafter for 14 days. Body weights recorded on days 0, 7, and 14. All subjected to gross necropsy.
Results: No deaths, clinical signs, local irritation of the application site, or gross necropsy lesions. All rats gained weight. The acute dermal LD50 exceeded 2,000 mg/kg in rats.
Comment: This study was equivalent to a limit test under OPPTS 870.1200 except that the group size was 3/sex rather than 5/sex.
Reference: Ref. 17

Type: Acute (24-hour) dermal toxicity
Species, strain, sex, number: Rabbit, New Zealand albino, male and female, numbers not reported
Dose: 7,900 mg/kg
Purity: near pure Proprietary J
Vehicle: None
Exposure period: 24 hours
Method: Undiluted test material applied to intact clipped dorsal skin. Treated areas occluded, washed (liquid unspecified) after 24 hours. Animals held for 14 days after which all subjected to gross necropsy.

Results: The acute dermal LD50 exceeded 7,900 mg/kg. The study did not report necropsy findings or specific mortality results.
Reference: Ref. 34

As described in a robust summary, mortality was 1/10 among New Zealand White rabbits (5/sex) that received a dose of 2,000 mg/kg [Formulation 5] (see Note e in Table 1) on intact and abraded skin and were observed for 14 days (Ref. 54 cited in Ref. 1). Clinical signs included depression and mild diarrhea. No gross lesions were observed at necropsy. A letter from Ref. 52 to EPA suggests that this study was conducted under 1978 EPA proposed test guidelines.

Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300; OECD Guideline 403)

Conclusion:

The available acute inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The only relevant data were for a study available only as a robust summary and for which the Proprietary J content was uncertain.

As described in a robust summary, no mortality and no body weight effects were observed among Sprague-Dawley rats (5/sex) that were exposed for 4 hours to an aerosol of [Formulation 5] (see Note e in Table 1) at the highest attainable concentration, 3.1 mg/L (Ref. 54 cited in Ref. 1); the particle size distribution of 2.5-2.8 µm suggests that the particles were respirable. Ruffled fur was the only clinical sign observed over a period of 14 days. The only gross lesions observed were lung effects (reddened or whitish coloration) in two females.

Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)

Conclusion:

The available eye irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Despite some uncertainty as to the purity of test substances, the available studies used methods equivalent to the guidelines and agreed that Proprietary J was not an eye irritant.

Type: Acute eye irritation
Species, strain, sex, number: Rabbit, New Zealand White, 3 (sex not reported)
Doses: 0.1 mL
Purity: Not reported; isomeric mixture of Proprietary J as [Formulation 7]

Vehicle: None
Method: Cites OECD Guideline 405. Eyes examined after 1 hour, then 1, 2, 3, 4, and 7 days.
Results: No positive responses; no damage to cornea or iris. Mild conjunctival inflammation was observed in 3/3 animals 1 hour after instillation only. All normal by 24 hours.
Reference: Ref. 27

Type: Acute (4-hour) eye irritation
Species, strain, sex, number: Rabbit, New Zealand White, 3 females
Doses: 0.1 mL
Purity: Not reported; isomeric mixture of Proprietary J as [Formulation 10]. Ref. 20 reports composition of 60-100% [Chemical Class 1] and 7-13% [Chemical 3].
Vehicle: None
Method: Instilled into eye. Eyes assessed via Draize method at 1, 24, 48, and 72 hours.
Results: No eye irritation was observed at any timepoint.
Comment: Although the study was designated "non-definitive", it was consistent with the OPPTS guideline.
Reference: Ref. 18

Additional information

As described in a robust summary, 0.1 mL [Formulation 5] (see Note e in Table 1) was a mild ocular irritant to rabbits (Ref. 56 cited in Ref. 1). Mild redness of the conjunctiva persisted to 24 hours in 2/9 and to 48 hours in 1/9, but was resolved by 72 hours. The eye irritation observed in this study may reflect compositional differences between [Formulation 5] and the other Proprietary J materials tested.

Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)

Conclusion:

The available dermal irritation data were judged adequate to meet the endpoint.

Basis for Conclusion:

Despite some uncertainty as to the purity of test substances, the available studies used methods equivalent to the guidelines. Results indicated no or mild dermal irritation.

Critical Studies:

Type: Acute (4-hour) dermal irritation
Species, strain, sex, number: Rabbit, New Zealand White, 3
Doses: 0.5 mL

Purity: Not reported; isomeric mixture of Proprietary J as [Formulation 7] (relationship to the composition of [Formulation 3] reported in Table 1 is not known)
Vehicle: None
Method: Followed OECD Guideline 404. Hair clipped. Material applied for 4 hours to approximately 10-cm square area on back, semi-occlusive dressing. Site rinsed with water, examined after 30 minutes and days 2, 3, and 4; additional observations on days 5 through 11.
Results: Very slight or well-defined erythema with or without very slight edema was seen in two animals immediately, persisting though day 8 and day 10. Very slight erythema without edema in third animal on days 2 and 3 only. A 4-hour exposure to the test material elicited mild reversible irritation.
Reference: Ref. 26

Type: Acute (4-hour) dermal irritation
Species, strain, sex, number: Rabbit, New Zealand White, 2 males and 1 female
Doses: 0.5 mL
Purity: Not reported; isomeric mixture of Proprietary J as [Formulation 10]. Ref. 20 reports composition of 60-100% [Chemical Class 1] and 7-13% [Chemical 3].
Vehicle: None
Method: Test material applied to clipped, intact skin and occluded. After 4 hours, sites were wiped clean with methanol and rinsed with tap water. Scoring for irritation was done 30 minutes after wiping and then daily for 3 days. Clinical signs were observed.
Results: No signs of irritation (erythema or edema) were noted at any timepoint. The primary irritation index was 0/8.0; the material was non-irritating to intact rabbit skin
Reference: Ref. 19

As described in a robust summary, [Formulation 5] (see Note e in Table 1) was a mild dermal irritant to rabbits, yielding a primary irritation score of 0.50 (Ref. 57 cited in Ref. 1).

Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)

Conclusion:

The available skin sensitization data were judged inadequate to meet the endpoint.

Basis for Conclusions:

No pertinent studies were located that followed or were similar to the guideline listed above, or were otherwise relevant to skin sensitization.

