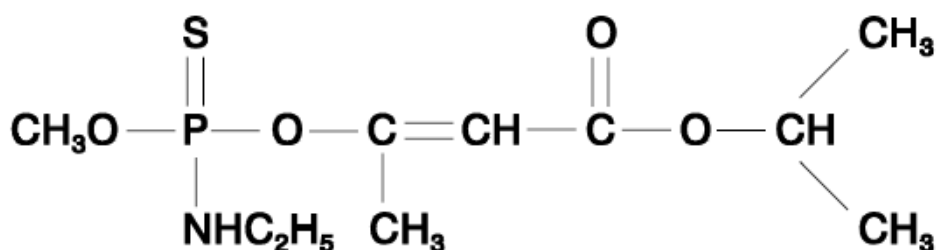


PROPETAMPHOS

RISK CHARACTERIZATION DOCUMENT



 California Environmental Protection Agency
Department of Pesticide Regulation

December 1999

RCD 99-04

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION**

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PROPETAMPHOS
(CATALYST™)

RISK CHARACTERIZATION DOCUMENT

Medical Toxicology and Worker Health and Safety Branches

DEPARTMENT OF PESTICIDE REGULATION

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

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I. SUMMARY

Propetamphos, (E)-1-methylethyl-3[[ethylamino)methoxyphosphinothioyl]oxy]-2-butenate, is an insecticide that is registered mainly for indoor structural use. It was placed in reevaluation by DPR due to the increasing number of illnesses associated with its use. DPR was also concerned about potential over-exposures of humans that come in contact with treated rooms. This risk assessment was conducted to evaluate the potential adverse health effects in humans from occupational and residential exposure to propetamphos.

Propetamphos is an organophosphoramidothioate pesticide whose primary biological activity is through its inhibition of cholinesterase (ChE) enzymes. The effects observed in laboratory animals after acute exposure are primarily cholinergic signs (tremors, ataxia, fasciculations, salivation, lacrimation). No-Observed-Effect Levels (NOELs) could not be established in any of the standard battery of acute toxicity studies. A NOEL for acute effects was seen in pregnant rats during the first few days of exposure. This study was selected as the definitive study for evaluating acute occupational and residential exposure to propetamphos with a critical NOEL of 1.5 mg/kg based on tremors, exophthalmos, and drowsiness. Effects seen in laboratory animals with subchronic and chronic exposure included cholinergic signs, brain ChE inhibition, dermal irritation, reduced body weights and food consumption, reduced mating index, reduced litter size, reduced number of implantation sites, increased pup mortality, decreased pup body weights, hematological changes indicative of anemia, clinical chemistry changes indicative of hepatotoxicity, increased liver weights, hepatic necrosis, and thickened mucosa of the small intestine. Not all effects were seen in all species. A 1-year dog study was selected as the definitive study for evaluating chronic occupational and residential exposure to propetamphos with a critical NOEL of 0.59 mg/kg/day based on diarrhea, vomiting, prolonged anestrus, reduced brain ChE activity (M: 79%; F: 82% of controls), increased liver weights, thickened mucosa of small intestine, and hepatic necrosis.

No monitoring data were available for occupational exposure of propetamphos; therefore, exposure data from application of similar formulations containing propoxur and chlorpyrifos were used as surrogate data. The absorbed daily dosage (ADD) for applicators ranged from 12.8 µg/kg/day for the 1% ready-to-use trigger pump spray to 109.6 µg/kg/day for the emulsifiable concentrate mix for soil injection. Assuming applicators are exposed 233 days per year, the annual average daily dosage (AADD) ranged from 8.2 to 69.9 µg/kg/day. The residential exposure was estimated using two different methods. In one method, residential exposure was estimated using passive dosimetry where volunteers performed Jazzercise® routines 3, 6, and 9 hours after the rooms had been treated with propetamphos. The other method estimated exposure assuming that the residues on the skin were in equilibrium with the dislodgeable residues on the carpet. Using passive dosimetry, the ADDs for adults and children were 28.3 and 44.0 µg/kg/day, respectively. Assuming 24 applications per year and 5 days of exposure following each application, the AADDs were 9.3 and 14.5 µg/kg/day for adults and children, respectively. Using dislodgeable carpet residues, the ADDs for adults and children were 12.3 and 18.9 µg/kg/day, respectively. The AADDs were 4.0 and 6.2 for adults and children, respectively.

The margin of exposure is the ratio of the NOEL from the laboratory animal studies to the estimated human exposure dosage (ADD or AADD). Generally, a margin of exposure greater than 100 is considered protective of human health when it is calculated from a NOEL derived from an animal study. The MOEs for acute occupational exposure were 117, 109, and 14 for the 1% pump spray, 1% aerosol, and 1% emulsifiable concentrate mix for soil injection,

respectively. The MOEs for chronic occupational exposure were 72, 67, and 8 for the 1% pump spray, 1% aerosol, and 1% emulsifiable concentrate mix for soil injection, respectively. The acute MOEs for residential exposure based on passive dosimetry were 53 and 34 for adults and children, respectively. The chronic MOEs for adults and children were 63 and 41, respectively. Using the dislodgeable carpet residues, the acute MOEs for residential exposure were 122 and 79 for adults and children, respectively. The chronic MOEs for adults and children were 147 and 95, respectively.

II. INTRODUCTION

A. REGULATORY BACKGROUND

Propetamphos, (E)-1-methylethyl-3[[[(ethylamino)methoxyphosphinothioyl]oxy]-2-butenate, is an insecticide that is registered mainly for structural pest control. It was placed in reevaluation by DPR (then part of the California Department of Food and Agriculture) in March 1990 due to the increasing number of illnesses associated with its use (DPR, 1994). DPR was also concerned about potential over-exposures of humans that come in contact with treated rooms. In September 1990, DPR requested additional data from the registrant on dermal sensitization, odor threshold, indoor exposure and dermal absorption. Data on dermal sensitization and indoor exposure have been submitted and reviewed by the Worker Health and Safety Branch. A sensory irritation study was submitted in place of an odor threshold study. The registrant requested that DPR assume a default value for dermal absorption in lieu of a dermal absorption study. This risk assessment was conducted to evaluate the potential adverse health effects in humans from occupational and residential exposure to propetamphos. There are food and feed additive tolerances for propetamphos due its use in food and animal feed handling establishments. However, a dietary exposure analysis was not performed because these food/feed tolerances are not specific to any food/feed items.

B. CHEMICAL IDENTIFICATION

Propetamphos is an organophosphoramidothioate pesticide whose primary biological activity is through its inhibition of cholinesterase (ChE) enzymes. ChEs are a family of enzymes found throughout the body that hydrolyze choline esters. In the nervous system, acetylcholinesterase (AChE) is involved in the termination of impulses across nerve synapses including neuromuscular junctions by rapidly hydrolyzing the neural transmitter, acetylcholine. The active metabolite of organophosphate pesticides, such as propetamphos, bind to the active site (a serine hydroxyl group) of the AChE protein forming a transient intermediate complex which eventually hydrolyzes with the loss of a leaving group, resulting in a stable, phosphorylated, and essentially unreactive enzyme complex (Ecobichon, 1996). The oxygen analog of propetamphos is the active metabolite that binds to serine site on AChE (Mason *et al.*, 1993). The phosphorylated enzyme can only be spontaneously reactivated at a very slow rate under normal circumstances. If "aging" (dealkylation of an ester group) of the intermediate phosphorylated enzyme occurs, the inhibition of AChE is considered irreversible presumably due to a perturbation of the active site preventing dephosphorylation. Mason *et al.* (1993) observed no spontaneous reactivation of propetamphos inhibited human plasma ChE *in vitro* up to 45 hours after initial inhibition and only slight reactivation after administration of pralidoxime methiodide (only 29-35%) suggesting that most of the propetamphos inhibited ChE had aged.

Butyrylcholinesterase (BuChE), sometimes referred to as plasma ChE, pseudo-cholinesterase, or serum esterase, is also inhibited by propetamphos. Any reference in this document to "cholinesterase", without specifically indicating that the enzyme is serum or plasma ChE, should be interpreted as AChE. BuChE only occurs to a limited extent in neuronal elements of the central and peripheral nervous systems. In addition to plasma, it is also present in the liver, lung and other organs, although its physiological function is unknown (Lefkowitz *et al.*, 1990; Brimijoin, 1992; U.S. EPA, 1993; Pantuck, 1993). An atypical genetic variant of plasma cholinesterase has been associated with an increased susceptibility to various

B. CHEMICAL IDENTIFICATION (cont.)

drugs, such as succinylcholine and cocaine (Lockridge, 1990; Pantuck, 1993). However, it is unclear if this increased susceptibility to certain drugs in people with the atypical plasma ChE translates to a possible adverse effect when plasma ChE is inhibited by organophosphates. In an in vitro study, it was shown that the atypical and normal plasma ChE was equally sensitive to the organophosphate inhibitors, diisopropylfluorophosphonate (DFP) and tetraethylpyrophosphonate (TEPP), but the atypical plasma ChE was less sensitive than the normal plasma ChE to 14 drugs, especially succinylcholine and decamethonium (Kalow and Davis, 1958). In another study, rats that were depleted of plasma AChE by injecting them intravenously with antibodies specific to this enzyme were not more susceptible to paraoxon toxicity than untreated controls based on their performance in a functional observational battery and AChE activity in the brain and diaphragm (Padilla et al., 1992). The investigators concluded that based on the results with plasma AChE, it was unlikely that plasma BuChE or erythrocyte AChE would offer significant protection against paraoxon toxicity, either.

The inhibition of AChE results in the accumulation of endogenous acetylcholine in nerve tissue and effector organs. In acutely toxic episodes, muscarinic, nicotinic and central nervous system (CNS) receptors are stimulated with characteristic signs and symptoms occurring throughout the peripheral and central nervous systems (Ellenhorn and Barceloux, 1988; Murphy, 1986). Muscarinic effects can include increased intestinal motility, bronchial constriction and increased bronchial secretions, bladder contraction, miosis, secretory gland stimulation and bradycardia. Nicotinic effects include muscle weakness, twitching, cramps and general fasciculations. Accumulation of acetylcholine in the CNS can cause headache, restlessness, insomnia, anxiety and other non-specific symptoms. Severe poisoning results in slurred speech, tremors, ataxia, convulsions, depression of respiratory and circulatory centers and, eventually, coma.

C. TECHNICAL AND PRODUCT FORMULATION

Currently, there is only 1 product registered in California that contains propetamphos (18.9%) as an active ingredient that is registered by Wellmark International. This product is for indoor use in structures against various insects including silverfish, cockroaches, earwigs, beetles, fleas, ants, wasps, spiders, mites, ticks and other miscellaneous insects. This product can be sold to the general public for home use; however, generally, only licensed pesticide control operators use it.

D. USAGE

In 1995, 78,683 lbs. of propetamphos were used in California by licensed pesticide applicators (DPR, 1996). Of this amount, 99% was for structural pest control. Other reported uses included landscape maintenance, public health pest control, regulatory pest control, rights-of-way, and vertebrate pest control. Because the propetamphos products can be sold to the general public for home use which is not included in the DPR Use Report, the amount reported underestimates the total amount of propetamphos used in California.

The propetamphos liquid concentrate may be applied as spot, surface, and crack and crevice treatments via low pressure spray or injected into the soil for termites. The application rates ranged from 0.5 to 1.0% active ingredient per gallon of spray mix for these uses.

E. ILLNESS REPORTS

In California, there were 371 cases of illnesses/injuries related to exposure to propetamphos alone or in combination with other pesticides between 1982 and 1993 (DPR, 1995). Most of the cases (208) involved non-pesticide handlers (office workers, teachers, restaurant workers, and residents) that had systemic effects compatible with, but not specific to cholinesterase inhibition after exposure to propetamphos alone. Another 120 non-pesticide handlers had systemic effects after exposure to propetamphos in combination with other pesticides. Of these cases, 56% were classified as definite/probable incidents related to exposure to propetamphos. From 1989 to 1993, the illnesses/injuries were reported by gender. During this time, 80% of the cases involved adult females who were non-pesticide handlers.

Sherman (1995) published a summary of 41 cases of organophosphate poisoning, of which 37 cases involved chlopyrifos. Two of these 37 cases also involved exposure to propetamphos. One case involved a male infant less than 1 year old whose home was treated. The infant exhibited peripheral and central nervous system signs, chest congestion, and diarrhea. The other case involved a 50-year-old woman whose home was treated. She developed chest congestion and sleep disturbance.

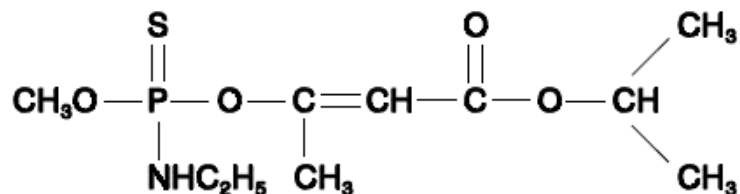
U.S. EPA reported 8 incidents of illness/injuries related to exposure to propetamphos between 1991 to 1996 in their Office of Pesticide Programs (OPP) Incident Data System (IDS) (U.S. EPA, 1998a). Two incidents were not considered likely to be related to exposure. Of the other 6 incidents, 3 incidents involved workers that developed symptoms after their work area had been treated. Workers in two of these cases developed possible allergic reactions. Eye irritation was seen in 2 office workers wearing contacts in the other incident. An applicator developed a swollen face (possible allergic reaction) every time he used propetamphos in a fourth incident. In a fifth incident, a homeowner developed a corneal ulcer after their house was treated with propetamphos and cypermethrin. The sixth incident involved a child which was taken to the emergency room after exposure, but no details were available on the effects or how the child was exposed. OPP also supports the National Pesticide Telecommunication Network (NPTN) which is a toll free information service. Between 1984-1991, NPTN received calls involving 276 incidents in humans and 47 incidents in animals (mostly pets). From April 1995 to May 1998, NPTN received 20 calls concerning health effects possibly related to propetamphos.

F. PHYSICAL/CHEMICAL PROPERTIES (Sandoz, 1978)

1. Chemical Name: (E)-1-methylethyl 3-[[[(ethylamino)methoxyphosphinothioyl]oxy]-2-butenoate
2. Common Name: Propetamphos
3. Trade Name: Catalyst, Safrotin
4. CAS Registry Number: 31218-83-4
5. Empirical Formula: $C_{10}H_{20}NO_4PS$

F. PHYSICAL/CHEMICAL PROPERTIES (cont.)

6. Structural Formula:



- | | |
|-----------------------|---|
| 7. Molecular Weight: | 281.3 |
| 8. Physical State: | oily liquid |
| 9. Color: | light brown to straw |
| 10. Flash Point: | >100°C (Pensky Martins Closed Cup) |
| 11. Boiling Point: | 87-89°C at 0.005 mmHg |
| 12. Specific Gravity: | 1.12 ± 0.03 g/cm ³ at 20°C |
| 13. Solubility: | Soluble in organic solvents, i.e., xylene, hexane, acetone; soluble in water at 110 mg/l at 24°C |
| 14. Stability: | The half-life is greater than 5 years at 20°C. In a buffered aqueous solution at 20°C the half-lives ranged from 37 to 47 days between pH 5 and 9. The half-life in an aqueous media exposed to sunlight is approximately 5 days. |
| 15. Vapor Pressure: | 8.1 x 10 ⁻⁵ mmHg (25°C) |

G. ENVIRONMENTAL FATE

Propetamphos has no agricultural use and, therefore, no environmental fate studies are required under the Pesticide Contamination Prevention Act (AB2021). However, one published study was available which examined the degradation of propetamphos in soil, water and sediment (Jain *et al.*, 1987). The dissipation from soil was more rapid when applied at 250 g/ha than at 500 g/ha with no residues detected by 7 and 15 days, respectively. A similar pattern was seen in water containing sediment where residues persisted longer when applied at the higher rate. No residues were detected in water after 7 days when applied at 100 g/ha and after 15 days when applied at 200 g/ha. The dissipation of residues from water containing sediment were attributed to the adsorption of propetamphos to the sediment. Dissipation from water without sediment was much slower (80% by day 3) when compared to water with sediment (100% by day 3). Residues in the sediment at both application rates increased from days 3 to 15 after application, after which they began to decrease slowly.

In a 1986 chemical spill from the Sandoz plant in Switzerland, several chemicals entered the Rhine River (Brüggemann and Halfon, 1990). Eight chemicals (disulfoton, dinitro-*o*-cresol,

G. ENVIRONMENTAL FATE (cont.)

propramphos, thiometon, parathion, etrimfos, metoxuron and fenitrothion) that were found in the river were evaluated for their potential environmental hazard. Two ranking methods were used. The first method combined environmental fate and toxicity data using a standardized index with range 0-1 in a statistical model. The other method involves organizing the chemicals in a diagram based on set theory and systems analysis. The most hazardous chemicals identified by both methods were parathion, propramphos and dinitro-*o*-cresol. However, the investigators did not compare these ranking with the actual residues found in the river or evidence of toxicity in wildlife.

The dissipation of propramphos from various surfaces such as glass, painted and unpainted wood, and vinyl was examined because of its structural use. Several studies reported that the dissipation of propramphos was slowest from glass surfaces (Johnson, 1974; Badie and Whitacre, 1975; Winkler, 1982). The percent of applied material remaining after 21 days was the greatest for glass ranging from 48 to 70%. The percentage of propramphos remaining on vinyl and wood surfaces was significantly lower ranging from 0 to 5% on unpainted wood. The dissipation from these latter surfaces appears to be due to its penetration through the wood regardless of whether it was painted or not or covered with vinyl (Badie and Whitacre, 1975). It was not possible to determine how much of the applied material penetrated the wood, but these surfaces retained enough propramphos sufficient to kill exposed roaches. The LT_{50} values (time required for half the animals to die) were <0.5, 11.5, 8.0 and 6.1 days for glass, vinyl, painted and unpainted wood, respectively. The findings of a published study conducted by Agnihotri *et al.* (1987) appear to conflict with these previous studies in that the dissipation of propramphos from ceramic, sunmica, and glass was much greater than from plywood and soil. Approximately 92% of the residues were lost within 3 days after application to ceramic, sunmica, and glass. Only 61 and 70% of the residues were lost from plywood and soil, respectively. The residues were non-detectable on ceramic, sunmica, and glass by 28 days. The residues on plywood and soil were no longer detected 45 days after application.

Chemical and radioisotope analysis indicated that when propramphos is applied to glass it undergoes little, if any, degradation (Winkler, 1982). The loss of propramphos from glass was attributed to volatilization of the parent compound or degradation products. The known degradation products of propramphos are volatile acetoacetate intermediates which are formed both hydrolytically and biochemically by the cleavage of the P-O-vinyl bond.

Residues in foods were analyzed in 6 different food handling establishments (dairy, cannery, cookie plant, bakery, food market, and cafeteria) treated with propramphos (Graben and Januszonis, 1982). No apparent trend in the residue levels was found with respect to time over the 15 days after application in all 6 establishments. The residue levels were all less than 0.01 ppm, except in four instances. In each of these instances, only one of several food items had a detectable residue. The investigators suggested that this pattern of residues indicated that direct contact of the food item with residual propramphos, rather than by volatilization.

Airborne and surface residues were also analyzed in residences and an office treated with propramphos (Stumphy, 1975). The airborne residues ranged from 0.36 to 4.54 $\mu\text{g}/\text{m}^3$ one hour after treatment and continued to dissipate with time. The surface residues were more variable, ranging from 4 to 2900 ng/cm^2 . Airborne residues of propramphos were monitored for 50 hours after a broadcast application to 6 apartments for cat fleas (Koehler and Moye, 1995). In non-ventilated apartments the highest air concentration were found at 0 and 2 hours

G. ENVIRONMENTAL FATE (cont.)

after application and ranged from 24 to 49 ng/L. In ventilated apartments, the peak air concentrations ranged from 6 to 36 ng/L.

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Summary

Propetamphos appears to be readily absorbed and metabolized by the oral route with 97% excreted in the urine and expired air within 96 hours after administration. The oral absorption was assumed to be 100%. No dermal absorption data were available for propetamphos, so a default assumption of 50% was used. A default assumption of 50% respiratory retention and 100% absorption was also used for propetamphos. The major metabolic pathway proposed for propetamphos involves hydrolytic reactions, breaking the P-O-vinyl bond to form an acetoacetate metabolite which then decarboxylates to acetone and CO₂ after ester hydrolysis.

Absorption

Female Wistar rats/dose were administered a single oral dose of ¹⁴C-propetamphos (radiolabeled on 1 and 3 carbons of the butenoic acid moiety) at 0.6, 6, or 16 mg/kg by gavage in polyethylene glycol-400 (Bhuta, 1979). Three rats/dose/time had blood drawn at 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72 or 96 hours. Based on radioactivity in the blood, the absorption half-life was estimated to be 2.5 hrs. The investigators concluded that greater than 95% of the applied dose would be absorbed within 10 hours of dosing. This conclusion was supported by only 3% of the applied dose being excreted in the feces in the 96 hours immediately following dosing.

In another study conducted by Patel *et al.* (1982), unlabeled propetamphos was administered to Wistar rats at 6.4 mg/kg/day by oral gavage in polyethylene glycol-400 for 7 days, followed by a single oral dose of ¹⁴C-propetamphos (radiolabeled on 1 and 3 carbons of the butenoic acid moiety) within 24 hours. Blood was collected serially from 5 rats/sex at 0, 1, 2, 4, 12, 24, 72 and 120 hours following the radioactive dose. An absorption half-life was not estimated; however, the mean fecal excretion after 120 hours was only 7% of the applied dose indicating that the absorption was essentially complete.

In a third study, 5 or 6 Sprague-Dawley rats/sex/dose were administered a single dose of ¹⁴C-propetamphos (label on 1 and 3 carbons of butenoic acid moiety) by oral gavage at 0.5 and 18 mg/kg (Ferdinandi, 1993). Another group was administered unlabeled propetamphos for 14 days at 0.5 mg/kg and then given a single oral dose of ¹⁴C-propetamphos on day 15. Based on the radioactivity recovered in the urine, expired air, cage wash, tissues, skin and carcass in the 72 hours following dosing, the oral absorption ranged from 87.0% to 92.7%. Based on the plasma concentration curves, the estimated absorption half-lives were 0.11 and 0.10 hour in males and females at 0.5 mg/kg, respectively, and 0.27 and 0.17 hour in males and females at 18 mg/kg. Although there were some slight differences in the absorption kinetics based on gender and dose, the investigators did not consider them biologically significant. Based on these three studies, the oral absorption for propetamphos was assumed to be 100%.

No dermal absorption data was available for propetamphos; therefore, a default value of 50% was used for humans. The use of 50% instead of 100% as a default value for dermal absorption in humans is a science policy developed by the Worker Health and Safety Branch of DPR based on a review of dermal absorption data for 40 pesticides (Donahue, 1996). The mean rat dermal absorption for these 40 pesticides was 19 ± 14%. The 95th percentile was

A. PHARMACOKINETICS (cont.)

approximately 42%. The use of this default value should theoretically result in an overestimation of human exposure by the dermal route in most cases since the dermal absorption in humans is generally two to ten-fold lower than rats (Wester and Maibach, 1993).

Distribution

In the single-dose study conducted by Bhuta (1979), the elimination of propetamphos at 0.6 mg/kg followed a monophasic pattern with an estimated half-life of 60 hours based on the radioactivity in blood. At 6 mg/kg, the elimination followed a biphasic pattern with estimated half-lives of 12 and 110 hours. The investigators suggested that these long half-lives do not indicate bioaccumulation, but rather reflect the distribution and incorporation of the radiolabeled metabolites into natural constituents in tissues through the carbon pool. Within an hour of administration, the blood levels were lower than most surrounding tissues. The rats sacrificed at 1, 2, 4, 8, 24, 72 or 96 hours for blood were also analyzed for tissue residues. The highest tissue levels were found in the bone marrow and reproductive organs. The investigators suggested that the radioactivity in the fat and bone marrow were from the metabolism of propetamphos into fragments that were then incorporated into the natural constituents in tissues, such as, fatty acids, amino acids, sugars, etc.

As with a single dose at 6 mg/kg/day, the elimination of propetamphos after multiple doses at 6.4 mg/kg/day followed a biphasic pattern with estimated half-lives of 8 and 106 hours for females and 6 and 120 hours for males (Patel *et al.*, 1982). Groups of 5 rats/sex/time were sacrificed at 24, 72 or 120 hours for analysis of tissue residues. Unlike the single dose experiment, the highest tissue residue levels were in the lung, skin and fat. The investigators suggested that the difference in the tissue residues between single and multiple doses may be due to an increased metabolism in the steady state condition.

The distribution of propetamphos was also examined in 6 male and 5 female Fisher 344 rats after administration of ¹⁴C-propetamphos (labeled on 1 and 3 carbons of the butenoic acid moiety) via an indwelling jugular cannula at 12 mg/kg (Dix *et al.*, 1992). Propetamphos was highly bound to the plasma proteins over a total plasma concentration range of 12-196 µg/ml (free fraction = 0.06). There was no statistical difference between males and females in the mean area under the concentration curve (M= 23.5; F=18.2 min·mg/L), mean clearance (M=0.559; F=0.828 L/min/kg), mean residence times (M=28.3; F=14.4 min) and mean volume of distribution at steady state (M=14.7; F=12.3 L/kg). However, the mean terminal elimination rate constant was significantly different (M=0.015; F=0.037 min⁻¹). Despite the similarity in most of these pharmacokinetic parameters, females were reported to exhibit more clinical signs of toxicity than males. Because of the rapid elimination of propetamphos from the plasma, these investigators concluded that it is unlikely that propetamphos would bioaccumulate.

In the study conducted by Ferdinandi (1993), the elimination kinetics of the plasma radioactivity fit a two compartment model best with an alpha-phase half-life of 1.09 to 2.48 hours and a beta-phase half-life of 23.9 to 28.3 hours. There was not a significant gender or dose effect. The volume of distribution ranged from 464 mL (0.5 mg/kg) to 528 mL (18 mg/kg) in males and from 339 mL (0.5 mg/kg) to 326 mL (18 mg/kg). There was a significant gender, but not dose, effect on the volume of distribution. The total body clearance in males was 71.1 and 64.8 mL/hour at 0.5 and 18 mg/kg, respectively, and in females was 59.3 and 38.3 mL/hour at 0.5 and 18 mg/kg, respectively. There was a significant gender effect and a significant dose effect in females.

A. PHARMACOKINETICS (cont.)

Biotransformation

The metabolism of ^{14}C -propramphos (radiolabeled on 1 and 3 carbons of the butenoic acid moiety) in the rat was studied after oral administration of single doses (0.6, 6, and 16 mg/kg) and multiple doses at 6.4 mg/kg/day (Patel and Winkler, 1982). The major non-conjugated and conjugated metabolites were volatiles consisting of acetone and acetate-type compounds. Minor non-volatile metabolites excreted in the urine were desmethyl, desisopropyl and desmethyl-desisopropyl propramphos. Neither the oxygen analog nor the N-desethyl metabolite was found. Based on their findings, the investigators proposed that propramphos is metabolized by hydrolytic reactions, breaking the P-O-vinyl bond to form an acetoacetate moiety which decarboxylates to acetone and CO_2 after ester hydrolysis (Figure 1). As with other organophosphorothioate compounds, the oxygen analog of propramphos is presumably the active metabolite which is formed by desulfuration via cytochrome P-450 (Ecobichon, 1996). This metabolite may not have been found in this study because it can readily be hydrolyzed by aryl and aliphatic hydrolases in mammals.

The *in vitro* metabolism of ^{14}C -propramphos (labeled on the vinyl and carbonyl carbons) was examined in housefly (insecticide-resistant and susceptible), cockroach and mouse liver preparations (Wells *et al.*, 1986a&b). The oxygen analog was isolated from housefly and cockroach preparations, but not mouse liver preparations. Mouse liver preparations metabolized propramphos 10 times more rapidly than the housefly and cockroach preparations. The major metabolic pathway in mouse liver homogenates involved the dealkylation of propramphos via microsomal enzymes to form desisopropyl propramphos. The major metabolic pathway in housefly preparations involved glutathione conjugation to form S-3-(isopropylcrotonyl)glutathione and (S)-3-[[[(ethylamino)methoxy]phosphino]thio]oxy]-butanoic acid, 1-methylethyl ester, glutathione. The insecticide-resistant housefly preparations had a greater capacity for glutathione conjugation than the susceptible housefly preparations. Hydrolysis of propramphos occurred in all preparations with the major products being O-methyl ethylphosphoramidothioic acid (mouse, housefly, cockroach), isopropyl acetoacetate (mouse), and acetoacetic acid (mouse, cockroach). The *in vivo* metabolism of propramphos in the housefly was also examined by Wells *et al.* (1986a). The phosphoramidothioic acid and isopropyl acetoacetate were further metabolized *in vivo* to CO_2 and acetone.

Ferdinandi (1993) also examined the biotransformation of propramphos in rats. CO_2 was the major biotransformation product resulting from the catabolism of the butenoic acid moiety. This metabolic pathway appeared to be saturated at high doses. O-Desmethyl propramphos and isopropyl 3-(N-acetyl-L-cysteinyl)-2-butenate were minor metabolites identified in the urine. Oxidative O-demethylation to form O-desmethyl propramphos followed by glucuronic acid conjugation was proposed as a significant alternate metabolic pathway. The major urinary metabolite was not definitively identified, but indirect evidence suggest that it is a glucuronic acid conjugate of O-desmethyl propramphos. Glutathione conjugation was suggested as a minor metabolic pathway.

Excretion

In the single-dose study conducted by Bhuta (1979), 10 female rats/dose were placed in metabolism cages for 96 hrs to collect urine and feces. An additional 4 female rats/dose were placed in metabolism cages designed for CO_2 collection for 7 or 48 hrs. Based on the CO_2

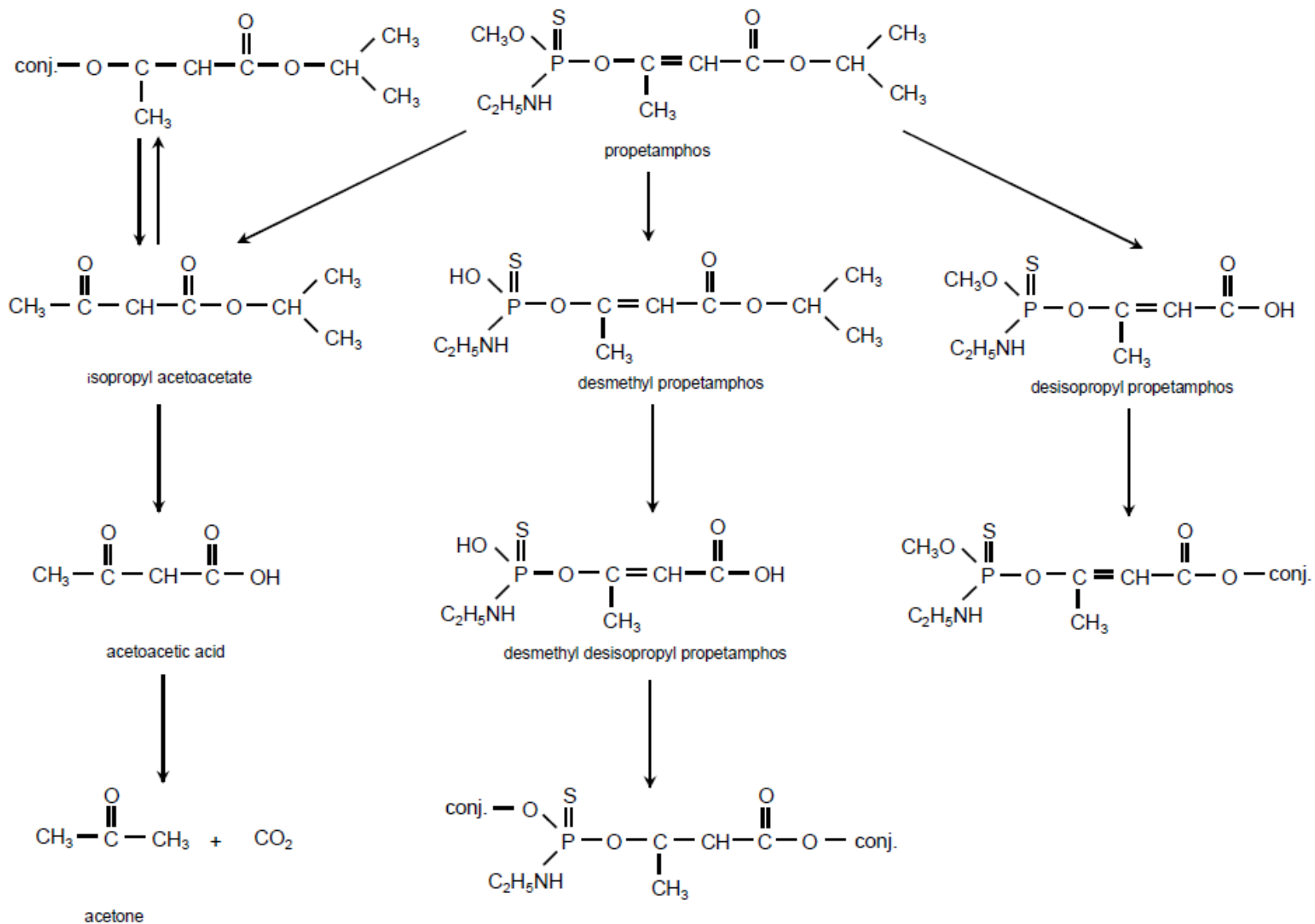


Figure 1. Proposed Metabolic Pathways for Propetamphos

A. PHARMACOKINETICS (cont.)

excretion during the first 7 hours, the total excretion of propetamphos as CO₂ was estimated to be 80, 60 and 40% at 0.6, 6, and 16 mg/kg, respectively. Approximately 12, 20, and 38% of the radioactivity were excreted in the urine at these respective dosages. The investigators suggested that the lower CO₂ excretion and higher urinary excretion at the higher doses indicates saturation of the oxidative metabolic pathways. Fecal excretion was less than 3% of the administered dose at all dose levels.