SUBCHRONIC TOXICITY

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

Conclusion:

The available subchronic oral toxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

A 90-day oral toxicity assay on 73% [Formulation 11] was similar to guidelines except for the lack of testing for ophthalmological effects and neurological function. The Proprietary J content of tested materials was less than 50% in a 1-month assay.

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**

Ref. 42 exposed groups of Sprague-Dawley rats (10/sex/group) to diets providing [Formulation 2] (43% Proprietary J, see Table 1) at target doses of 0, 250, 500, 750, 1,000, or 2,000 mg/kg/day (nominal doses of 213, 442, 660, 898, and 1,710 for males and 234, 454, 690, 898, and 1,867 for females) for 1 month. Reduced food consumption was observed in males at 2,000 mg/kg/day; reduced body weight gain in males at ≥750 mg/kg/day and females at 2,000 mg/kg/day. There were no deaths, but hepatic enlargement was noted in all groups in a dose-related fashion; discoloration of kidneys was observed in male rats at ≥500 mg/kg/day. The lowest dose was a LOAEL; methodological limitations of the study include the lack of examinations for histopathology, hematology, or clinical chemistry.

- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**

Type: 90-day oral (diet) toxicity in rodents
Species, strain, sex, number: Rat, Sprague-Dawley (20/sex/group)
Doses: 0, 100, 400, or 1,600 ppm [Formulation 5]; average intakes of 0, 6.6, 26.7 or 107.5 mg/kg/day in males and 0, 7.7, 30.0 or 124.8 mg/kg/day in females.
Purity: About 73% isomeric mixture of [Formulation 11] and 27% triphenyl phosphate as [Formulation 5].
Vehicle: Feed
Method: Rats were examined twice daily for clinical signs and mortality, weekly physical examinations (with palpation) and measurements of body weights and food consumption. Hematology, clinical chemistry and urinalyses were performed prior to testing, at mid-test and just prior to termination. At termination, all animals were subjected to gross necropsy; organ weights of adrenal, brain, heart, liver, kidney and gonads were recorded. More than 30 organs/tissues were examined for histopathology in all groups. Brain cholinesterase was measured at termination in all groups.
Results: Treatment had no significant effect on survival, food consumption, body weight gain, hematology or clinical chemistry parameters, cholinesterase values, or the incidence of gross or microscopic lesions (including reproductive organs, brain and spinal cord). At the highest dose,

there were significant increases in absolute and relative liver weights in males, relative liver weights in females, relative kidney weights in males, and absolute and relative adrenal weights in females; relative liver weights were also slightly elevated in mid-dose males. In this study, 20 mg/kg/day was a NOAEL and 80 mg/kg/day was a LOAEL for increased liver weights in males and adrenal weights in females.
Reference: (Ref. 59, 60, 63)

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**

No relevant studies were located that followed or were similar to the guideline listed above.

Subchronic Dermal Toxicity (21/28-day or 90-day)

***Conclusion*:**

The available subchronic dermal toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available study was conducted on a substance with a Proprietary J content of less than 50%.

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**

[Formulation 2] (43% Proprietary J; see Table 1) was applied to intact and abraded skin of New Zealand White rabbits (10/sex/group) at doses levels of 10, 100, or 1,000 mg/kg/day, 5 days/week for 3 weeks (Ref. 6); controls were treated with distilled water. Treatment-related effects included skin changes at the application site (edema at 1,000 mg/kg/day in males and ≥10 mg/kg/day in females; atonia at ≥100 mg/kg/day in both sexes; desquamation at ≥10 mg/kg/day in both sexes; and fissuring at 1,000 mg/kg/day in both sexes), higher blood urea nitrogen values at 1,000 mg/kg/day in both sexes, and dose-related depression of plasma cholinesterase at ≥100 mg/kg/day, and of erythrocyte and brain cholinesterase at ≥10 mg/kg/day in both sexes. Changes in other parameters (mortality, clinical signs, body weight, hematology, clinical chemistry, organ weights, gross or microscopic lesions) were not related to treatment.

- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

No relevant studies were located that followed or were similar to the guideline listed above.

Subchronic Inhalation Toxicity (90-day)

Conclusion:

The available subchronic inhalation toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that followed or were similar to the guideline listed below, or were otherwise relevant to subchronic inhalation toxicity.

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies were located that followed or were similar to the three guidelines listed below. No histopathology of the male (testes, epididymides, prostate) or female (ovary, uterus, cervix, vagina) reproductive organs was observed in rats fed diets containing up to 1600 ppm [Formulation 5] (73% [Formulation 11]; see Note e to Table 1) for 3 months (Ref. 59, 60, 63).

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The only available developmental toxicity data are for formulations containing only about 43% Proprietary J.

Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)

Ref. 32, 33 evaluated the developmental toxicity of [Formulation 2] (43% Proprietary J, see Table 1) in rats. In a pilot study (Ref. 32), pregnant CD rats (5/group) received undiluted [Formulation 2] at doses of 250, 500, 1,000, 2,500, or 5,000 mg/kg/day by oral gavage on gestational days (GD) 6-19; controls received 4.2 mL of water per day. Treatment had no effect on survival, behavior, or maternal necropsy findings. Anogenital staining was observed in all test groups (incidences of 1/5, 2/5, 2/5, 5/5, and 4/5 in the lowest-to-highest dose groups, respectively) and red and/or brown matter around the nose, mouth, and forelimbs in all receiving 5,000 mg/kg/day. Dose-related reductions in body weight gain for GD 0-20 were observed at ≥1,000 mg/kg/day, but were only biologically significant at the highest dose (-33% compared to control). At the highest dose, decreases in viable fetuses and increases in mean postimplantation losses compared to historical controls were observed at 5,000 mg/kg/day (values for concurrent controls were higher than historical control value).

In the main study (Ref. 33), groups of 25 pregnant CD rats received 2.542 mL of water or undiluted [Formulation 2] at doses of 300, 100, or 3,000 mg/kg/day by oral gavage on GD 6-19. Treatment had no significant effect on maternal survival, behavior, body weight gain, the incidence of gross necropsy findings, or most reproductive/developmental parameters (mean number of viable fetuses, postimplantation loss, early or late resorptions, total implantations, corpora lutea, fetal sex distribution, mean fetal body weight, and incidences of external malformations and visceral variations). High-dose dams had a higher incidence of clinical signs (all with yellow staining of anogenital area and half with dried red matter on nose and forepaws) compared to other groups. At 3,000 mg/kg/day, there was a slight increase compared to controls in the percentage of litters with skeletal malformations (3/24 or12% vs 1/20 or 5%); the percentage in historical controls was 6.23%

No relevant studies were located that followed or were similar to the two tests listed below.

- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies following or similar to the guidelines listed below or otherwise relevant to chronic toxicity were located.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies following or similar to the guidelines listed below or otherwise relevant to carcinogenicity were located.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No studies examined developmental neurotoxicity or neurological function. Acceptable negative are available for delayed neurotoxicity in adults. In the 90-day oral toxicity assay by (Ref. 59, 60, 63) described above, rats exposed to [Formulation 5] (73% Formulation 11]; see Note e to Table 1) in the diet at concentrations up to 1600 ppm exhibited no neurohistopathology and no inhibition of brain cholinesterase activity.

Delayed Neurotoxicity

Conclusion:

The available delayed neurotoxicity data were judged adequate to meet the endpoint.

Basis for Conclusion:

The available studies were consistent with guidelines and overall suggest that exposure to large doses of Proprietary J does not evoke delayed neurotoxicity in hens

- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Critical Studies

Type: Acute oral delayed neurotoxicity
Species, strain, sex, number: Hen, "hybrid", females, older than 14 months, 4 water controls and 8 treated with Proprietary J
Purity: Not reported; >99% Proprietary J as [Formulation 3] (see Table 1)
Doses: The plan was 1,000 mg/kg, 5 times daily for 5 consecutive days (total 25,000 mg/kg); because of shortage of material, only 3 doses were given on day 4, so 7 doses were given on day 5 to make up the difference.
Vehicle: None
Positive control: None
Route: Oral gavage
Exposure duration, frequency: 5 days, 5 times daily
Method: Observations for up to 32 days. Birds examined daily for signs of neurotoxicity; body weights, food consumption, egg numbers, and egg weights recorded twice weekly.
Results: There were no signs of ataxia. Mortality rates, body weight gain, and feed consumption did not differ between test and control groups; egg production in test group was about 50% of controls although egg weights were slightly higher in test animals.
Reference: Ref. 28

Type: Acute oral delayed neurotoxicity
Species, strain, sex, number: Chicken, White Leghorn, females, 9/group
Purity: near pure Proprietary J
Doses: 10,000 mg/kg, twice daily (20 mg/kg/day)
Vehicle: None
Positive control: Corn oil
Route: Oral gavage
Exposure duration, frequency: Twice daily for three consecutive days; dosing regimen repeated 21 days later.

Method: Daily observations for mortality and neurotoxicity for up to 42 days. Body weights recorded at 0, 21, and 42 days. At gross necropsy, brain, spinal cord, and sciatic nerve were examined for histopathology. The neurotoxicity study was preceded by an acute oral toxicity assay in hens given 10,000 mg/kg.
Results: There were no signs of ataxia or neurohistopathological lesions in 9 hens treated with Proprietary J at cumulative doses of 120,000 mg/kg. Other [Chemical Class 3] chemicals tested at the same time were neurotoxic. The positive control, tri-*ortho*-cresyl phosphate (TOCP), caused neurotoxicity in 4/4 hens treated with 300 mg/kg/day for 5 days (cumulative dose of 1,500 mg/kg). The acute oral LD50 in hens exceeded 10,000 mg/kg (no mortality data reported).
Reference: Ref. 34

Type: Acute oral delayed neurotoxicity
Species, strain, sex, number: Hen, female, older than 14 months, 4 control and 8 test birds
Purity: Not reported; [Formulation 3] is >99% Proprietary J and <1% stabilizers (Ref. 7)
Doses: 1,000 mg/kg five times daily for five consecutive days (= 25,000 mg/kg total)
Vehicle: None
Positive control: None
Negative control: Water
Route: Oral gavage
Exposure duration, frequency: five days, five times daily
Method: Observations for up to 32 days. Birds examined daily for signs of neurotoxicity; body weights, food consumption, egg numbers, and egg weights recorded twice weekly.
Results: No ataxia observed; no treatment-related effects on mortality or body weight gain. Mean daily food consumption in test animals was about 15% lower than in controls, largely because intake was reduced by 47% during days 0-4. In test group, egg production was about 70% of controls and egg weights about 11% lower than in controls.
Reference: Ref. 30

Additional Studies:

Several components of the [Formulation 6] series of flame retardants were isolated to >99% purity and tested at doses as high as 1,000 mg/kg in mature hens for neurotoxicity and suppression of neurotoxic esterase (Ref. 24). Details of these studies were not located. [Chemical 2], [Chemical 1], and Proprietary J elicited no signs of neurotoxicity and no suppression of NTE levels. [Chemical 7] was also judged to be non-neurotoxic, eliciting no ataxia or other signs of neurotoxicity and insignificant suppression of NTE (-4% or -15%) in two tests. However, [Chemical 8] was neurotoxic, eliciting ataxia and neurotoxicity, as well as suppression of NTE levels (by -71% and -57 to -62% in two tests) at 1 mL/kg. The author suggested that neurotoxicity was associated with [Chemical Class 1] with an oxidizable alpha-hydrogen.

Hens given [Formulation 4] (100% [Chemical Class 1]; 30-35% Proprietary J, see Table 1) at a dose of 5,000 mg/kg/day on five consecutive days by oral gavage lost weight and developed

paralysis (4/4) and 3/4 died before the end of the test (Ref. 14). The study authors suggested that residual [Chemical Class 4] chemicals may have been responsible for the observed neurotoxicity.

Hens treated with 2,000 mg/kg of [Formulation 10] did not elicit clinical signs of neurotoxicity, lesions of the nervous system, or depression in NTE, whereas hens treated with TOCP at 500 mg/kg showed all of these effects (Ref. 35 abstract as described in Ref. 61).

There was no effect on survival or walking behavior among a group of 15 hens (12-14 months old) given oral doses of 11, 679 mg/kg [Formulation 5] (see Note e in Table 1) on days 1 and 21 under EPA proposed guidelines (Ref. 58). All showed slight motor incoordination on day 1; body weights were reduced on day 38, but terminal weights were as in corn oil controls. Neurohistopathology and feed consumption were equivalent to corn oil controls. Hens treated with TOCP had increased mortality, progressive leg weakness, persistently reduced feed intake and body weight loss, and significant axonal degeneration.

No neurotoxicity studies were located that were relevant to the categories listed below.

Neurotoxicity (Adult)

- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity

- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

Additional neurotoxicity studies:

- Schedule-Controlled Operant Behavior (mouse or rat); OPPTS Harmonized Guideline 870.6500
- Peripheral Nerve Function (rodent); OPPTS Harmonized Guideline 870.6850
- Sensory Evoked Potentials (rat, pigmented strain preferred); OPPTS Harmonized Guideline 870.6855

These additional neurotoxicity studies may be indicated, for example, to follow up neurotoxic signs seen in other studies, or because of structural similarity of the substance to neurotoxicants that affect these endpoints. These studies may be combined with other toxicity studies.

Other Neurotoxicity Data

Cholinesterase inhibition

In five hens that received 25,000 mg/kg of [Formulation 7] in divided doses (8, 8, and 9 g/kg at 4-hour intervals) by oral gavage, plasma cholinesterase (pChE) levels 30-60 minutes later were about 60-70% of pre-dose levels (Ref. 29); 9 days later, pChE levels had risen to 83.1% of the pre-dose level. One bird that showed clinical signs (quiet with subdued behavior) after dosing did not show appreciable recovery of pChE on day 9. The authors concluded that because of the

very high dose administered, the test material was not a significant inhibitor of plasma cholinesterase.

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that followed or were similar to the guideline listed below, or were otherwise relevant to immunotoxicity.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

The available studies followed methods equivalent to guidelines, but tested materials for which the Proprietary J content was low (less than 50%) or uncertain; the latter studies were only available as robust summaries. None of the studies indicate the Proprietary J-containing mixtures are mutagenic in bacteria or mammalian cells.

Gene Mutation in Vitro:

- **Bacterial Reverse Mutation test (OPPTS Harmonized Guideline 870.5100; OECD Guideline 471)**

[Formulation 1] (typical analysis 43% Proprietary J; see Table 1) was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 with or without metabolic activation (Ref. 15).

[Formulation 2] (typical analysis 43.2% Proprietary J, see Table 1) at concentrations between 0.01 and 10 µL/plate produced negative results in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 and *Saccharomyces cerevesiae* D4 with or without metabolic activation (Ref. 36).

As described in a robust summary, [Formulation 5] (see Note e in Table 1) at concentrations between 0.005 and 10 µg/plate produced negative results in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 with or without metabolic activation (Ref. 38); cytotoxicity was observed at 0.1 µg/plate and higher.

- **In vitro Mammalian Cell Gene Mutation Test (OPPTS Harmonized Guideline 870.5300; OECD Guideline 476)**

[Formulation 2] (typically 43% Proprietary J, see Table 1) at concentrations between 0.011 and 0.1 µL/mL (0.2 µL/mL was cytotoxic) did not induce forward mutations in cultured mouse lymphoma L5178Y/TK$^{+/-}$ cells with or without metabolic activation (Ref. 37).

As described in a robust summary, [Formulation 5] (see Note e in Table 1) at concentrations between 0.975 and 125 nL/mL (≥15.6 nL/mL was cytotoxic) did not induce forward mutations in cultured mouse lymphoma L5178Y/TK$^{+/-}$ cells with or without metabolic activation (Ref. 39).

Chromosomal Aberration in Vitro

- **In Vitro Mammalian Chromosome Aberration Test (OPPTS Harmonized Guideline 870.5375)**

As described in a robust summary, [Formulation 5] (see Note e in Table 1) at concentrations between 0.625 and 20 nL/mL (≥2.5 nL/mL was cytotoxic) did not increase the frequency of chromosomal aberrations in cultured mouse lymphoma L5178Y/TK$^{+/-}$ cells with or without metabolic activation (Ref. 40).

No studies were located that were relevant to the categories listed below.

Gene Mutation in Vivo
Chromosomal Aberration in Vivo
DNA Damage and Repair

Other

- **In vitro Sister Chromatid Exchange Assay (OPPTS Harmonized Guideline 870.5900)**

As described in a robust summary, [Formulation 5] (see Note e in Table 1) at concentrations between 0.625 and 20 nL/mL (≥2.5 nL/mL was cytotoxic) did not increase the frequency of sister chromatid exchanges in cultured mouse lymphoma L5178Y/TK$^{+/-}$ cells with or without metabolic activation (Ref. 40).

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

Summary data were located for a screening-level assessment of the acute toxicity of Proprietary J to rainbow trout and bluegill (Ref. 31). Proprietary J was dissolved in acetone and added to water. Fish were exposed to aqueous solutions of 0.1, 1.0, 10.0, or 100 mg Proprietary J/L for 96 hours. The estimated 96-hour LC_{50} values for rainbow trout and bluegill were 1.1 and 1.0 mg/L, respectively. The two highest test concentrations exceeded the reported water solubility of Proprietary J (Ref. 49). The summary did not provide sufficient information regarding study conditions, including test substance purity, to allow for an independent evaluation of the studies.

Summary data were located for studies of the toxicity of Proprietary J to *Daphnia magna* and the midge *Chironomus tentans* (Ref. 62). The reported 48-hour LC_{50} values for *D. magna* and *C. tentans* were 0.30 and 0.15 mg/L, respectively. Study details, including test substance purity, were not presented in the summary, so the results could not be independently evaluated.

Summaries were located for studies of the acute toxicity of the commercial aryl phosphate ester mixtures [Formulation 8], [Formulation 9], and [Formulation 2] to fish, aquatic invertebrates, and algae (revised HPV Robust Summaries submitted by Ref. 2, as part of the HPV Challenge Program). Although some of the tested products may have contained Proprietary J, their actual composition was not presented in the study summaries. Without precise knowledge of the composition of the tested materials, it is not possible to use these studies to make a definitive statement regarding the toxicity of Proprietary J. [Formulation 2] has been reported (by a different chemical company) to contain <50% Proprietary J (Table 1).

Studies of the acute toxicity of [Formulation 8] to rainbow trout, bluegill, fathead minnow, channel catfish (Ref. 8), *D. magna*, the midge *C. plumosus*, the amphipod *Gammarus pseudolimnaeus*, and algae (Ref. 50) were located. [Formulation 8] contains 15-20% [Chemical 3] and unspecified amounts of at least five other compounds (Ref. 8). Chemical analysis of the aqueous test solutions in a chronic toxicity study (discussed below) (Ref. 8) suggested that the concentration of Proprietary J in the test waters may have been 40% or less of nominal concentrations of [Formulation 8]. Given that the organisms in these tests were exposed to a mixture of compounds, which was predominantly not Proprietary J, it is concluded that it is not possible to use these studies to make a definitive statement regarding the toxicity of Proprietary J.