In the multiple-dose study conducted by Patel *et al.* (1982), 5 rats/sex were placed in metabolism cages for urine and feces collection for 120 hours following the last dose. Two rats/sex were placed in metabolism cages designed for CO₂ collection for 24 hours. Approximately 42 and 62% of the radioactivity were excreted as CO₂ in females and males, respectively, during the first 24 hours. Urinary excretion was approximately 44 and 33% in females and males, respectively, during the 120 hours following the final dose. Fecal excretion was 8.6 and 4.7% in females and males, respectively. Based on these findings, the investigators suggested that the male rats have a higher metabolic rate than female rats.

In the study conducted by Ferdinandi (1993), rats administered 0.5 mg/kg excreted 67-73% of the applied dose in expired air as CO₂. Approximately 15-18% of the applied dose was excreted in the urine. Only 2-3% of the applied dose was excreted in the feces. At 18 mg/kg, the amount excreted in expired air was significantly reduced (28-33%) while the amount excreted in the urine (48-49%) and feces (3-5%) increased. There was no difference due to gender or with repeated dosing. Approximately 80-91% was excreted during the first 24 hours, except for females at 18 mg/kg which excreted only 59%.

B. ACUTE TOXICITY

Summary

The standard battery of acute toxicity tests was available for both the technical grade propetamphos and the liquid concentrate. Five of the 14 available acute toxicity tests were acceptable based on FIFRA guidelines. The clinical signs observed in animals after acute exposure to technical grade propetamphos were typical cholinergic signs (e.g., tremors, ataxia, gasping/labored breathing, facial and urogenital stains). A no-observed-effect-level was not established in any of the acute toxicity studies for technical grade propetamphos. However, the lowest-observed-effect level (LOEL) in an inhalation LC₅₀ study with rats was 6.25 mg/L (1,000 mg/kg) based on salivation, tachypnea, hypoactivity, ocular and nasal discharge, and hypersensitivity. The LOEL in the oral toxicity study for technical grade propetamphos was 50 mg/kg based on hypoactivity, diarrhea, tachypnea, excessive urination, flaccidity, ataxia, salivation, and nasal discharge. Due to the insufficient information a LOEL could not be determined in the dermal toxicity study. Very slight erythema was observed with dermal exposure. Slight conjunctival irritation was observed with ocular exposure. No dermal sensitization was observed with either the technical material or the formulation in the guinea pig.

Technical Grade Propetamphos

The acute toxicity of technical grade propetamphos is summarized in Table 1. Due to differences in the acute toxicity of the isomers, 90% of the technical grade propetamphos is the

B. ACUTE TOXICITY (cont.)

Table 1. The Acute Toxicity of Technical Grade Propetamphos

Species	Sex	Results	References ^a
Acute Inhalation LC₅₀			
Rat	M	19.3 mg/L (4-hr, whole body)	1 ^b
	F	15.4 mg/L (4-hr, whole body)	
Acute Oral LD₅₀			
Rat	M	75.4 mg/kg	1
	F	82.8 mg/kg	
	NR	122 mg/kg (<i>cis</i> isomer)	2
	NR	8 mg/kg (<i>trans</i> isomer)	
Acute Dermal LD₅₀			
Rabbit	M/F	474 mg/kg	1
	NR	2100 mg/kg (<i>cis</i> isomer)	2
	NR	128 mg/kg (<i>trans</i> isomer)	
Primary Dermal Irritation			
Rabbit	M/F	Mild irritation	1,3
Primary Eye Irritation			
Rabbit	M/F	Slight irritation	1
	M/F	No irritation	4
Dermal Sensitization			
Guinea Pig	M/F	No Sensitization	5
	M/F	No Sensitization	6
^a References: 1. Wazeter and Goldenthal, 1974; 2. Leber, 1972; 3. Hamburger and Klotzsche, 1978a; 4. Hamburger and Klotzsche, 1978b; 5. Hamburger and Klotzsche, 1980; 6. Wilkinson and Singer, 1990.			
^b LC ₅₀ values expressed as a nominal concentration.			

E or *cis* isomer and less than 1% is the Z or *trans* isomer (Jucker and Kaparally, 1982). The *cis* isomer is less acutely toxic than the *trans* isomer by at least an order of magnitude (Leber, 1972). Clinical signs were observed at all dosages during and after a single 4-hour inhalation exposure (whole body) to technical grade propetamphos (Wazeter and Goldenthal, 1974). The signs included (in decreasing order with dosage) gasping, dyspnea, prostration, tremors, ataxia, eye squint, lacrimation, bradypnea, fasciculations, salivation, tachypnea, hypoactivity, ocular and nasal discharge, and hypersensitivity. Deaths occurred at 12.5 mg/L (nominal) and higher. Gross pathological findings included lung congestion at 12.5 mg/L (nominal) and higher. Thymic petechiation, corneal opacity and hyperemic nares were observed occasionally. The

B. ACUTE TOXICITY (cont.)

lowest-observed-effect level (LOEL) for this study was 6.25 mg/L (nominal: 1,000 mg/kg)¹ based on salivation, tachypnea, hypoactivity, ocular and nasal discharge, and hypersensitivity. A no-observed-effect level (NOEL) was not established in this study. Clinical signs were seen at all dosages when technical grade propetamphos was administered orally (Wazeter and Goldenthal, 1974). Death was observed at 79.4 mg/kg and higher. The signs seen at the LOEL, 50 mg/kg, were hypoactivity, diarrhea, tachypnea, excessive urination, flaccidity, ataxia, salivation, and nasal discharge. Necropsy findings at 79.4 mg/kg and higher were congested lungs, stomach mucosa petechiation, thymic petechiation, kidney petechiation and yellowish/brownish material in stomach. A NOEL was not established for this study. Clinical observations (including local effects) and necropsies were not performed in the only available acute dermal toxicity study for technical grade propetamphos (Wazeter and Goldenthal, 1974). Deaths were observed down to 632 mg/kg. The lowest dose tested was 200 mg/kg. Technical grade propetamphos caused mild skin irritation which included very slight erythema on abraded sites; the erythema was still present in some animals at 72 hrs (Wazeter and Goldenthal, 1974; Hamburger and Klotzsche, 1978a). The ocular responses to technical propetamphos varied from no irritation to slight irritation (Wazeter and Goldenthal, 1974; Hamburger and Klotzsche, 1978b). The slight irritation included slight redness and swelling of the conjunctiva that cleared by 48 hrs. No evidence of sensitization was found with technical grade propetamphos using guinea pigs (Hamburger and Klotzsche, 1980; Wilkinson and Singer, 1990).

The acute toxicity of the 18.9% propetamphos liquid concentrate is summarized in Table 2. The registrant submitted a study for a 50% emulsifiable concentrate formulation not currently registered in California in lieu of conducting an inhalation study for this formulation (Hoffman, 1992). The clinical signs observed after inhalation exposure to the 50% emulsifiable concentrate were similar to the technical grade material with the exception that labored breathing, irregular gait, limb impairment, reduced righting reflex, body weight loss, and corneal irregularity were also observed with the liquid concentrate (Hoffman, 1992). The clinical signs observed with acute oral exposure to the 18.9% liquid concentrate were similar to the technical grade material except that gasping, depression, bulging eyes, and coma were also observed with the liquid concentrate (Kreuzmann, 1990a). Necropsy findings with oral administration included pale, dark and/or mottled lungs and liver, and thin and transparent stomach and intestines. The clinical signs seen after acute dermal exposure to the 18.9% liquid concentrate included shallow/labored breathing, prostration, incoordination, tremors, hypothermia, depression, hypoactivity, hunched posture, piloerection, emaciation, dehydration, nasal and ocular discharge, salivation, loose, soft or mucoid feces, reduced feces, and muscle fasciculations, erythema, edema, and desquamation at the test site (Kreuzmann, 1990b; Rush, 1994). Necropsy findings with dermal administration included pale and mottled lungs and liver, bright red lungs, pale and congested kidneys, dark red foci/reddened thymus, reddish-brown and black foci in stomach mucosa, and stomach wall thickened (Kreuzmann, 1990b; Rush, 1994). Mild dermal irritation in the form of very slight erythema and edema was seen with the liquid concentrate which cleared by 48 hrs (Kreuzmann, 1990c). Mild ocular irritation in the form of conjunctival redness, swelling and discharge was observed with the liquid concentrate which cleared by day 1 (Kreuzman, 1990d). No evidence of sensitization was found with the liquid concentrate using guinea pigs (Kreuzmann, 1990e).

¹ Estimated assuming a rat breathes 40 L/kg/hr (Zielhuis and van der Kreek, 1979).

B. ACUTE TOXICITY (cont.)

Table 2. The Acute Toxicity of Propetamphos Liquid Concentrate (18.9%)

Species	Sex	Results	References ^a
Acute Inhalation LC₅₀			
Rat	M	1.20 mg formulation/L (4-hr, whole body)	1 ^{b*}
	F	0.67 mg formulation/L (4-hr, whole body)	
Acute Oral LD₅₀			
Rat	M	630 mg formulation/kg	2*
	F	392 mg formulation/kg	
Acute Dermal LD₅₀			
Rabbit	M/F	>2,100 mg formulation/kg	3
	M	3,499 mg formulation/kg	4*
	F	2,499 mg formulation/kg	
Primary Dermal Irritation			
Rabbit	M/F	Mild Irritation	5*
Primary Eye Irritation			
Rabbit	M/F	Mild Irritation	6*
Dermal Sensitization			
Guinea Pig	M/F	No Sensitization	7
^a References: 1. Hoffman, 1992; 2. Kreuzmann, 1990a; 3. Kreuzmann, 1990b; 4. Rush, 1994; 5. Kreuzmann, 1990c; 6. Kreuzmann, 1990d; 7. Kreuzmann, 1990e. ^b An inhalation LC ₅₀ study for a 50% propetamphos emulsifiable concentrate was submitted in lieu of a study for the 18.9% liquid concentrate. The LC ₅₀ value is expressed as an analytical concentration. * Acceptable study based on FIFRA guidelines.			

C. SUBCHRONIC TOXICITY

Summary

Nine subchronic toxicity studies (2 inhalation, 4 dietary, and 3 dermal) were available for propetamphos. However, interpretation of the findings from several of these studies (2 inhalation and 2 dermal studies) was difficult because a propetamphos emulsifiable concentrate was administered rather than the technical grade material. The adverse effects seen in the studies with the technical grade propetamphos were vomiting, diarrhea, tremors, reduced body weights and food consumption, and brain ChE inhibition. In general, DPR does not consider plasma and erythrocyte ChE inhibition in the absence of clinical signs or symptoms an adverse effect because the ChEs in blood have no known physiological function. However, plasma and erythrocyte ChE inhibition are considered an indication of exposure. Only statistically significant brain ChE inhibition was considered an adverse effect. The lowest NOEL was 0.09 mg/kg/day

C. SUBCHRONIC TOXICITY (cont.)

based on reduced brain ChE activity in male dogs (64% of controls). None of the subchronic studies met FIFRA guidelines.

Inhalation-Rat

Groups of 5 Spartan rats/sex/dose were exposed to propetamphos emulsifiable concentrate (purity not reported) in a mist at 0, 1, 3, or 6 mg/L (nominal; 0, 160, 480 or 960 mg/kg/day²) for 4 hours/day, 5 days/week for 2 weeks (Wazeter and Goldenthal, 1975b). Four rats (2 males and 2 females) at 3 mg/L and 6 rats (1 males and 5 females) at 6 mg/L died or were sacrificed *in extremis* during the study. Rats in all of the treatment groups exhibited various cholinergic signs including increased respiratory rate, dyspnea, salivation, lacrimation, fasciculations, flaccidity, ataxia, tremors, hypothermia, exophthalmos, ocular and nasal discharges, and soft stools. Rats had slight decreases in their mean body weights at 3 mg/L (M & F: 11%) and 6 mg/L (M: 13%) by the study termination. No effect on food consumption, hematology, and urinalysis were observed. Several male rats in the treatment groups had elevated serum aspartate aminotransferase activity. At study termination, the mean plasma ChE activity was reduced at 1 mg/L (M: 44%; F: 20% of controls), 3 mg/L (M: 33%; F: 17% of controls), and 6 mg/L (M: 33% of controls). The mean erythrocyte ChE activity was also reduced at 1 mg/L (M: 88%; F: 83% of controls), 3 mg/L (M: 75%; F: 78% of controls), and 6 mg/L (M: 71% of controls). Stomach hemorrhages and mucosal thickening at 3 and 6 mg/L were considered compound-related. Bone marrow hypoplasia in a few rats at 3 and 6 mg/L was also considered compound-related. A NOEL was not established for this study based on increased respiratory rate, salivation, lacrimation, nasal discharge, flaccidity, hypersensitivity, soft stools and fasciculations observed at 1 mg/L (160 mg/kg/day). This study had several major deficiencies including no analysis of the test article or chamber concentrations, an inadequate exposure duration, too few animals per group, an incomplete clinical chemistry analysis, no ophthalmological examination, and an incomplete histopathological examination.

In another inhalation study, 10 Sprague-Dawley rats/sex/dose were exposed to a propetamphos emulsifiable concentrate (50%) in a mist at 0, 53, 97, 304, or 1,009 µg/L (actual; 0, 8.5, 15.5, 48.6 or 161.4 mg/kg/day³) for 4 hours/day, 5 days/week for 2 weeks (Leuschner *et al.*, 1978). Due to the high mortality rate in rats at 1,009 µg/L, animals at this dose level exposure were terminated at day 7. At 304 µg/L, 12 animals died (7 males and 5 females) between the 3rd and 11th day of the study. No deaths occurred at 53 and 97 µg/L. Clinical signs (exophthalmus, ataxia, piloerection, apathy, and prostration) were observed at 97 µg/L and higher. At study termination, the mean body weights were also reduced at 97 µg/L (M: 4%; F: 7%) and 304 µg/L (M: 28%; F: 29%). Food consumption was reduced only at 1,009 µg/L. By study termination, several hematological changes were observed in both sexes at 304 µg/L, including a reduction in RBC count, hematocrit, hemoglobin, and lymphocytes and an increase in immature neutrophils. The number of leukocytes was reduced in both sexes at 97 and 304 µg/L. Several serum clinical chemistry changes were observed in both sexes at 97 and 304 µg/L, including an elevation of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and alkaline phosphatase, and a reduction of glucose. Similar trends were observed at 1,009 µg/L, although statistical analysis was not possible due to the high mortality rate. No

² Estimated assuming a rat breathes 40 L/kg/hr (Zielhuis and van der Kreek, 1979).