No additional, pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

Studies of the chronic toxicity of the commercial phosphate ester compound [Formulation 8] to fathead minnow (Ref. 8), *Daphnia magna*, the midge *Chironomus plumosus*, and the amphipod *Gammarus pseudolimnaeus* (Ref. 50) were located. Formulation 8] contains 15-20% [Chemical 3] (Ref. 8). Measured concentrations of Proprietary J in the test waters were 25% to 40% of nominal concentrations of [Formulation 8] (Ref. 8). Thus, the organisms in these tests were exposed to aqueous solutions that contained a mixture of compounds that were predominantly not Proprietary J. Therefore, it is concluded that it is not possible to use these studies to make a definitive statement regarding the toxicity of Proprietary J.

No additional, pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary J: Aryl phosphate
CAS
MF
MW
SMILES

Water Solubility (mg/L):
Conclusion: The available water solubility data are adequate.
Basis for Conclusion: Ref. 49 gives a measured value for the water solubility of Proprietary J.

Solubility (mg/L)	References
3.20	Ref. 49, 51

Log K_{ow}:
Conclusion: The data for this endpoint are adequate.
Basis of Conclusion: The Log K_{ow} values of 5.12 are identical as found in two sources Ref. 49 and Ref. 3). Ref. 4 estimates the Log K_{ow} value based on HPLC that are in reasonable agreement with the key study indicated above. Ref. 45, however, gives a Log K_{ow} value of 13.2, which is much higher than that found in the other sources and this value does not appear reasonable for compounds of this class.

Log K_{ow}	Reference
5.12	Ref. 3, 49, 51
3.23 4.76 6.44	Ref. 4 (estimated from reverse phase HPLC data by Ref. 48)
13.2	Ref. 45
13.3	Ref. 13

Oxidation/Reduction: No data

Melting Point:
Conclusion: The data are adequate for this endpoint.
Basis for Conclusion: A value of -20 ˚C is given for the melting point of Proprietary J. Another study provides a pour point for Proprietary J that is in reasonable agreement with the melting point value.

Melting Point (˚C)	Reference
-20	Ref. 13
-21 (pour point)	Ref. 45

Boiling Point:
Conclusion: The available boiling point data are adequate to characterize this endpoint.
Basis for Conclusion: Two sources contained measured boiling point information. A third source required calculating the boiling point from the Clausius-Clapeyron equation using data measured by Ref. 9. The boiling points given here (including the calculated boiling point) are within a reasonable range of each other.

BP (˚C/torr)	References
261/6	Ref. 49, 51
425/760 dec. 405	Ref. 9 (extrapolated according to the Clausius-Clapeyron Equation using experimentally-derived parameters: Log P(torr) = -A/T + C, where T is in Kelvin, A= 4444, C=9.24) The decomposition temperature was reported in this same paper.
420/760	Ref. 4 (estimated using Meissner's method)
155/2	Ref. 13

Vapor Pressure (torr):
Conclusion: The majority of available vapor pressure data give an adequate endpoint.
Basis for Conclusion: Two sources contained measured vapor pressure data. These two values were in agreement with each other. The third source required calculating the boiling point from the Clausius-Clapeyron equation using data measured by Ref. 9. The calculated value was in reasonable agreement with the measured values.

VP (torr/˚C)	Reference
1.40×10^{-6}/25	Ref. 51; Ref. 4 (measured)
4.6×10^{-7}	Ref. 4 (estimated from b.p. using Method 2 in Ref. 21)
2.16×10^{-6}/25	Ref. 9 (extrapolated according to the Clausius-Clapeyron Equation using experimentally-derived parameters Log P(torr) = -A/T + C, where T is in Kelvin, A= 4444, C=9.24)
1.35/200	Ref. 45
10.2/250	Ref. 13

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion characteristics: No data

pH: No data

UV/VIS absorption: No data

Viscosity:
Conclusion: The viscosity of this compound has been adequately characterized.
Basis for Conclusion: A single study on the viscosity of Proprietary J was located and appears reasonable given the other physical/chemical properties available for this compound.

Viscosity at 25 ˚C	Reference
58	Ref. 13

Density/Relative Density/Bulk Density:
Conclusion: The density of this compound has been adequately characterized.
Basis for Conclusion: A single study on the density of Proprietary J was located and appears reasonable given the other physical/chemical properties available for this compound.

Density	Reference
1.175-1.185	Ref. 13

Dissociation Constant in Water: No data

Henry's Law Constant:
Conclusion: The data are adequate to characterize the Henry's Law constant.
Basis for Conclusion: The key study provides an estimated Henry's Law constant based on measured vapor pressure and water solubility data and is taken from Ref. 45. This is a reasonable method for estimating a Henry's Law constant. The other studies identified provide estimates although they are based on estimated vapor pressures and not experimental values and are not sufficiently reliable to categorize this end point.

Henry's Law Constant	Reference
8.48×10^{-7} atm-m^3/mole	Ref. 45, 51
7.2×10^{-8} atm-m^3/mole	Ref. 4 (calculated from vapor pressure of 4.6×10^{-7} mm Hg and water solubility 3.2)
2.2×10^{-7} atm-m^3/mole	Ref. 4 (calculated from vapor pressure of 1.4×10^{-6} mm Hg and water solubility 3.2)
2.15×10^{-5} atm-m^3/mole	Ref. 46

Environmental Fate

Bioconcentration

Fish:
Conclusion: The bioconcentration of Proprietary J has not been adequately characterized.
Basis for Conclusion: Studies conducted by Ref. 44 give three different methods for determining the BCF value for both rainbow trout and fathead minnows. The first two methods used were Biofac and initial rate. Biofac is a computer program that requires constant water concentration for its calculations. The "initial rate" method assumes that the rate of uptake of Proprietary J from water is much greater than the rate of clearance during the initial exposure period. The static test method yields equilibrium BCFs if the fish exposure continues until a maximum concentration is observed. The maximum concentration was not reached in rainbow trout, so the BCFs may be underestimated. Although the maximum concentrations appeared to have been reached in fathead minnows, further studies conducted by Ref. 46 show the BCF value for fathead minnows measured using the static test method may be very different to those measured previously (Ref. 44) using this same method. Given that none of these tests were conducted according to EPA or OECD guidelines, and that the results vary widely, this endpoint is not adequately characterized by the available experimental data.