³ *ibid.*

C. SUBCHRONIC TOXICITY (cont.)

significant sex-related difference in response was seen with either the hematological or clinical chemistry changes. At termination, the mean serum ChE levels were reduced at 53 µg/L (M: 57%; F: 56% of controls), 97 µg/L (M: 38%; F: 24% of controls), and 304 µg/L (M: 35%; F: 21% of controls). A slight reduction in the mean erythrocyte ChE activity (86% of control activity) was also observed in males at 304 µg/L, but the difference was not statistically significant. The specific gravity in the urine of both sexes was significantly increased at the 304 µg/L. An increased incidence of hemorrhagic erosions of the stomach was observed macroscopically in surviving rats of both sexes at 97 and 304 µg/L. Pulmonary congestion was observed in the rats that died. Absolute organ weights were reduced for liver, heart, lungs, spleen, adrenal glands, thymus, and gonads in both sexes at 304 and 1,009 µg/L, presumably due to reduced body weights since the relative weights for these organs were not reduced. The NOEL was 53 µg/L (8.5 mg/kg/day) based on exophthalmus, ataxia, piloerection, apathy, reduced body weights, clinical chemistry changes, and hemorrhagic erosion of the stomach. This study had several major deficiencies including no analysis of the test article, no particle size analysis, an inadequate exposure duration, an inadequate clinical chemistry analysis, and no ophthalmological examination.

Dietary-Mouse

In a 4-week study, 20 CD-1 mice/sex/dose were fed propetamphos (91.8%) in the diet at 0.05, 0.1, or 0.5 mg/kg/day (Machi *et al.*, 1979). Four mortalities occurred during the study at 0.1 and 0.5 mg/kg/day (2 at each dose level). No clinical signs were observed in any animals including the four that died. The mean body weights in males were significantly lower at 0.05, 0.1 and 0.5 mg/kg/day on days 21 (12%, 18%, and 12%, respectively) and 26 (11%, 18%, and 10%, respectively). There was no significant difference in the female body weights at any time. The administration of propetamphos did not affect food consumption significantly, although the high-dose females had consistently lower food consumption (13-16%). Plasma and erythrocyte ChE levels were not significantly different from the controls at any dose level. Liver ChE levels were significantly lower (74% of control activity) in females at 0.1 mg/kg/day. Brain ChE levels were significantly lower at 0.1 mg/kg/day (M: 87%; F: 72% of controls) and 0.5 mg/kg/day (M: 78%; F: 74% of controls). No gross pathological anomalies attributable to the administration of propetamphos were observed. The NOEL for females was 0.05 mg/kg/day based on the deaths and reduced brain ChE activity (72% of controls). The NOEL for males appears to be less than 0.05 mg/kg/day based on the weight loss (12%). This study had major deficiencies including an inadequate exposure duration, an inadequate clinical chemistry analysis, no hematological analysis, and no ophthalmological or histopathological examination.

Groups of 8 CD-1 mice/sex/dose were fed propetamphos (91.4%) in the diet at 1, 7, 15, 28, or 59 mg/kg/day for 8 weeks (Bagdon *et al.*, 1978). The highest dose was increased to 103 mg/kg/day for weeks 6 and 7 and to 172 mg/kg/day during week 8. One male and 1 female died in the high-dose group when the propetamphos in the diet was increased to 172 mg/kg/day. Weakness, decreased locomotor activity, and/or pallor were observed in the high-dose male that died and in one high-dose female that survived. The animals at the high dose had significantly reduced mean body weights (M:15-36%; F: 14-25%) throughout the 8-week study. The mean body weights in the 28 mg/kg/day group were significantly reduced during weeks 1-6 for the males (12-24%) and during weeks 3-5 for the females (10-13%). Food consumption was not affected by the administration of propetamphos, except in the high-dose group where it was reduced in both sexes (M: 19-22%; F: 17-41%) when the dose level was increased to 103-172 mg/kg/day (weeks 6-8). At week 7, the mean plasma ChE activity was

C. SUBCHRONIC TOXICITY (cont.)

significantly reduced at 1 mg/kg/day (M: 55%; F: 71% of controls), 7 mg/kg/day (M: 21%; F: 26% of controls), 15 mg/kg/day (M: 13%; F: 14% of controls), 28 mg/kg/day (M & F: 10% of controls), and 59 mg/kg/day (M & F: 7% of controls). The mean erythrocyte ChE activity was also significantly reduced at 1 mg/kg/day (F: 55% of controls), 7 mg/kg/day (M: 38%; F: 54% of controls), 15 mg/kg/day (M & F: 20% of controls), 28 mg/kg/day (M: 17%; F: 12% of controls), and 59 mg/kg/day (M: 8%; F: 7% of controls). At week 8, the mean liver ChE activities were significantly lower at 1 mg/kg/day (M: 71% of controls), 7 mg/kg/day (M: 66%; F: 86% of controls), 15 mg/kg/day (M: 56%; F: 66% of controls), 28 mg/kg/day (M: 51%; F: 67% of controls), and 59 mg/kg/day (M: 19%; F: 14% of controls). The mean brain ChE activity was significantly reduced at 7 mg/kg/day (M: 72%; F: 59% of controls), 15 mg/kg/day (M: 46%; F: 49% of controls), 28 mg/kg/day (M & F: 31% of controls), and 59 mg/kg/day (M: 19%; F: 11%). No necropsies were performed on these animals. The NOEL was 1 mg/kg/day based on the reduced brain ChE activity (M: 72%; F: 59% of controls). This study also had major deficiencies including an inadequate exposure duration, an inadequate clinical chemistry analysis, no hematological analysis, no ophthalmological or histopathological examination, and no individual animal data.

Dietary-Dog

Four Beagle dogs/sex/dose were fed propetamphos (91.8%) in the diet at 0, 6, 12, or 24 ppm (M: 0, 89, 176 or 692 µg/kg/day; F: 0, 83, 165 or 702 µg/kg/day) for 6 months (Hamburger *et al.*, 1979). After 6 weeks the low and mid-doses were dropped to 2 and 4 ppm, respectively, since blood ChE inhibition was greater than 20%. None of the animals exhibited any signs of toxicity nor was there any treatment related effect on body weight gain, food and water consumption. No toxicologically significant differences in the hematology, urinalysis, ophthalmoscopy, and necropsy were found. No treatment-related differences in clinical chemistry values were noted, except ChE activity. At week 26, the mean plasma ChE activity was reduced significantly at 24 ppm (M: 60%; F: 61% of controls). The mean erythrocyte ChE activity was also reduced at 24 ppm (M: 37%; F: 50% of controls). The mean liver ChE activity (acetyl and butyryl combined) was significantly reduced in males at 24 ppm (40% of controls) and in females at 12-4 ppm (63% of controls) and 24 ppm (30% of controls). Brain cortical ChE activity was significantly reduced in males at 12-4 ppm (64% of controls) and 24 ppm (58% of controls) and in females at 24 ppm (35% of controls). Cerebellar ChE activity was not affected. The NOEL was 6-2 ppm (89 µg/kg/day) based on the reduced cortical ChE activity in males (64% of controls). This study had a few major deficiencies including changes in dose levels during the study and no analysis of the dosing material.

Two beagle dogs/sex were assigned to two groups (Allen *et al.*, 1989). The dogs in group 1 were fed a control diet on days 1-38 of the study and then a diet containing propetamphos (90.8%) at 100 ppm (3.97 mg/kg/day) on days 39 to 68. Group 2 dogs were administered propetamphos in the diet at 4, 30, 60, 120, and 180 ppm (0.17, 1.25, 2.39, 5.22 and 5.03 mg/kg/day) on days 1-10, 11-14, 15-21, 22-28, and 29-58, respectively. One male dog from group 2 was fed only the control diet after day 46. There were no deaths. A possible treatment-related effect was vomiting observed at 30 ppm and higher. Diarrhea was observed at 120 and 180 ppm. Tremors, deep respiration and salivation were observed at 180 ppm. The food consumption was reduced (M: ~50-75%; F: 30-70%) at 180 ppm. The body weights were reduced at 120 and 180 ppm (M: ~10%; F: ~30%). A reduction in the plasma ChE activity (M: 25-79%; F: 10-72% of baseline) was measured at 30 ppm and higher. The erythrocyte ChE activity was also reduced at 30 ppm and higher (M: 11-86%; F: 8-94% of baseline).

C. SUBCHRONIC TOXICITY (cont.)

Interpretation of the brain ChE activity is confounded by the study design since there were no dogs assigned to study that were untreated before they were sacrificed. Clinical chemistry for one treated female revealed increases in aspartate aminotransferase, alanine aminotransferase, glutamate dehydrogenase, alkaline phosphatase, gamma glutamyltransferase, blood urea, creatinine, bilirubin, total lipids, cholesterol, phospholipids, and magnesium values. Decreases in albumin, calcium, and chloride were also seen. The investigators suggested these changes were indicative of hepatotoxicity and other metabolic disturbances. Reduced prostate weight and testes weight were observed in several males. Because of frequent changes in the dosage for treated animals, a NOEL could not be established in this study. This study had major deficiencies including no concurrent control group, frequent dosage changes, an inadequate number of animals, an incomplete clinical chemistry analysis, no hematological analysis, no ophthalmological examination, and no histopathological examination.

Dermal-Rabbit

In a 3-week dermal study, groups of 4 New Zealand White rabbits/sex/dose were exposed dermally to an undiluted propetamphos emulsifiable concentrate (purity not reported) at 0, 20, 60, or 180 mg/kg/day for 6 hrs/day, 5 days/wk (Wazeter and Goldenthal, 1975a). Ataxia, fasciculations, dyspnea, respiratory congestion, prostration, cyanosis, convulsions, cachexia, flaccidity, and vocalization were observed at 20 mg/kg/day or above. All but one rabbit at 60 and 180 mg/kg/day died during the study. Dermal irritation also was observed including erythema, edema, atonia, desquamation, coriaceousness, and fissuring in all treatment groups. No treatment-related differences in body weights, hematology, clinical chemistry, and urinalysis values were noted. At day 21, the mean plasma and erythrocyte ChE activity for both sexes combined were reduced at 20 mg/kg/day (45% and 52% of controls, respectively). Gastrointestinal irritation and pneumonia were observed in the animals that died. Other than dermal irritation no treatment-related gross observations or changes in organ weights were seen in the survivors. Microscopic lesions including acanthosis, hyperkeratosis, dermal inflammation, thymic hypoplasia/involution, skeletal muscle fiber degeneration, and pneumonia were observed in animals at 20 mg/kg/day and higher. The NOEL was less than 20 mg/kg/day based on the dermal irritation, cholinergic signs and microscopic lesions in the skin, thymus, skeletal muscle and lungs. This study had several major deficiencies including no analysis of the test article or dosing material, an inadequate number of animals per group, an inadequate clinical chemistry analysis, and no individual animal data for dermal or clinical observations.

Four New Zealand White rabbits/sex/dose were exposed dermally to technical grade propetamphos (purity not reported) at 0.0, 0.5, 2.5 or 5.0 mg/kg/day for 6 hrs/day, 5 days/wk for 3 weeks (Wazeter and Goldenthal, 1976a). Fifty percent of the control animals had water applied to the application site while the other 50% had corn oil applied. Propetamphos was diluted in corn oil in the treatment groups. Pustule formation, erythema, edema, scabbing, and coriaceousness were observed in all the groups receiving corn oil, including the controls. In addition, treatment-related dermal irritation was observed in the form of atonia, desquamation, and occasional fissuring, blanching or bleeding at 0.5 mg/kg/day or higher. By study termination, the mean body weights were reduced at 2.5 mg/kg/day (F: 10%) and 5.0 mg/kg/day (M: 9%; F: 8%). The mean percentage of neutrophils was significantly increased and the mean percentage of lymphocytes was significantly decreased at all dose levels. The toxicological significance of these hematological changes is uncertain. No significant

C. SUBCHRONIC TOXICITY (cont.)

differences were observed in the other hematology, clinical chemistry and urinalysis values. The mean erythrocyte ChE activity of both sexes combined was reduced (89%, 75%, and 69% of controls) at 0.5, 2.5 and 5.0 mg/kg/day, respectively. Reductions in the mean plasma ChE activities were most pronounced on day 18 (70%, 67% and 54% of controls) at 0.5, 2.5 and 5.0 mg/kg/day, respectively. No treatment-related gross lesions or organ weight differences were noted. The death of one rabbit at the 2.5 mg/kg/day level on day 21 was attributed to complications in the collection of blood. Histopathological evidence of dermal irritation, characterized by acanthosis, hyperkeratosis and dermal inflammatory infiltrate, was observed in both the treated and control animals which the investigators attributed to the corn oil vehicle. Because of the possible contribution of the vehicle to the dermal irritation, it was uncertain if any of the skin lesions were treatment-related. The NOEL was 0.5 mg/kg/day based on the reduced body weights in females (10%) at 2.5 mg/kg/day. This study had several major deficiencies including no analysis of the test article or dosing material, an inadequate number of animals per group, an inadequate clinical chemistry analysis, and no individual animal data for dermal or clinical observations.

The propetamphos emulsifiable concentrate (purity not reported) used in a third 3-week dermal study in rabbits was diluted with water so that a constant volume was applied at 0, 1, 5, or 10 mg/kg/day (Wazeter and Goldenthal, 1976b). As in the previous studies, 4 New Zealand White rabbits/sex/dose were exposed for 6 hrs/day, 5 days/wk. Unlike the previous studies, no compound-related dermal irritation or clinical signs were observed. Nor were any differences in body weights, hematology, clinical chemistry or urinalysis noted. At day 21, the mean plasma ChE activity of both sexes combined was reduced (83% and 70% of controls) at 5 and 10 mg/kg/day, respectively. The mean erythrocyte ChE activity of both sexes was also reduced (83% and 66% of controls) at 5 and 10 mg/kg/day, respectively. No treatment-related gross lesions or variations in organ weights were observed. Several microscopic lesions (intratubular giant cells in the testes and inflammatory cell infiltrate in the lymph nodes draining the application site) observed at 5 and 10 mg/kg/day may have been compound-related. The NOEL was 1 mg/kg/day based on the intratubular giant cells in the testes, and inflammatory cell infiltrate in the lymph nodes. This study also had major deficiencies including no analysis of the test article or dosing material, an inadequate number of animals per group, an inadequate clinical chemistry analysis, and no individual animal data for dermal or clinical observations.

D. CHRONIC TOXICITY/ONCOGENICITY

Summary

Three chronic toxicity and/or oncogenicity studies with rats, mice and dogs were available in which propetamphos was administered in the feed. The adverse effects seen included death, weak limbs, hyperreflexia, vomiting, diarrhea, prolonged anestrus (female dogs), hematological changes indicative of anemia, serum chemistry changes indicative of hepatotoxicity, brain ChE inhibition, increased liver weights, thickened mucosa of the small intestine, and hepatic necrosis. The lowest NOEL was 0.59 mg/kg/day based on death, diarrhea, vomiting, prolonged anestrus, hematological and clinical chemistry changes, brain ChE inhibition, increased liver weights, thickened mucosa of the small intestine, and hepatic necrosis in dogs. All three studies met Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines.

D. CHRONIC TOXICITY/ONCOGENICITY (cont.)

Dietary-Rat

In a two-year combined chronic toxicity and oncogenicity study, 55 OFA (Sprague-Dawley strain) rats/sex/dose were fed diets containing propetamphos (91.8%) at 0, 6, 12, or 120 ppm (M: 0, 0.38, 0.63, or 5.89 mg/kg/day; F: 0, 0.41, 0.69 or 7.60 mg/kg/day) (Luginbuhl *et al.*, 1981). Due to the high mortality rate in the males (primarily in the control and mid-dose groups), all surviving males were sacrificed on week 91. The higher mortality rate in the males may have been related to the pronounced nephropathies that were observed in the males at necropsy. The surviving females were not sacrificed until week 108. The mortality rates were significantly lower in both sexes at 120 ppm. Clinical signs were observed at 120 ppm only and included erythema and alopecia on the abdomen, weak limbs and hyperreflexia. There were no significant differences in body weight gain or food consumption. No consistent dose-related differences in hematology, clinical chemistry, and urinalysis values were observed. At the study termination, the mean plasma ChE activity was significantly reduced at 12 ppm (F: 77% of controls) and 120 ppm (M: 51%; F: 48% of controls). The reduction in the mean erythrocyte ChE activity was significant at 12 ppm (M & F: 86% of controls) and 120 ppm (M: 61%; F: 68% of controls). A reduction in the mean brain ChE activity also was observed at 120 ppm (M: 66%; F: 64% of controls). No treatment-related changes in organ weights or in macroscopic observations were found. There was an increase in pancreatic islet cell adenomas in females at all dose levels when compared to controls (0/27, 3/21, 3/24 and 4/40 of females at risk at 0, 6, 12, and 120 ppm, respectively). However, the increase was only significant by pair-wise comparison at 6 and 12 ppm and there was no significant trend. Although the incidence in the treatment groups was higher than the concurrent controls, the incidence was similar to the historical control data. The incidence in historical controls for this strain of rat from the conducting laboratory between 1976 to 1980 ranged from 1 to 3 in approximately 50 rats (U.S. EPA, 1998b). In addition, the tumors occurred late in the study (first tumor seen at week 100). Furthermore, there was no increase in these tumors in males. An increased incidence of focal hyperplasia of pancreatic exocrine tissue, a common lesion in older rats according to the study pathologist, was seen at 120 ppm in both sexes (M: 7/55; F: 4/55) compared to controls (M: 1/55; F: 1/55). The increased incidence was probably related to the increased survival of both sexes at 120 ppm. The NOEL was 12 ppm (0.63 mg/kg/day) based on the dermal irritation, weak limbs, hyperreflexia, and reduced brain ChE activity (M: 66%; F: 64% of controls). The study was considered acceptable by DPR.

Dietary-Mouse

Groups of 80 CD-1 mice/sex/dose were fed propetamphos (91.8%) at 0, 0.05, 1, 6, or 21 mg/kg/day for 93 weeks, with the exception that the 0.05 and 6 mg/kg/day groups had only 10 and 70 mice/sex, respectively (LeQuire *et al.*, 1981). There was no compound-related effect on mortality or survival. No overt signs of toxicity were observed in any of the dose groups. There were no significant changes in body weight gain. A significant reduction in the mean food consumption up to 19%, 36%, and 44% in males and up to 26%, 26% and 41% in females was observed intermittently at 1, 6, and 21 mg/kg/day, respectively. The decreased food consumption appears to be due to problems with the palatability of the test compound at higher doses. There were no consistent dose-related changes in hematology and clinical chemistry values. There were significant reductions in ChE activity in the plasma, erythrocyte, liver, and brain in the three highest dose groups. At termination, the mean plasma ChE activity was reduced at 1 mg/kg/day (M: 56%; F: 84% of controls), 6 mg/kg/day (M: 22%; F: 45% of controls), and 21 mg/kg/day (M: 13%; F: 16% of controls). The mean erythrocyte ChE activity

D. CHRONIC TOXICITY/ONCOGENICITY (cont.)

was also reduced at 1 mg/kg/day (M: 75%; F: 77% of controls), 6 mg/kg/day (M: 23%; F: 65% of controls), and 21 mg/kg/day (M: 17%; F: 49% of controls) at termination. The mean liver ChE was significantly reduced only at 6 mg/kg/day (M: 73%; F: 58% of controls) and 21 mg/kg/day (M: 16%; F: 41% of controls). The mean brain ChE levels were reduced at 1 mg/kg/day (M: 87%; F: 94% of controls), 6 mg/kg/day (M: 51%; F: 45% of controls), and 21 mg/kg/day (M: 24%; F: 21% of controls). The reduction in brain ChE activity at 1 mg/kg/day was not considered toxicologically significant because it was very slight (M: 87%; F: 94% of controls) and there were no overt signs of toxicity even at 21 mg/kg/day. No compound-related variations in organ weights or gross pathological findings were observed. Nor were there any compound-related changes in the incidence of neoplasms or other histological findings. The NOEL was 1 mg/kg/day based on the reduced mean brain ChE activity (M: 51%; F: 45% of controls). DPR considered this study acceptable.

Dietary-Dog

Propetamphos (90.8% purity) was fed to 4 beagle dogs/sex/dose in the diet at 0, 4, 20 or 100 ppm (M: 0, 0.13, 0.59 or 3.03 mg/kg/day; F: 0, 0.14, 0.67 or 3.39 mg/kg/day) for 52 weeks (Allen *et al.*, 1991). One male at 100 ppm was sacrificed *in extremis* during week 33 of the study. From weeks 27 to 33, this male had a rapid body weight loss. The dog had pale mucous membranes the week before it was sacrificed and dark, liquid feces on the day it was sacrificed. Diarrhea and vomiting were observed in several animals at 100 ppm (Table 7). The frequency of these signs indicated a dose-response relationship, although the number of animals per group did not necessarily suggest a dose-response relationship. Two females at 100 ppm did not exhibit signs of estrous during the entire year while most other females had one or two cycles during this time (Table 7). Furthermore, the two females at 100 ppm which did exhibit estrous signs usually exhibited them later in the study than the females in the other groups. The mean food consumption was reduced in one or both sexes at 100 ppm from weeks 1 through 13. The reduction was most pronounced in males during week 4 (33%) and in females during week 10 (17%). There was no effect on body weights, ophthalmological findings or urinalysis.

Males at 100 ppm had significantly lower mean RBC counts (17% wk 13, 12% wk 26), hemoglobin (15% wk 13, 17% wk 26), and hematocrit values (13% wk 13, 16% wk 26), and higher mean corpuscular volumes (3% wk 13), reticulocyte counts (100% wk 26, 71% wk 51), and platelet counts (45% wk 51) than controls. A similar pattern was observed in the females at 100 ppm, although the differences were not statistically significant except for an increase in reticulocyte counts (200% wk 26). DPR considered these hematological changes toxicologically significant since they were indicative of anemia. Marked increases in several serum enzymes were seen in two males at 100 ppm, including aspartate aminotransferase, alanine aminotransferase, glutamate dehydrogenase, alkaline phosphatase, γ -glutamyl transferase, and ornithine carbamoyl transferase. At week 13, these serum enzymes were elevated in the dog that was sacrificed. At week 26, a different male dog had elevated serum enzymes. Despite the large increases in these individual dogs, the group means were not significantly different from controls at any time point examined. DPR considered the changes in these serum enzymes to be toxicologically significant because they were indicative of hepatotoxicity. Significantly lower mean total protein (11% wk 4, 13% wk 13 & 26) and albumin (8% wk 4, 14% wk 13) levels were found in males at 100 ppm. The mean plasma ChE activity was reduced at 20 ppm (M: 61%; F: 89% of controls) and 100 ppm (M: 38%; F: 51% of controls). The mean erythrocyte ChE activity was also reduced at 20 ppm (M: 55%; F: 71% of

D. CHRONIC TOXICITY/ONCOGENICITY (cont.)

Table 7. Treatment-Related Effects in Dogs Fed Propetamphos in the Diet for 1 Year^a

	Dose Level (ppm)			
	0	4	20	100
MALES				
Vomiting (occurrences per animal)	0.3±0.5 ^{++b} (1/4 ^c)	0.3±0.5 (1/4)	1.8±2.9 (2/4)	4.3±2.5* (4/4)
Diarrhea (occurrences per animal)	2.8±3.6 ⁺⁺⁺ (3/4)	0.3±0.5 (1/4)	4.8±5.3 (3/4)	90±60 ^{**} (4/4)
Brain ChE activity (µmol-SH/g/min)	4.42±0.31	4.55±0.38	4.60±0.53	3.49±0.33*
Liver weight (g)	277±16	293±15	343±31*	390±47 ^{**}
Thickened mucosa of small intestine	0/4 ⁺⁺⁺	0/4	0/4	4/4*
Hepatic necrosis	0/4 ⁺⁺	0/4	0/4	2/4
FEMALES				
Vomiting (occurrences per animal)	0.3±0.5 ^{++b} (1/4 ^c)	0.0±0.0 (0/4)	0.0±0.0 (0/4)	14.5±9.8 ^{**} (4/4)
Diarrhea (occurrences per animal)	66±132 (1/4)	1.0±0.8 (3/4)	1.3±1.0 (3/4)	52±44 (4/4)
Estrous cycles (cycles per animal)	2.0±0.8 ⁺⁺ (4/4)	1.8±0.5 (4/4)	1.8±0.5 (4/4)	0.5±0.6* (2/4)
Brain ChE activity (µmol-SH/g/min)	4.31±0.51	4.98±0.55	5.06±0.50	3.53±0.42
Thickened mucosa of small intestine	0/4 ⁺⁺⁺	0/4	0/4	3/4
^a	Allen <i>et al.</i> , 1991			
^b	Mean±S.D. of occurrences of this sign per animal during the study.			
^c	Number of dogs per group that exhibited this sign at any time during the study.			
⁺⁺ , ⁺⁺⁺	For the clinical signs, a significant trend was found based on orthogonal polynomial regression analysis at p < 0.01 and P < 0.001, respectively. For lesions, a significant trend was found based on the Cochran-Armitage trend test at p < 0.01 and 0.001, respectively (Gart <i>et al.</i> , 1986).			
[*] , ^{**}	For continuous data, the mean is significantly different from the control group based on the Dunnett's test at p < 0.05 and 0.01, respectively. For quantal data, the incidence is significantly different from the control group based on the Fisher's exact test at p < 0.05 and 0.01, respectively.			

controls) and 100 ppm (M: 20%; F: 25% of controls). The reduction in the mean brain ChE activity was only statistically significant at 100 ppm in males (79% of control activity); however, the reduction in females at 100 ppm (82% of controls) was considered toxicologically significant.

The mean liver weights were significantly higher in males at 20 ppm (24%) and 100 ppm (41%). The toxicological significance of the increased liver weights is uncertain since the male dog with the highest liver weight at 100 ppm was not one of the two dogs with elevated liver enzymes and hepatic necrosis. In fact, the dog that had the most severe hepatic necrosis and

D. CHRONIC TOXICITY/ONCOGENICITY (cont.)

later sacrificed *in extremis* was noted to have a liver that was reduced in size during gross pathological examination (organ weights were not reported for this dog). This is not surprising since one would expect that the liver weight would decrease if cells are dying. At 20 ppm, the liver enzyme levels in the serum were not elevated, despite elevated liver weights. DPR considered the possibility that the increased liver weights were due to fatty liver disease or inflammation. Focal inflammation of the liver was observed in all groups, including the control group; however, the incidence was lowest at 100 ppm. There was no evidence of fatty liver either from histopathological examination or in the clinical chemistry values (i.e., cholesterol, total lipids, triglycerides). The most probable explanation for the increased liver weights is microsomal enzyme induction. There was no evidence of liver hypertrophy to confirm this possibility; however, liver hypertrophy was not observed until liver weight increases were greater than 20% in rats (Amacher et al., 1998). Furthermore, there was no correlation between the magnitude of the liver weight increase or the hypertrophy grade with the magnitude of enzyme induction in rats. Without any evidence correlating the increased liver weights in dogs to adverse pathological changes, DPR assumed this increase in liver weights was due to microsomal enzyme induction. Although microsomal enzyme induction is a treatment-related effect, DPR considers it is an adaptive response, not an adverse effect. The testes weights were increased in males at 100 ppm, but it was not considered toxicologically significant in absence of any pathological findings in the testes.

The primary treatment-related macroscopic lesion was thickened mucosa of the small intestine that was observed in both sexes at 100 ppm. The dog that was sacrificed also had dark intestinal contents, enlarged lymph nodes, a small liver with irregular surfaces, ascites and dry sternal bone marrow. Hepatic necrosis was observed microscopically in two males at 100 ppm (including the dog that was sacrificed). These two males were the same males that had elevated serum enzymes levels at weeks 13 or 26. Microscopic lesions in the dog that was sacrificed also included a large gastric ulcer, serous atrophy of fatty tissue, lymphoid depletion with histiocytosis in several lymph nodes and atrophy of the bone marrow. The study pathologist concluded these findings were “non-specific and due to the poor general condition of the animal. Nevertheless, the condition of the animal may be treatment-related.” The chronic NOEL for this study was 20 ppm (0.59 mg/kg/day) based on the diarrhea, vomiting, prolonged anestrus in females, reduced brain ChE activity (M: 79%; F: 82% of controls), increased liver weights, thickened mucosa of the small intestine, and hepatic necrosis observed at 100 ppm (3.03 mg/kg/day). This study was considered acceptable by DPR.

E. GENOTOXICITY

Summary

Seven genetic toxicity studies for propetamphos were available of which one *in vivo* study for chromosomal aberrations in mice was positive. Only three of these studies met FIFRA guidelines including an Ames assay, an *in vivo* cytogenetics assay in rats, and an unscheduled DNA synthesis assay in primary rat hepatocytes.

Gene Mutation

Technical grade propetamphos (91.8%) did not induce an increase in the reverse mutation rate in the Ames assay when tested at 0, 0.1, 0.3, 1.0, 3.1, or 10 µl/plate using

E. GENOTOXICITY (cont.)

Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 (Haworth *et al.*, 1980). Triplicate plates were used at each dose level with and without activation. DPR considered this study acceptable.

No increase in the reverse mutation rate of *Saccharomyces cerevisiae* strains S138 and S211 with and without activation was observed when exposed to propetamphos (purity no stated) at 0, 0.5, 1.0, 10.0, 25.0, 50.0, 75.0, 100.0, or 150.0 µl/1.5 ml per well (Jagannath and Brusick, 1981). This study was not acceptable to DPR because of insufficient information regarding the test article characterization, no evidence of cytotoxicity at the high dose, and the positive controls were ineffective in either strain with activation.

No significant increase in the frequency of sex-linked recessive lethals or translocations was seen in adult male *Drosophila melanogaster* fed propetamphos (purity not reported) in a 5% sucrose solution at 0, 2, 3, or 4 ppm for 6 hours and then mated with tester females (Kumari and Krishnamurthy, 1986). There was also no significant increase in the frequency of sex-linked recessive lethals or translocations in larvae fed propetamphos at 0, 0.04, 0.05 or 0.06 ppm and then mated with tester females. This study had several major deficiencies including no analysis of test article, number of flies tested not reported, no positive controls and no individual data.

Chromosome Aberration

In an *in vivo* micronucleus assay, 4 CD-1 mice/sex/dose were administered propetamphos (91.8%) twice 24 hours apart at 0, 0.0009, or 0.009 mg/kg by oral gavage (Matheson and Brusick, 1978). The mice were sacrificed 6 hours after the last dose. No increase in the number of micronuclei was observed. This study was not acceptable to DPR due to the lack of a maximum tolerated dose and only a single sacrifice time.

In an *in vivo* cytogenetics assay, 4-5 Sprague-Dawley CD® rats/sex were administered propetamphos (90.3%) intraperitoneally at 0 (corn oil) or 58 mg/kg and sacrificed at 6, 24, and 48 hrs (Marshall, 1990). Fifty metaphases/animal were examined for chromosomal aberrations. There was no significant increase in the incidence of the chromosomal aberrations when compared to concurrent controls. Aberration frequencies were also within the historical vehicle control range at all sampling times. This study was found acceptable to DPR.

Propetamphos (purity not reported) was administered to Swiss albino mice (number per dose not reported) at 0, 32, 64 or 80 mg/kg (Kumari and Krishnamurthy, 1986). Mice administered two doses 24 hours apart and sacrificed 6 hours later had a slight increase in micronucleated erythrocytes at 80 mg/kg. Mice administered propetamphos for two days and sacrificed 31 days after the first dose also had a slight increase in chromosomal aberrations at 80 mg/kg. Male mice administered propetamphos for 5 days and sacrificed 35 days after the initial dose had slight increase in abnormal sperm heads at 80 mg/kg. This study had major deficiencies including no analysis of test article, number of animals tested not reported, no positive controls and no individual data.

E. GENOTOXICITY (cont.)

DNA Damage

No increase in unscheduled DNA synthesis was observed in primary rat hepatocytes exposed to propetamphos (91.8%) at 0, 0.25, 0.5, 1.0, 10.0, 25.0, 50.0, or 100 nl/ml for 18 hrs (Myhr and Brusick, 1981). This study was acceptable to DPR.