Reference	Species	BCF	Key Design Parameters				Comments
			Exp. type	Range (ppb)	Study length	T (˚C)	
Ref. 44	Rainbow trout	1096	Static	1.8-55	1-24 hours	10	The calculation of BCF from this method comes from the following equation: k_1=[CFish(max)k_2]/[A exp(-Btmax)] and is based on the total ^{14}C.
Ref. 44	Rainbow trout	1335	Biofac	1.8-55	1-24 hours	10	k_1 and k_2 values were estimated by use of this nonlinear regression program. In these calculations, the initial exposure concentration (0 hr) was used.
Ref. 44	Rainbow trout	2298	Initial rate	1.8-55	1-24 hours	10	The calculation of BCF from this method comes from the following equation: k_1=(ΔCFish/Δt)Cw

Reference	Species	BCF	Key Design Parameters				Comments
			Exp. type	Range (ppb)	Study length	T (˚C)	
Ref. 44	Fathead minnow	498	Biofac	0.8-36.5	1-24 hours	10	k_1 and k_2 values were estimated by use of this nonlinear regression program. In these calculations, the initial exposure concentration (0 hours) was used.
Ref. 44	Fathead minnow	785	Static	0.8-36.5	1-24 hours	10	The calculation of BCF from this method comes from the following equation: k_1=[CFish(max)k_2]/[A exp(-Btmax)]
Ref. 44	Fathead minnow	3316	Initial rate	0.8-36.5	1-24 hours	10	The calculation of BCF from this method comes from the following equation: k_1=(ΔCFish/Δt)Cw
Ref. 45	Rainbow trout	1096	Static	5-50	24 hours		Ref. 45 takes this value from Ref. 44.
Ref. 45	Fathead minnow	785	Static	5-50	24 hours		Ref. 45 takes this value from Ref. 44.
Ref. 46	Fathead minnow	528		50	8 hours		
Ref. 4	Estimated	4400					The value is estimated from measured values of Log K_{ow} from Ref. 49 and Ref. 41 using the equation in Ref. 5).

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation and Transport

Photolysis in the Atmosphere: No data

Photolysis in Water:
Conclusion: This endpoint has been adequately characterized.
Basis for Conclusion: The products from the photolysis of Proprietary J in water as determined by GC/MS have been summarized (Ref. 13). The products are [Chemical 9] and [Chemical 10].

Photolysis in Soil: No data

Aerobic Biodegradation:
Conclusion: The biodegradation of Proprietary J under aerobic conditions has not been adequately characterized.
***Basis for Conclusion*:** Several different types of studies have been carried out and the weight of evidence indicates that Proprietary J is likely to biodegrade under aerobic conditions. Only the studies by Ref. 23 differ greatly from those in other literature sources, which is likely a result of the water/sediment innoculum used.

Study type/ Method	Innoculum	Acclim	Degradation	Time	Comments	Reference
Thompson-Duthie-Sturm Procedure	Activated sludge		90% as CO_2 Evolution	28 days		Ref. 43
Monsanto Shake Flask Procedure	Activated sludge		43% as CO_2 Evolution	28 days		Ref. 43
River Die-away		4 days	50%	11 days	The initial concentration was 1 ppm; after 4 days, 50% primary degradation occurred.	Ref. 43, 49
Simulated Biological Treatment/ SCAS	Activated sludge		93+ 84+/-3	9 weeks 8 weeks	3 mg/L/24 hours 13 mg/L/24 hours	Ref. 13, 49
	Activated sludge	24-hour cycle	>93 84+/-3	1 day	3 ppm/cycle 13ppm/cycle	Ref. 43

Study type/ Method	Innoculum	Acclim	Degradation	Time	Comments	Reference
SCAS and RDA Analytical Method (Method AC-72-M-S)	Activated sludge with domestic sewage feed		75.9% recovery	24 hours	Mixed liquor extraction	Ref. 43

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation:
Conclusion: The biodegradation of Proprietary J in the presence of pond and/or river sediment has been adequately characterized.
Basis for Conclusion: Biodegradation of Proprietary J has been studied under a variety of conditions and temperatures in the presence of both river and pond sediment. The weight of evidence indicates the potential for Proprietary J to degrade under these environmental conditions.

Sediment	Temp.	$T_{1/2}$	Comments	Reference
Pond water	25	0.44 days	Time interval was 0-3 days.	Ref. 46
Pond sediment	25	39	Static conditions. Sediment was collected from a pond made specifically for this experiment at Glenlea Research Station, University of Manitoba. Initial Proprietary J concentration 0.10 µg/mL. Sediment:water ratio 1:10. Time interval was 2-105 days.	Ref. 46
Pond sediment	25	4.2	Time interval was 0-6 days.	Ref. 47
Pond sediment	10	5.5	Time interval was 0-6 days.	Ref. 47

Sediment	Temp.	$T_{1/2}$	Comments	Reference
Sediment-water microcosms			39% (0.1 mg concentration), 18% (1 mg concentration), and 5% (10 mg concentration) mineralization after 8 weeks with innoculum from Lake Chicot, AR after 1 week of lag time.	Ref. 23
Sediment-water microcosms			14% (0.1 mg concentration), 8% (1 mg concentration), and 2% (10 mg concentration) mineralization after 8 weeks with innoculum from Little Dixie Reservoir, MO after 1 week of lag time.	Ref. 23
Sediment-water microcosms			12.5% (0.1 mg concentration and 10 mg concentration) mineralization after 8 weeks with innoculum from Redfish Bay, TX.	Ref. 23
Sediment-water microcosms			1.9% (0.1 mg concentration) and 1.8% (10 mg concentration) mineralization after 8 weeks with innoculum DeGray Reservior, AR.	Ref. 23
Sediment-water microcosms			9.9% (0.1 mg concentration) and 6% (10 mg concentration) mineralization after 8 weeks with innoculum Arkansas River, AR.	Ref. 23
Pond sediment	5	16.1	Time interval was 0-6 days.	Ref. 47

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption:
Conclusion: The K_{oc} has not been adequately characterized.
Basis for Conclusion: In both literature reports (Ref. 45 and Ref. 4), the values obtained for the K_{oc} are calculated. No experimental values for this endpoint were located.