F. REPRODUCTIVE TOXICITY

Summary

Four reproductive toxicity studies in rats were available for propetamphos; however, only one study met FIFRA guidelines. Exposure involved one, two or three generations. Adverse reproductive effects were observed in two studies, including reduced mating index, reduced litter size, reduced number of implantation sites, increased pup mortality, and decreased pup body weights. The lowest reproductive NOEL was 2.1 mg/kg/day based on these reproductive effects in a two-generation study. Other general adverse effects included tremors, hyperreflexia, exophthalmos, reduced body weights and food consumption, and brain ChE inhibition. The lowest parental NOEL was 0.3 mg/kg/day based on reduced body weights in females and brain ChE inhibition.

Dietary-Rat

A reproductive toxicity study was conducted which consisted of 3 different tests: a fertility/early gestation exposure test, a teratogenicity test, and a late gestation/postnatal exposure test (Nakashima *et al.*, 1980). In all three tests, approximately 25 JCL-SD rats/sex/dose were administered propetamphos (92%) by oral gavage in olive oil at 0, 0.125, 0.5 or 2 mg/kg/day. In the first test, males and females were exposed for 9 and 2 weeks, respectively, prior to and during mating. The females continued to receive propetamphos until day 7 of gestation. In the teratology test, pregnant females were exposed from day 7 to 17 of gestation. In the third test, dams were exposed from day 17 of gestation to day 21 of lactation. No adverse effects were observed in any of the three tests. However, DPR found this study unacceptable due to the design of the study and the lack of evidence that a maximum tolerated dose was used.

No adverse effects on reproduction or survival of offspring were observed in a 3-generation, 2-litter reproductive toxicity study (Eschbach and Klotzsche, 1981a). In this study groups of 35 Sprague-Dawley rats/sex/dose were fed propetamphos (91.8%) in the diet at 0, 5, 10 or 20 ppm (0, 0.25, 0.5 or 1.0 mg/kg/day)⁴. Adults received the diet for 100 or 120 days before mating. The reproductive NOEL was greater than 20 ppm (1 mg/kg/day), the highest dose tested. The study was not acceptable to DPR due to the lack of clear parental toxicity at the highest dose tested.

A one-generation pilot reproduction study was conducted in which 7 Wistar Crl:(WI) br rats/sex/dose were fed propetamphos (90.3%) in the diet at 0, 6, 30, 120, or 180 ppm (M: 0,

⁴ Based on a default assumption that an older rat weighing 400 g consumes 20 g of feed per day (FDA, 1959).

F. REPRODUCTIVE TOXICITY (cont.)

0.5, 2.2, 10.0 or 16.8 mg/kg/day; F: 0.7, 3.5, 13.9 or 19.1 mg/kg/day) (Eschbach *et al.*, 1991a). One female at 180 ppm was sacrificed *in extremis* due to a prolapsed uterus. It is unclear if this was treatment-related. Cholinergic signs, primarily tremors, hyperreflexia, and exophthalmos, were observed at 120 and 180 ppm. Body weights were reduced during pre-mating at 30, 120 and 180 ppm (F: 13%, M & F: 11%, and M & F: 26-46%, respectively). Reduced body weight gains continued through gestation, except at 120 ppm. Reduced food consumption (9-38%) was also observed in females at 120 ppm and in both sexes at 180 ppm during the first two weeks of the pre-mating period. A high incidence of postnatal mortality, decreased pup weight gain and reduced number of males among the live births was observed at 120 and 180 ppm. A slight reduction in the fertility index (71%) was also observed at 180 ppm. At sacrifice, the mean plasma ChE activity was significantly reduced at 6 ppm (F: 63% of controls), 30 ppm (M: 46%; F: 27% of controls), 120 ppm (M: 22%; F: 12% of controls) and 180 ppm (M: 23%; F: 5% of controls). The mean erythrocyte ChE activity was also reduced at 6 ppm (F: 67% of controls), 30 ppm (M: 66%; F: 45% of controls), 120 ppm (M: 34%; F: 35% of controls), and 180 ppm (M: 27%; F: 31% of controls). The mean brain ChE activity was significantly reduced at 30 ppm (M: 80%; F: 52% of controls), 120 ppm (M: 33%; F: 24% of controls) and 180 ppm (M: 26%; F: 22% of controls). The parental NOEL was 6 ppm (0.5 mg/kg/day) based on the reduced body weights in the females and reduced brain ChE activity (M: 80%; F: 52% of controls). The reproductive NOEL was 30 ppm (2.2 mg/kg/day) based on the increased postnatal mortality, decreased pup weight gain, and reduced number of male pups among the live births. This study was not acceptable to DPR because only one generation was exposed.

A definitive two-generation reproduction study was conducted based on the findings of the previous range-finding study (Eschbach *et al.*, 1991b). Groups of 25 Wistar CrI:(WI) br rats/sex/dose were fed propetamphos (91.8%) in the diet at 0, 4, 30, or 75 ppm (F₀M: 0, 0.3, 2.1 or 5.5 mg/kg/day; F₁M: 0, 0.4, 3.0 or 8.0 mg/kg/day; F₀F: 0, 0.4, 3.1 or 6.6 mg/kg/day; F₁F: 0, 0.5, 3.6 or 10.7 mg/kg/day). Cholinergic signs, consisting mainly of tremors and hyperreflexia, were observed in both generations at 75 ppm. One or two females died or were sacrificed *in extremis* in all treatment groups, but there was no dose-response relationship. A decrease in the mean body weight gain was observed in the F₀ females at 30 ppm (16%) and 75 ppm (18%) during the first five weeks of pre-mating. Similar reductions in the mean body weight gains were observed in F₀ (11%) and F₁ (6%) females at 75 ppm during gestation. F₁ females at 75 ppm also had reduced body weight changes (3-12%) during lactation. Decreased relative liver weights were observed in the F₁ adult females. The mean plasma ChE activity was reduced at 30 ppm (F₀M: 67%; F₀F: 47%; F₁M: 66%; F₁F: 48% of controls) and 75 ppm (F₀M: 40%; F₀F: 33%; F₁M: 37%; F₁F: 19% of controls) at sacrifice. The mean erythrocyte ChE was reduced at 30 ppm (F₁M: 88%; F₁F: 89% of controls) and 75 ppm (F₀M: 92%; F₀F: 92%; F₁M: 86%; F₁F: 85% of controls). The mean brain ChE activity was reduced at 30 ppm (F₀F: 55%; F₁M: 81%; F₁F: 52% of controls) and 75 ppm (F₀M: 57%; F₀F: 35%; F₁M: 54%; F₁F: 39% of controls) at sacrifice. In 21-day-old pups, the plasma ChE activity were significantly reduced at 30 ppm (F₂F: 84% of controls) and 75 ppm (F₁M: 60%; F₁F: 59%; F₂M: 54%; F₂F: 59% of controls). The erythrocyte ChE activity was also significantly reduced at 30 ppm (F₁F: 90% of controls) and 75 ppm (F₁M: 91%; F₁F: 85%; F₂M: 86% of controls) in 21-day-old pups. The brain ChE activity was only reduced in the F₁ pups at 75 ppm (M: 82%; F: 81% of control activity) on day 21. Several reproductive effects were observed at 75 ppm including a reduced mating index (F₁: 72%), reduced mean litter size (F₁: 19%), reduced mean number of implantation sites (F₁: 20%), increased pup mortality (F₁: 72%; F₂: 260%), and reduced mean pup bodyweight gain (F₁ & F₂: ~15%). The investigators re-mated the females at 75 ppm which had a negative vaginal smear with proven males at 75 ppm and showed an increased mating index (83%). The

F. REPRODUCTIVE TOXICITY (cont.)

investigators suggested that this re-mating indicated a treatment-related infertility in the males at 75 ppm. However, the mating index in the remated females was still slightly lower than the other treatment groups (88-100%) and noticeably lower than the control groups (92-96%). The reproduction NOEL was 30 ppm (2.1 mg/kg/day) based on the reduced mating index, reduced litter size, reduced number of implantation sites, increased pup mortality, and decreased pup body weights. The parental NOEL was 4 ppm (0.3 mg/kg/day) based on the reduced body weights in F₀ females (16%) and reduced brain ChE activity in both sexes (F₀F: 55%; F₁M: 81%; F₁F: 52% of controls). This study was acceptable to DPR.

G. DEVELOPMENTAL TOXICITY

Summary

Five developmental toxicity studies (2 with rats and 3 with rabbits) were available for propetamphos. One rat and one rabbit study met FIFRA guidelines. No adverse developmental effects were seen in any of these studies. Adverse maternal effects included drowsiness, exophthalmos, tremors, ataxia, salivation, diarrhea, reduced body weight gains, and respiratory congestion. The lowest maternal NOEL in an acceptable study was 1.5 mg/kg/day based on exophthalmos, tremors, and drowsiness in rats.

Dietary-Rat

A satellite teratology study was conducted as part of the 3-generation study discussed earlier where propetamphos (91.8%) was administered by oral gavage in olive oil at 0, 5, 10 or 20 ppm (0, 0.25, 0.5 or 1 mg/kg/day; Eschbach and Klotzsche, 1981b). After the first litter, the parental generation was mated again. Ten females/dose were sacrificed on day 20 of gestation and the fetuses subjected to external and skeletal examinations. No adverse effects were observed. This study was not acceptable to DPR due to the lack of clear parental toxicity at the highest dose tested and the lack of visceral examination of the fetuses.

Gavage-Rat

Groups of approximately 25 pregnant female Han Wistar rats/dose were administered propetamphos (89%) in 2% gelatin by oral gavage at 0, 1.5, 3.0, or 6.0 mg/kg/day on days 6 through 15 of gestation (Eschbach and Klotzsche, 1984). No mortalities occurred. Clinical signs (drowsiness, exophthalmos, and tremors) were observed in the dams at 3 and 6 mg/kg/day (Table 9). The onset for drowsiness, exophthalmos, and tremors at 6 mg/kg/day was treatment day 3, day 3 and day 2, respectively. The onset of signs at 3 mg/kg/day was generally later, but one dam exhibited exophthalmos as early as treatment day 3 and another exhibited it on day 4. During the treatment period, the body weight gain at 6 mg/kg/day was 10% lower than the controls; however, the mean body weights were only 2% lower than controls. After day 15, the weight gain at 6 mg/kg/day exceeded the controls indicating this was a transient effect. No evidence of developmental toxicity was found. The maternal NOEL was 1.5 mg/kg/day based on the exophthalmus, tremors, and drowsiness at 3 mg/kg/day. The developmental NOEL was greater than 6 mg/kg/day based on the lack of embryotoxicity or teratogenicity. This study was acceptable to DPR.

G. DEVELOPMENTAL TOXICITY (cont.)

Table 9. Clinical Signs and Body Weight Reductions in Pregnant Rats Administered Propetamphos by Oral Gavage During Gestation Days 6-15^a

	Dose Level (mg/kg/day)			
	0	1.5	3	6
Clinical Signs				
Exophthalmus	1/28 ⁺⁺⁺ (day 16) ^b	0/26	12/25 ^{***} (day 3)	16/25 ^{***} (day 3)
Muscle Tremors	0/28 ⁺⁺⁺	0/26	4/25* (day 5)	9/25 ^{***} (day 2)
Drowsiness	0/28 ⁺⁺⁺	0/26	2/25 (day 9)	14/25 ^{***} (day 3)
Body Weights				
End of Treatment (g)	285±16	280±16	283±16	280±14
Gain During Treatment (g)	35±6	33±4	33±5	31±8
^a Eschbach and Klotzsche, 1984 ^b Day of onset relative to treatment; first day of treatment is day 1. ⁺⁺⁺ A significant trend was found based on the Cochran-Armitage trend test at p < 0.001 (Gart <i>et al.</i> , 1986). *, ^{***} The incidence is significantly different from the control group based on the Fisher's exact test at p < 0.05 and 0.001, respectively.				

Gavage-Rabbit

A teratology study was conducted in which 20-30 Dutch Belted rabbits/dose were administered propetamphos (94%) in 0.5% Methocel by oral gavage at 0, 1, 5, or 10 mg/kg/day on gestation days 6 to 18 (Wazeter and Goldenthal, 1976c). Four, 8, 13 and 23 does died at 0, 1, 5, and 10 mg/kg/day, respectively. The earliest deaths occurred on treatment day 3, one at both 5 and 10 mg/kg/day. The most common findings at necropsy in females that died were congested trachea mucosa, congested lungs, and petechiae in the stomach mucosa. Respiratory congestion, ataxia, and excessive salivation were observed at 5 and 10 mg/kg/day. The onset of these signs was not reported. There was no effect on weight gain at 1 and 5 mg/kg/day. The high mortality rate at 10 mg/kg/day made analysis of body weight gains in this group difficult. No evidence of embryotoxicity or teratogenicity was indicated at any dose. The maternal NOEL was 1 mg/kg/day based on respiratory congestion, ataxia, excessive salivation, and deaths. The developmental NOEL was equal to or greater than 10 mg/kg/day, the highest dose tested. This study was unacceptable to DPR due to the high mortality rate and the lack of analysis of the dosing solution.

In another rabbit teratology study, approximately 15 New Zealand White females/dose were administered propetamphos (92%) in 0.5% carboxymethyl cellulose by oral gavage at 0, 1, 4, and 8 mg/kg/day on days 6 to 18 of gestation (Hartman *et al.*, 1978). Only one animal at 8 mg/kg/day died on treatment day 10. No treatment related clinical signs were observed.

G. DEVELOPMENTAL TOXICITY (cont.)

Rabbits at 8 mg/kg/day had a 1% loss in their mean body weights during the treatment period whereas the controls had a 3% gain in their mean body weights. No evidence of embryotoxicity or teratogenicity was found. The maternal NOEL was 4 mg/kg/day based on the death and weight loss at 8 mg/kg/day. The developmental NOEL was equal to or greater than 8 mg/kg/day, the highest dose tested. This study also was unacceptable to DPR because an insufficient number of fetuses were examined for visceral anomalies and some dams delivered before C-sections could be performed.

A third teratology study was conducted in which propetamphos (90.9%) was administered in 0.5% carboxymethyl cellulose by oral gavage to approximately 20 pregnant female New Zealand White rabbits/dose at 0, 1, 4, or 8 mg/kg/day on gestation days 6 through 18 (Hoberman *et al.*, 1984). No treatment-related deaths occurred. A significant increase in diarrhea was observed at 1 mg/kg/day (7/20) and 8 mg/kg/day (10/20) with an onset of treatment day 10 and day 4, respectively. The toxicological significance of the diarrhea at 1 mg/kg/day was uncertain since the incidence decreased at 4 mg/kg/day (4/20). Excessive salivation was also observed (2/20) at 8 mg/kg/day with an onset of treatment day 5. An increase in anorexia was observed in all treatment groups; however, DPR did not consider it treatment-related since it did not exhibit a dose-related trend. There was a dose-related reduction in the mean body weight gain (41 and 77%) during the exposure period at 4 and 8 mg/kg/day, respectively; however, the respective mean body weights were only 1 and 2% lower than controls on gestation day 19. The difference in neither mean body weight gain nor mean body weights were statistically significant. No embryotoxicity or teratogenicity was observed. The maternal NOEL was 4 mg/kg/day based on the diarrhea and excessive salivation. The developmental NOEL was equal to or greater than 8 mg/kg/day which was the highest dose tested. The study was acceptable to DPR.

H. NEUROTOXICITY

Summary

No evidence of organophosphate-induced delayed neuropathy was observed in three studies conducted in hens; however, only one study met FIFRA guidelines.

Gavage-Hen

No evidence of delayed neuropathy was found in a study where 4 hens/dose were administered single doses of technical grade propetamphos (94%) by oral gavage at 47.2, 94.4, or 188.7 mg/kg ($LD_{50} = 94$ mg/kg) on day 0 and 21 without atropine protection (Fletcher *et al.*, 1975). This study was conducted by Industrial Bio-Test Laboratories, Inc. and was determined to be invalid by U.S. EPA.

In a study conducted by Ben-Dyke and Rinehart (1980), 10 White Leghorn hens were administered single doses of technical grade propetamphos (91.8%) by oral gavage at 200 mg/kg ($LD_{50} = 78$ mg/kg) on day 0 and 21 with atropine and 2-PAM protection. No evidence of delayed neuropathy was observed in this study. This study was considered acceptable by DPR.

H. NEUROTOXICITY (cont.)

There was also no evidence of delayed neuropathy based on neuropathy target esterase (NTE) activity or clinical signs in a third study conducted by Abou-Donia and Wilmoth (1994) where 3 to 5 hens were administered propetamphos (98%) at 100 or 150 mg/kg. However, when administered in combination with chlorpyrifos at 100 mg/kg, propetamphos at 50 or 100 mg/kg appeared to potentiate the delayed neuropathy caused by chlorpyrifos. Chlorpyrifos administered alone at 100 mg/kg produced < 50% NTE inhibition and mild ataxia and gait disturbances. When chlorpyrifos at 100 mg/kg is combined with propetamphos at 50 or 100 mg/kg, NTE inhibition (up to 73%), severe ataxia, hindlimb paralysis and enlarged axons and nerve degeneration in the spinal cord were seen. These effects, although indicative of a potentiate response to the combined treatment, were elicited at a level in excess of the LD₅₀ value for either compound. This study was not a standard FIFRA guideline study for delayed neurotoxicity.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

Acute Toxicity

Several acute LD₅₀/LC₅₀ studies were conducted for the various propetamphos formulations; however, only a few studies were available for technical grade propetamphos (Table 10). The effects observed with inhalation exposure included gasping, dyspnea, prostration, tremors, ataxia, eye squint, lacrimation, bradypnea, fasciculations, salivation, tachypnea, hypoactivity, ocular and nasal discharge, and hypersensitivity. Gross pathological findings with inhalation exposure included lung congestion, thymic petechiation, corneal opacity, and hyperemic nares. A NOEL was not established for these effects, but the LOEL was 6.25 mg/L (1,000 mg/kg) based on salivation, tachypnea, hypoactivity, ocular and nasal discharge and hypersensitivity (Wazeter and Goldenthal, 1974). Similar clinical signs were seen with oral exposure, except that gasping, dyspnea, lacrimation, and hypersensitivity were not seen.

Table 10. Acute Adverse Effects of Technical Grade Propetamphos and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg)	LOEL (mg/kg)	Ref. ^a
Inhalation					
Rat ^b	Single, 4-hr	Gasping, prostration, tremors, ataxia, fasciculations, lacrimation, salivation and other cholinergic signs	----	1,000 ^c	1
Oral					
Rat ^b	Single, gavage	Hypoactivity, diarrhea, tachypnea, excessive urination, flaccidity, ataxia, and nasal discharge	----	50	1
Rat ^d	10 days, gavage	Exophthalmos (onset day 3), tremors (onset day 5)	1.5	3	2 ^{*e}
Rabbit ^d	13 days, gavage	Death (onset day 3), respiratory congestion, ataxia, excessive salivation (onset not reported)	1	5	3
Rabbit ^d	13 days, gavage	Diarrhea (onset day 4), excessive salivation (onset day 5)	4	8	4 [*]
<p>a References: 1. Wazeter and Goldenthal, 1974; 2. Eschbach and Klotzsche, 1984; 3. Wazeter and Goldenthal, 1976c; 4. Hoberman <i>et al.</i>, 1984.</p> <p>b LD₅₀/LC₅₀ study</p> <p>c Assuming a rat breathes 40 L/kg/hr (Zielhuis and van der Kreek, 1979).</p> <p>d Developmental toxicity study: All fetal effects were considered acute effects; however, only maternal effects observed within the first few days of exposure were considered acute exposure.</p> <p>e Selected as the definitive study for calculating the margin of exposure for acute effects.</p> <p>* Acceptable study based on FIFRA guidelines</p>					

A. HAZARD IDENTIFICATION (cont.)

Several additional signs were observed with oral exposure including diarrhea, excessive urination and flaccidity. The gross pathological findings observed with oral exposure were also similar to those seen with inhalation exposure, except that hyperemic nares were not observed. Several additional gross pathological findings with oral exposure were petechiation of the stomach mucosa and kidney and yellowish/brownish material in the stomach. A NOEL was also not established in the oral LD₅₀ study, but the LOEL was 50 mg/kg based on hypoactivity, diarrhea, tachypnea, excessive urination, flaccidity, ataxia, salivation and nasal discharge (Wazeter and Goldenthal, 1974). The dermal LD₅₀ study conducted for technical grade propetamphos was not useful for establishing an acute NOEL since only the incidence of mortalities was reported. In addition, two acute neurotoxicity studies in hens were available for propetamphos. However, these studies were also not useful for establishing an acute NOEL since only high doses (47.2-200 mg/kg) were tested.

Certain effects observed in developmental toxicity studies were also considered acute effects. Since occupational and residential exposure is likely to involve exposure over several consecutive days, any maternal effects observed in the first few days of dosing were considered acute. Also, all fetal effects were considered acute effects since these might result from a single day of exposure. In a rat developmental toxicity study, exophthalmus was observed in the dams at 3 and 6 mg/kg/day with an onset on treatment day 3 (Eschbach and Klotzsche, 1984). Tremors were also observed at 3 and 6 mg/kg/day with an onset on treatment day 5 and 2, respectively. In a rabbit developmental toxicity study, diarrhea was observed in the does at 8 mg/kg/day with an onset on treatment day 4 (Hoberman *et al.*, 1984). Excessive salivation was also observed at 8 mg/kg/day with an onset of treatment day 5. In another rabbit developmental toxicity study, death, respiratory congestion, ataxia and excessive salivation were observed in the does (Wazeter and Goldenthal, 1976c). The maternal deaths occurred as early as treatment day 3, but the onset of the clinical signs was not reported. This study had other deficiencies including a high mortality rate even in the control group and no analysis of dosing material. No embryo or fetal toxicity was seen in either rats or rabbits. The rat developmental toxicity study was considered the definitive study for evaluating the risk for adverse health effects in humans from acute exposure (Eschbach and Klotzsche, 1984). This study was also acceptable to DPR based on FIFRA guidelines. The critical acute NOEL derived from the definitive study was 1.5 mg/kg based on exophthalmus and tremors seen at 3 mg/kg/day.

Subchronic Toxicity

The adverse effects associated with subchronic exposure to propetamphos are summarized in Table 11. Included in Table 11 are also effects from reproductive toxicity studies and cumulative effects from the developmental toxicity studies. Weakness, hypoactivity and pallor were observed in mice at 59 mg/kg/day and higher (Bagdon *et al.*, 1978). Vomiting and diarrhea were seen in dogs at 1.25 mg/kg/day (Allen *et al.*, 1989). Tremors, salivation and deep respiration were observed at 5.03 mg/kg/day. A NOEL could not be established for the cholinergic effects in this dog study because of the study design; however, no clinical signs were observed in another 6-month dog study at 0.70 mg/kg/day, the highest dose tested (Hamburger *et al.*, 1979). When propetamphos was applied repeatedly to the skin of rabbits over several weeks, dermal irritation was observed (Wazeter and Goldenthal, 1976a). Some of the dermal effects (pustule formation, erythema, edema, scabbing, and coriaceousness) were also observed in the controls and were attributed to the vehicle, corn oil. Other dermal effects (atonia, desquamation, fissuring, blanching, and bleeding) may be treatment-related because

A. HAZARD IDENTIFICATION (cont.)

Table 11. Subchronic Adverse Effects of Technical Grade Propetamphos and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg/day)	LOEL	Ref. ^a
Inhalation					
Rat	2 wks, 4 hr/day, 5 days/wk	Cholinergic signs	----	160	1
Rat	2 wks, 4 hr/day, 5 days/wk	Cholinergic signs, reduced body weights, clin. chem. changes, hemorrhagic erosion of stomach	8.5	15.5	2
Oral					
Rabbit ^b	13 days, gavage	Death, body weight loss (F: -0.7%)	4	8	3
Mouse	4 weeks, diet	Reduced body weights (M: 12%)	----	0.05	4
Mouse	8 weeks, diet	Reduced brain ChE activity (M: 72%; F: 59% of controls)	1	7	5
Rat ^c	1-gen., 70 days pre mating, diet	Parental: Reduced body weights (F: 13%), reduced brain ChE activity (M: 80%; F: 52% of controls)	0.5	2.2	6
		Reproductive: Increased postnatal mortality, decreased pup weight gain, reduced number of male pups	2.2	10.0	
Rat ^c	2-gen., 70 days pre mating, diet	Parental: Reduced body weights (F: 16%), reduced brain ChE activity (M: 80%; F: 52-55% of controls)	0.3	2.1	7*
		Reproductive: Reduced mating index, reduced litter size, reduced number of implantation sites, increased pup mortality, decreased pup body weights	2.1	5.5	
Dog	6 months, diet	Reduced brain ChE activity (M: 64% of controls)	0.09	0.18	8
Dermal					
Rabbit ^c	6 hrs/day, 5 days/wk, 3 wks	Body weight reduction (F: 10%)	0.5	2.5	9
<p>a References: 1. Wazeter and Goldenthal, 1975b; 2. Leuschner <i>et al.</i>, 1978; 3. Hartman <i>et al.</i>, 1978; 4. Machi <i>et al.</i>, 1979; 5. Bagdon <i>et al.</i>, 1978; 6. Eschbach <i>et al.</i>, 1991a; 7. Eschbach <i>et al.</i>, 1991b; 8. Hamburger <i>et al.</i>, 1979; 9. Wazeter and Goldenthal, 1976a.</p> <p>b Developmental toxicity study: Only maternal effects observed after day 7 were included or delayed fetal development such as delayed ossification or reduced body weights.</p> <p>c Reproductive toxicity study</p> <p>* Acceptable study based on FIFRA guidelines</p>					

A. HAZARD IDENTIFICATION (cont.)

they were only observed in treated animals; however, the toxicological significance of these lesions was uncertain because of the possible contribution of the corn oil. This study also had numerous deficiencies including no analysis of test article or dosing material, inadequate number of animals per group, inadequate clinical chemistry analysis, and no individual data for dermal or clinical observations. Reduced body weight gains or weight losses (>10%) were a common effect observed in several of the subchronic studies. The lowest NOEL for this endpoint in an acceptable study was seen in a two-generation rat reproduction study at 0.3 mg/kg/day (Eschbach *et al.*, 1991b). Brain ChE inhibition was another common effect seen in the subchronic studies. The lowest NOEL for this endpoint in an acceptable study was also 0.3 mg/kg/day based on the two-generation rat reproduction study (Eschbach *et al.*, 1991b). Adverse reproductive effects were observed in two studies, including reduced mating index, reduced litter size, reduced number of implantation sites, increased pup mortality, and decreased pup body weights. The lowest reproductive NOEL was 2.1 mg/kg/day based on the effects seen in the two-generation rat reproduction study. A critical subchronic NOEL was not selected for propetamphos since there is no seasonal exposure due to its potential year-round use indoors.

Chronic Toxicity

The chronic toxicity of propetamphos was evaluated in three species by the oral route (Table 12). In rats exposed to propetamphos in the diet for 2 years, the adverse effects observed included weak limbs, hyperreflexia, erythema and alopecia of the abdomen, and reduced brain ChE activity (M: 66%; F: 64% of controls) at 6.75 mg/kg/day (Luginbuhl *et al.*, 1981). Reduced brain ChE activity (M: 51%; F: 45% of controls) was the only adverse effect observed in mice exposed to propetamphos in the diet for 93 weeks at 6 mg/kg/day (LeQuire *et al.*, 1981). A significant reduction in brain ChE inhibition was also observed in mice at 1 mg/kg/day (M: 87%; F: 94% of controls); however, the reduction was not considered toxicologically significant because it was very slight and there were no overt signs of toxicity up to 21 mg/kg/day. Dogs exhibited numerous chronic effects after being exposed for one year at 3.03 mg/kg/day (Allen *et al.*, 1991). These effects included death, diarrhea, vomiting, prolonged anestrus in females, reduced brain ChE activity (M: 79%; F: 82% of controls), increased liver weights, thickened mucosa of the small intestine and liver necrosis.

The lowest NOEL for the chronic studies was 0.59 mg/kg/day observed in the 1-year dog study (Allen *et al.*, 1991). A lower NOEL of 0.09 mg/kg/day was observed in a 6-month dog study based on reduced brain ChE activity (M: 64% of controls) (Hamburger *et al.*, 1979). The reason for the difference in the dosage required to produce significant brain ChE inhibition in the two dog studies is uncertain. Differences in the cholinesterase assay is one possible explanation. However, interpretation of the findings from the 6-month study is confounded by changes in dose levels in two groups during the study and no analysis of feed to verify propetamphos concentration. A lower NOEL of 0.3 mg/kg/day was also observed in an acceptable rat reproductive toxicity study based on body weight reduction (F: 16%) and reduced brain ChE activity (M: 80%; F: 52-55% of controls) in adults at 2.1 mg/kg/day (Eschbach *et al.*, 1991b). The lower NOEL in the rat reproductive toxicity study was probably the result of dose selection since the NOEL in the 2-year rat study (0.63/mg/kg/day) was lower than the LOEL in rat reproductive toxicity study. Because the dog appears to be more sensitive based on the numerous effects seen, the 1-year dog study was selected as the definitive chronic toxicity study. Therefore, the critical chronic NOEL was 0.59 mg/kg/day based on diarrhea, vomiting, prolonged anestrus in females, brain ChE inhibition, increased liver weights,

A. HAZARD IDENTIFICATION (cont.)

Table 12. Chronic Adverse Effects of Technical Grade Propetamphos and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg/day)	LOEL	Ref. ^a
Rat	2 years, diet	Weak limbs, hyperreflexia, erythema, alopecia, reduced brain ChE activity (M: 66%; F: 64% of controls)	0.63	5.89	1*
Mouse	93 weeks, diet	Reduced brain ChE activity (M: 51%; F: 45% of controls)	1	6	2*
Dog	52 weeks, diet	Diarrhea, vomiting, prolonged anestrus (F), reduced brain ChE activity (M: 79%; F: 82% of controls), increased liver weights, thickened mucosa of small intestine, hepatic necrosis	0.59	3.03	3 ^b

a References: 1. Luginbuhl *et al.*, 1981; 2. LeQuire *et al.*, 1981; 3. Allen *et al.*, 1991.
b Selected as the definitive study for calculating the margin of exposure for chronic effects.
* Acceptable study based on FIFRA guidelines

thickened mucosa of the small intestine and liver necrosis in dogs exposed to propetamphos in the diet for 52 weeks.

Oncogenicity/Genotoxicity

The only evidence that propetamphos might be oncogenic was an increase in pancreatic islet cell adenomas in female rats (Luginbuhl *et al.*, 1981). However, the increase was not significant by trend analysis or by pairwise comparison at the high-dose level, 120 ppm. Although the incidence in the treatment groups was higher than concurrent controls, the incidence was similar to the historical control data. In addition, the tumors occurred late in the study. Furthermore, there was no increase in these tumors in male rats or either sex of mice (LeQuire *et al.*, 1981). Both studies met FIFRA guidelines. The genotoxicity studies for propetamphos were negative, except for a published *in vivo* chromosomal aberrations study in mice (Kumari and Krishnamurthy, 1986). However, this study had major deficiencies including no analysis of test article for purity, positive controls, number of animals, tested not reported and no individual data. The negative studies included two reverse mutation assays, one with *Salmonella typhimurium* strains and the other with *Saccharomyces cerevisiae* strains, a *Drosophila* sex-linked recessive lethal assay, an *in vivo* micronucleus assay in mice, an *in vivo* cytogenetics assay in rats, and an unscheduled DNA synthesis (UDS) assay with primary rat hepatocytes (Haworth *et al.*, 1980; Jagannath and Brusick, 1981; Kumari and Krishnamurthy, 1986; Matheson and Brusick, 1978; Marshall, 1990; Myhr and Brusick, 1981). Three of these studies met FIFRA guidelines, including the reverse mutation assay with *Salmonella*, the *in vivo* cytogenetics assay with rats, and the UDS assay. Therefore, DPR did not consider the weight of evidence sufficient to warrant a low-dose extrapolation for humans.

B. EXPOSURE ASSESSMENT

An exposure assessment document for propetamphos, entitled “Estimation of Exposure of Persons in California to Pesticide Products That Contain Propetamphos,” HS-1731 (August 9, 1996) was prepared by the Worker Health and Safety Branch of the Department of Pesticide Regulation. The following section is a brief summary of the information in this document. A detailed description of the calculation of the exposure dosages for occupational and residential exposure can be found in the exposure assessment document for propetamphos.