K_{oc}	Source	Reference
14600	Calculated from K_{ow} using the Kenaga and Goring equation	Ref. 45
2300	Calculated from water solubility using the Kenaga and Goring equation	Ref. 4

Flame Retardant Alternatives

Proprietary K: Aryl phosphate

Draft Hazard Review

December 2004

Proprietary K: Aryl phosphate
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	
Dermal	
Inhalation	
Eye irritation	
Dermal irritation	
Skin sensitization	
Subchronic Toxicity	
28-Day oral	
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	

Proprietary K: Aryl phosphate
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	
Daphnia acute EC50	
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary K: Aryl phosphate
CAS
MF
MW
SMILES

Human Health Endpoints

ACUTE TOXICITY

Conclusion:

The available acute toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No acute toxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)**
- **Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)**
- **Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300 (OECD Guideline 403)**
- **Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)**
- **Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)**
- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

SUBCHRONIC TOXICITY

Conclusion:

The available subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**
- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**,
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422), respectively**.

Subchronic Dermal Toxicity (21/28-day or 90-day).

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90 day)

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No neurotoxicity studies were located that addressed the endpoints in the guidelines listed below.

Delayed Neurotoxicity
- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Neurotoxicity (Adult)
- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity
- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No immunotoxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No genotoxicity studies relevant to the below categories or to other types of genotoxic effects were located.

Gene Mutation in Vitro
Gene Mutation in Vivo
Chromosomal Aberrations in Vitro
Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary K: Aryl phosphate
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

Flame Retardant Alternatives

Proprietary L: Aryl phosphate

Draft Hazard Review

December 2004

Proprietary L: Aryl phosphate
Existing Data Summary Table – Human Health Endpoints

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

Acute Toxicity	
Oral	
Dermal	
Inhalation	
Eye irritation	
Dermal irritation	
Skin sensitization	
Subchronic Toxicity	
28-Day oral	
90-Day oral	
Combined repeated dose with reproduction/ developmental toxicity screen	
21/28-Day dermal	
90-Day dermal	
90-Day inhalation	
Reproductive Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Reproduction and fertility effects	

Developmental Toxicity	
Reproduction/ developmental toxicity screen	
Combined repeated dose with reproduction/ developmental toxicity screen	
Prenatal developmental	
Chronic Toxicity	
Chronic toxicity (two species)	
Combined chronic toxicity/ carcinogenicity	
Carcinogenicity	
Carcinogenicity (rat and mouse)	
Combined chronic toxicity/ carcinogenicity	

Neurotoxicity	
Acute and 28-day delayed neurotoxicity of organophosphorus substances (hen)	
Neurotoxicity screening battery (adult)	
Developmental neurotoxicity	
Additional neurotoxicity studies	
Immunotoxicity	
Immunotoxicity	
Genotoxicity	
Gene mutation in vitro	
Gene mutation in vivo	
Chromosomal aberrations in vitro	
Chromosomal aberrations in vivo	
DNA damage and repair	
Other	

Proprietary L: Aryl phosphate
Existing Data Summary Table – Properties, Fate, and Ecotoxicity

✓= Endpoint characterized by existing data * = Data available but not adequate ✘ = Endpoint not applicable

As noted in this key, a check mark indicates that an endpoint was adequately characterized by existing, publicly available studies. It does not indicate a positive or negative result for that particular endpoint.

P/Chem Properties	
Water solubility	
Octanol/water partition coefficient	
Oxidation/reduction	
Melting point	
Boiling point	
Vapor pressure	
Odor	
Oxidation/reduction chemical incompatibility	
Flammability	
Explosivity	
Corrosion characteristics	
pH	
UV/visible absorption	
Viscosity	
Density/relative density/bulk density	
Dissociation constant in water	
Henry's Law constant	

Environmental Fate	
Bioconcentration	
Fish	
Daphnids	
Green algae	
Oysters	
Earthworms	
Metabolism in fish	
Degradation and Transport	
Photolysis, atmosphere	
Photolysis, water	
Photolysis in soil	
Aerobic biodegradation	
Anaerobic biodegradation	
Porous pot test	
Pyrolysis	
Hydrolysis as a function of pH	
Sediment/water biodegradation	
Soil biodegradation w/ product identification	
Indirect photolysis in water	
Sediment/soil adsorption/desorption	

Ecotoxicity	
Aquatic Toxicity	
Fish acute LC50	
Daphnia acute EC50	
Mysid shrimp acute LC50	
Green algae EC50, NOAEC, LOAEC	
Fish chronic NOAEC, LOAEC	
Daphnia chronic NOAEC, LOAEC	
Mysid shrimp chronic NOAEC, LOAEC	
Terrestrial Organism Toxicity	
Bird LD50 (two species)	
Bird LC50 (two species)	
Bird reproduction	
Earthworm subchronic EC50, LC50, NOAEC, LOAEC	

Chemical Identity

Proprietary L: Aryl phosphate
Synonyms
CAS
MF
MW
SMILES

Human Health Endpoints

ACUTE TOXICITY

Conclusion:

The available acute toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No acute toxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity (OPPTS Harmonized Guideline 870.1100; OECD Guidelines 425, 420, 423, 401)**
- **Acute Dermal Toxicity (OPPTS Harmonized Guideline 870.1200; OECD Guideline 402)**
- **Acute Inhalation Toxicity (OPPTS Harmonized Guideline 870.1300 (OECD Guideline 403)**
- **Acute Eye Irritation (OPPTS Harmonized Guideline 870.2400; OECD Guideline 405)**
- **Acute Dermal Irritation (OPPTS Harmonized Guideline 870.2500; OECD Guideline 404)**
- **Skin Sensitization (OPPTS Harmonized Guideline 870.2600; OECD Guideline 429)**

SUBCHRONIC TOXICITY

Conclusion:

The available subchronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the subchronic toxicity endpoints in the guidelines listed below.

Subchronic Oral Toxicity (28-day, 90-day, or combined with reproductive/developmental)

- **Repeated Dose 28-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3050; OECD Guideline 407)**
- **90-Day Oral Toxicity in Rodents (OPPTS Harmonized Guideline 870.3100; OECD Guideline 408)**,
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422), respectively**.

Subchronic Dermal Toxicity (21/28-day or 90-day).

- **21/28-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3200 (OECD Guideline 410)**
- **90-Day Dermal Toxicity (OPPTS Harmonized Guideline 870.3250; OECD Guideline 411)**

Subchronic Inhalation Toxicity (90 day)

- **90-Day Inhalation Toxicity (OPPTS Harmonized Guideline 870.3465; OECD Guideline 413)**

REPRODUCTIVE TOXICITY

Conclusion:

The available reproductive toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the reproductive toxicity endpoints in the guidelines listed below.

- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction and Fertility Effects (OPPTS Harmonized Guideline 870.3800; OECD Guideline 416)**

DEVELOPMENTAL TOXICITY

Conclusion:

The available developmental toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the developmental toxicity endpoints in the guidelines listed below.

- **Prenatal Developmental Toxicity Study (OPPTS Harmonized Guideline 870.3700; OECD Guideline 414)**
- **Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OPPTS Harmonized Guideline 870.3650; OECD Guideline 422)**
- **Reproduction/Developmental Toxicity Screening (OPPTS Harmonized Guideline 870.3550; OECD Guideline 421)**

CHRONIC TOXICITY

Conclusion:

The available chronic toxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the chronic toxicity endpoints in the guidelines listed below.

- **Chronic Toxicity (OPPTS Harmonized Guideline 870.4100; OECD Guideline 452)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

CARCINOGENICITY

Conclusion:

The available carcinogenicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No pertinent studies were located that addressed the carcinogenicity endpoints in the guidelines listed below.

- **Carcinogenicity (OPPTS Harmonized Guideline 870.4200; OECD Guideline 451)**
- **Combined Chronic Toxicity/Carcinogenicity (OPPTS Harmonized Guideline 870.4300; OECD Guideline 453)**

NEUROTOXICITY

Conclusion:

The available neurotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No neurotoxicity studies were located that addressed the endpoints in the guidelines listed below.

Delayed Neurotoxicity
- **Acute and 28-Day Delayed Neurotoxicity of Organophosphorus Substances (OPPTS Harmonized Guideline 870.6100; OECD Guideline 418, 419)**

Neurotoxicity (Adult)
- **Neurotoxicity Screening Battery (OPPTS Harmonized Guideline 870.6200; OECD Guideline 424)**

Developmental Neurotoxicity
- **Developmental Neurotoxicity: Developmental Neurotoxicity Study (OPPTS Harmonized Guideline 870.6300)**

IMMUNOTOXICITY

Conclusion:

The available immunotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No immunotoxicity studies were located that addressed the endpoints in the guidelines listed below.

- **Immunotoxicity (OPPTS Harmonized Guideline 870.7800)**

GENOTOXICITY

Conclusion:

The available genotoxicity data were judged inadequate to meet the endpoint.

Basis for Conclusion:

No genotoxicity studies relevant to the below categories or to other types of genotoxic effects were located.

Gene Mutation in Vitro
Gene Mutation in Vivo
Chromosomal Aberrations in Vitro
Chromosomal Aberrations in Vivo
DNA Damage and Repair

Ecotoxicity

Acute Toxicity to Aquatic Organisms

Conclusion:

The available acute toxicity data for fish, aquatic invertebrates, and algae were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute toxicity studies with fish, aquatic invertebrates, or algae were located that addressed the endpoints in the guidelines listed below.

- **Acute Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1075; OECD Guideline 203)**
- **Acute Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1010; OECD Guideline 202)**
- **Acute Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1035)**
- **Algal Toxicity (OPPTS Harmonized Guideline 850.5400; OECD Guideline 201)**

Chronic Toxicity to Aquatic Organisms

Conclusion:

The available chronic toxicity data for fish and aquatic invertebrates were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent chronic toxicity studies with fish or aquatic invertebrates were located that addressed the endpoints in the guidelines listed below.

- **Chronic Toxicity to Freshwater and Marine Fish (OPPTS Harmonized Guideline 850.1400; OECD Guideline 210)**
- **Chronic Toxicity to Freshwater Invertebrates (OPPTS Harmonized Guideline 850.1300; OECD Guideline 211)**
- **Chronic Toxicity to Marine/Estuarine Invertebrates (OPPTS Harmonized Guideline 850.1350)**

Acute and Subchronic Toxicity to Terrestrial Organisms

Conclusion:

The available acute and subchronic toxicity data for terrestrial organisms were judged inadequate to meet the endpoints.

Basis for Conclusion:

No pertinent acute oral, acute dietary, or reproductive toxicity studies with birds and no subchronic toxicity studies with earthworms were located that addressed the endpoints in the guidelines listed below.

- **Acute Oral Toxicity in Birds (OPPTS Harmonized Guideline 850.2100)**
- **Acute Dietary Toxicity in Birds (OPPTS Harmonized Guideline 850.2200; OECD Guideline 205)**
- **Reproductive Toxicity in Birds (OPPTS Harmonized Guideline 850.2300; OECD Guideline 206)**
- **Earthworm Subchronic Toxicity (OPPTS Harmonized Guideline 850.6200; OECD Guideline 207)**

Physical/Chemical Properties

Proprietary L: Aryl phosphate
CAS
MF
MW
SMILES

Water Solubility (mg/L): No data

Log K_{ow}: No data

Oxidation/Reduction: No data

Melting Point: No data

Vapor Pressure (torr): No data

Odor: No data

Oxidation/Reduction Chemical Incompatibility: No data

Flammability: No data

Explosivity: No data

Corrosion Characteristics: No data

pH: No data

UV/VIS Absorption: No data

Viscosity: No data

Density/Relative Density/Bulk Density: No data

Dissociation Constant in Water: No data

Henry's Law Constant: No data

Environmental Fate

Bioconcentration

Fish: No data

Daphnids: No data

Green Algae: No data

Oysters: No data

Earthworms: No data

Fish Metabolism: No data

Degradation

Photolysis in the Atmosphere: No data

Photolysis in Water: No data

Photolysis in Soil: No data

Aerobic Biodegradation: No data

Anaerobic Biodegradation: No data

Porous Pot Test: No data

Pyrolysis: No data

Hydrolysis as a Function of pH: No data

Sediment/Water Biodegradation: No data

Soil Biodegradation with Product Identification: No data

Indirect Photolysis in Water: No data

Sediment/Soil Adsorption/Desorption: No data

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