Occupational Exposure

No exposure studies were available that monitored the exposure of applicators (i.e., pesticide control operators) to propetamphos during indoor use; therefore, exposure data for propoxur and chlorpyrifos applicators were used as surrogate data to estimate the exposure for applicators using identical or similar formulations of propetamphos. Exposure during application of the 1% aerosol and ready-to-use (RTU) pump spray was based on propoxur exposure data. Exposure during the application of the liquid concentrate was based on chlorpyrifos data. Table 13 summarizes the estimated potential daily exposure to propetamphos for applicators. The mean absorbed daily dosages (ADDs) for applicators using the 1% aerosol and the 1% RTU pump spray were 13.8 and 12.8 $\mu\text{g}/\text{kg}/\text{day}$, respectively. The ADDs were calculated assuming a default value of 50% for both dermal absorption and respiratory uptake, 2 hours of actual application time/day and a male body weight of 75.9 kg. The annual average daily dosages (AADDs) were 8.8 and 8.2 $\mu\text{g}/\text{kg}/\text{day}$ for the 1% aerosol and 1% RTU pump spray, respectively. The AADDs were calculated assuming applicators were exposed 233 days per year. The ADD and AADD for applicators using the 1% emulsifiable concentrate mix for soil injection were significantly higher at 109.6 and 69.9 $\mu\text{g}/\text{kg}/\text{day}$, respectively.

Table 13. Estimated Potential Daily Exposure for Applicators Handling Various Propetamphos Formulations

Formulation	n ^a	ADD ^b $\mu\text{g}/\text{kg}/\text{day}$	AADD ^c $\mu\text{g}/\text{kg}/\text{day}$
1% aerosol	32	13.8	8.8
1% ready-to-use trigger pump spray	32	12.8	8.2
1% emulsifiable concentrate mix for soil injection	8	109.6 ^d	69.9

^a Number of replicates
^b ADD = Absorbed Daily Dosage, assuming a dermal absorption of 50%, inhalation uptake of 50%, 2 hours of actual application time/day, and a male body weight of 75.9 kg. Protective clothing was assumed to be long-sleeved shirt, long pants and chemical-resistant gloves.
^c AADD = Annual Average Daily Dosage, assuming an average of 233 days of work per year (365 days).
^d Applicators worked 2.8 hours of actual application time per day.

Residential Exposure

The estimated potential exposure of occupants entering structures treated with propetamphos is summarized in Table 14. Rosenheck and Hudlow (1993) estimated indoor

B. EXPOSURE ASSESSMENT (cont.)

Table 14. Estimated Potential Daily and Annual Exposure to Occupants of Rooms Treated with Propetamphos

Occupant	ADD ^a µg/kg/day	AADD ^b µg/kg/day
<u>Passive Dosimetry with Jazzercise® Routine</u>		
Adult	28.3	9.3
Child	44.0	14.5
<u>Equilibrium Model Using Dislodgeable Carpet Residues</u>		
Adult	12.3	4.0
Child	18.9	6.2
^a	ADD = Absorbed Daily Dosage, assuming a dermal absorption of 50%, inhalation uptake of 50%, and oral absorption of 100%.	
^b	AADD = Annual Average Daily Dosage, assuming a total of 24 applications per year and 5 days of exposure following each application.	

exposure using two different methods, passive dosimetry and dislodgeable carpet residues. With passive dosimetry, human volunteers wearing long underwear, socks, and gloves performed Jazzercise® routines for 20 minutes in hotel rooms treated with propetamphos at 3, 6 and 9 hours after application. Face and neck wipes were collected to estimate exposure to uncovered areas of the body. Hand rinses were collected to remove any residues that passed through the gloves. Inhalation exposure was estimated for children and adults from air samples taken from the center of each room at a height of 6 and 36 inches, respectively. Oral exposure was estimated as a fraction of hand exposure, assuming 5 and 50% of hand exposure for adults and children, respectively. The estimated mean ADDs for adults and children, using the passive dosimetry data, were 28.3 and 44.0 µg/kg, respectively. The ADDs were calculated assuming a dermal absorption of 50%, a respiratory uptake of 50%, and an oral absorption of 100%. The estimated AADDs were 9.3 and 14.5 µg/kg/day for adults and children, respectively. The AADDs were calculated assuming a total of 24 applications per year and 5 days of exposure following each application.

With dislodgeable carpet residues, the assumption was made that the concentration of residues on the body was in equilibrium with the dislodgeable residue concentration on the carpet. Samples were collected using a roller over 0.165 m² cotton cloth placed on the treated carpets at each reentry interval. Oral and inhalation exposure was estimated for the second method the same way as the first method. The estimated ADDs were 12.3 and 18.9 µg/kg/day for adults and children, respectively. The estimated AADDs for adults and children were 4.0 and 6.2 µg/kg/day, respectively. The same assumptions used in calculating the ADDs and AADDs with the passive dosimetry data were used with the dislodgeable carpet residues.

Dietary Exposure

Propetamphos has a food additive tolerance of 0.1 ppm based on its potential use in food handling establishments. It also has a feed additive tolerance of 0.1 ppm based its

B. EXPOSURE ASSESSMENT (cont.)

potential use in animal feed handling establishments. Since these food/feed tolerances are not specific to any food/feed items, a dietary exposure analysis was not performed.

C. RISK CHARACTERIZATION

The risk for human health effects can be expressed as a margin of exposure (MOE). The MOE is the ratio of the NOEL from experimental animal or human studies to the human exposure dosage.

$$\text{Margin of Exposure} = \frac{\text{NOEL}}{\text{Exposure Dosage}}$$

Acute Toxicity

The estimated MOEs for occupational exposure are summarized in Table 15. The acute MOEs were calculated for propetamphos applicators using the NOEL of 1.5 mg/kg for exophthalmos and tremors in rats and the ADDs for the different formulations in Table 13. The acute MOEs for applicators ranged from 14 for 1% emulsifiable concentrate mix for soil injection to 117 for the 1% ready-to-use trigger pump spray.

Table 15. Estimated Margins of Exposure for Applicators Handling Various Propetamphos Formulations^a

Formulation	Acute ^b	Chronic ^c
1% aerosol	109	67
1% ready-to-use trigger pump spray	117	72
1% emulsifiable concentrate mix for soil injection	14	8

^a Margin of Exposure = NOEL / Exposure Dosage. See Table 13 for exposure dosages for applicators.
^b The acute NOEL was 1.5 mg/kg (rats - exophthalmos and tremors).
^c The chronic NOEL was 0.59 mg/kg/day (dog - diarrhea, vomiting, prolonged anestrus (F), reduced brain ChE activity (M: 79%; F: 82% of controls), increased liver weights, thickened mucosa of small intestine, hepatic necrosis).

The estimated MOEs from residential exposure are summarized in Table 16. The acute MOEs were calculated for occupants of rooms treated with propetamphos using the acute NOEL of 1.5 mg/kg in rats and the ADDs for adults and children in Table 14 based on the passive dosimetry and dislodgeable residue data. Based on the passive dosimetry data, the estimated acute MOEs were 53 and 34 for adults and children, respectively. Using the equilibrium model, the estimated acute MOEs were 122 and 79 for adults and children, respectively.

C. RISK CHARACTERIZATION (cont.)

Table 16. Estimated Margins of Exposure for Occupants of Rooms Treated with Propetamphos^a

Occupant	Acute ^b	Chronic ^c
<u>Passive Dosimetry with Jazzercise® Routine</u>		
Adult	53	63
Child	34	41
<u>Equilibrium Model Using Dislodgeable Carpet Residues</u>		
Adult	122	147
Child	79	95
^a Margin of Exposure = NOEL / Exposure Dosage. See Table 14 for exposure dosages for occupants of treated rooms. ^b The acute NOEL was 1.5 mg/kg (rats - exophthalmos and tremors). ^c The chronic NOEL was 0.59 mg/kg/day (dog - diarrhea, vomiting, prolonged anestrus (F), reduced brain ChE activity (M: 79%; F: 82% of controls), increased liver weights, thickened mucosa of small intestine, hepatic necrosis).		

Chronic Toxicity

The chronic MOEs for propetamphos applicators were calculated using the chronic NOEL of 0.59 mg/kg/day in dogs for diarrhea, vomiting, prolonged anestrus (F), reduced brain ChE activity (M: 79%; F: 82% of controls), increased liver weights, thickened mucosa of small intestine, hepatic necrosis and the AADDs for the different formulations in Table 13. The chronic MOEs ranged from 8 for applicators using the 1% emulsifiable concentrate mix for soil injection to 72 for applicators using the 1% RTU pump spray (Table 15).

The chronic MOEs for occupants of rooms treated with propetamphos were calculated using the chronic NOEL of 0.59 mg/kg/day in dogs and the AADDs for adults and children in Table 14 based on the passive dosimetry and dislodgeable residue data. Based on the passive dosimetry data, the chronic MOEs for adults and children were 63 and 41, respectively (Table 16). Using the dislodgeable residue data, the chronic MOEs for adults and children were 147 and 95, respectively.

V. RISK APPRAISAL

Introduction

Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that the adverse effects observed in toxicity studies with laboratory animals will occur in humans under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. These, in turn, result in uncertainty in the risk characterization which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment for propetamphos are delineated in the following discussion.

Hazard Identification

The primary mechanism of toxicity for propetamphos is the inhibition of AChE in the nervous system. AChE is involved in the termination of impulses across certain nerve synapses. Inhibition of AChE leads to accumulations of acetylcholine in the synaptic cleft which results in overstimulation of the nerves followed by depression or paralysis of the cholinergic nerves. Consequently, brain ChE inhibition was considered an adverse effect for propetamphos. The toxicological significance of brain ChE inhibition in the absence of cholinergic signs is uncertain because of the poor correlation between the severity of cholinergic signs and the level of ChE inhibition in the brain (U.S. EPA, 1988b). However, this was not a major issue with propetamphos since other clearly adverse effects (e.g., histological lesions) were observed at the same dose level that produced brain ChE inhibition.

The critical NOEL selected for evaluating the acute occupational and residential exposure to propetamphos was estimated from a rat developmental toxicity study where exophthalmos and tremors that were observed in rats at 3 mg/kg/day as early as treatment day 3 and 5, respectively (Eschbach and Klotzche, 1984). Another approach might have been to estimate a NOEL by dividing the LOEL (50 mg/kg) in the oral LD₅₀ study by an uncertainty factor of 10 (Wazeter and Goldenthal, 1974). However, this study had several deficiencies including no analysis of test article or dosing material, no summary tables for clinical signs, body weights and gross pathological lesions, and no individual data. Furthermore, the NOEL is more uncertain when estimated this way since the uncertainty factor of 10 is a default and does not take into consideration the severity of the signs observed at the LOEL or the steepness of the dose-response curve. Consequently, this approach may significantly underestimate or overestimate the NOEL. The LOEL in the oral LD₅₀ study was significantly higher than the LOEL for acute effects in the developmental toxicity study. This could simply be due to the selection of dose levels or it may be an indication that multiple doses may have been a significant factor in the development of effects at a lower dose level. Since workers and residents are likely to be exposed to propetamphos over several days, the exposure in the developmental toxicity study is more similar to the actual exposure conditions than in the LD₅₀ study. Therefore, DPR considered it preferable to use the established NOEL from the developmental study based on effects observed after 3 days of exposure versus using an estimated NOEL from the oral LD₅₀ study. However, if DPR had used the estimated NOEL of 5

V. RISK APPRAISAL (cont.)

mg/kg from the oral LD₅₀ study for the critical NOEL, the acute MOEs would be approximately 3-fold greater than estimated.

U.S. EPA made available a draft copy of the HED chapter of the Reregistration Eligibility Document for propetamphos (U.S. EPA, 1999). They selected a NOEL of 0.05 mg/kg/day for brain ChE inhibition from a 4-week oral range-finding study in mice to analyze the acute dietary exposure (Machi *et al.*, 1979). Their justification was this was the shortest-term study in which brain ChE activity had been measured. However, differences in the findings in this 4-week study when compared with the 8-week and 93-week feeding studies in mice raises questions about the conduct of this study (Bagdon *et al.*, 1978; LeQuire *et al.*, 1981). For example, there were several mortalities in the 4-week study at 0.1 and 0.5 mg/kg/day. However, no signs of toxicity were seen in any of these mice before they died. No mortalities were seen in the 8-week study until 172 mg/kg/day and clinical signs were seen at this dose level. In the 93-week study, an increase in mortality rate was not seen even at the highest dose level, 21 mg/kg/day. In the 4-week mouse study, body weight reductions were observed in males at 0.05, 0.1 and 0.5 mg/kg/day, but did not exhibit a clear dose-response relationship (11%, 18%, and 10%, respectively, at day 26). In the 8-week study, body weight reductions were not seen until 28 mg/kg/day. In the 93-week study, no significant body weight reductions were seen up to 21 mg/kg/day. Finally, reduced brain cholinesterase activity (M: 87%; F: 72% of controls) was seen in the 4-week study at 0.1 mg/kg/day which did not produce significant blood ChE inhibition. However, the NOEL for brain ChE inhibition was equal to or greater than the NOEL for blood ChE inhibition in the other mouse studies. In the 8-week mouse study, reduced brain ChE activity was not observed until 7 mg/kg/day, but significant reductions in plasma ChE activity (M: 55%; F: 71% of controls) and erythrocyte ChE activity (F: 55% of controls) were seen at 1 mg/kg/day. In the 93-week mouse study, a slight reduction in brain ChE activity (M: 87%; F: 94% of controls) was seen at 1 mg/kg/day which DPR did not consider toxicologically significant because there were no clinical signs of toxicity even at 21 mg/kg/day. Slightly greater reductions were seen in the plasma ChE activity (M: 56%; F: 84% of controls) and erythrocyte ChE activity (M: 75%; F: 77% of controls) at 1 mg/kg/day.

The critical NOEL of 0.59 mg/kg/day was selected for evaluating chronic exposure to propetamphos was based on effects observed in a one-year dog study (Allen *et al.*, 1991). These chronic effects included diarrhea, vomiting, prolonged anestrus (females), brain ChE inhibition, increased liver weights, liver necrosis, and thickened mucosa of the small intestine. A lower NOEL of 0.09 mg/kg/day based on reduced brain ChE activity (M: 64% of controls) was observed in a 6-month dog study (Hamburger *et al.*, 1979). The reason for the difference in the dosage required to produce significant brain ChE inhibition in the two dog studies is uncertain. Tolerance does not appear to be responsible since this is generally thought of as a reduction in cholinergic signs due to a reduction or "down-regulation" of cholinergic receptors that usually occurs despite a continued inhibition of ChE activity (Costa *et al.*, 1982). Induction of metabolic enzymes involved in the detoxification of propetamphos is a more likely explanation. This would result in lower blood levels of the active metabolite and, consequently, lower levels of ChE inhibition. However, blood ChE levels remained fairly constant throughout the chronic studies in rats, mice, and dogs suggesting there was no induction of metabolic enzymes (Luginbuhl *et al.*, 1982; LeQuire *et al.*, 1981; Allen *et al.*, 1991). Differences in the brain regions analyzed does not appear to be a factor because both studies analyzed the cerebral cortex for ChE activity. Differences in the methods used for analyzing ChE activity may be responsible since different automated instruments were used. No detailed description of the methodology was provided for either study. There does not appear to be any analysis of the feed to verify

V. RISK APPRAISAL (cont.)

the concentration of propetamphos in the 6-month study, so it is possible this difference could be due to improper mixing of the compound into the feed. U.S. EPA selected this 6-month study to evaluate short-term, intermediate-term and chronic dermal exposure to propetamphos in their draft RED document (U.S. EPA, 1999). They used the low NOEL in the 4-week mouse study (Machi *et al.*, 1979) to support the low NOEL in the 6-month dog study. However, these two studies stand out not only because of the extremely low NOELs for brain ChE inhibition reported, but also because they were the only toxicity studies for propetamphos where brain ChE inhibition was seen at a dose level below that which produced blood ChE inhibition. Since the findings in these two studies are not consistent with the other toxicity studies and there are questions about the conduct of both of these studies, DPR did not select either of these studies to evaluate exposure to propetamphos. However, if DPR had used the NOEL for brain ChE inhibition from the 4-week mouse study as the critical NOEL for acute toxicity, the MOEs would be 30-fold lower than estimated. If DPR had used the NOEL for brain ChE inhibition from the 6-month dog study as the critical NOEL for chronic toxicity, the MOEs would be approximately 6-fold lower than estimated.

Exposure Assessment

Surrogate data from two different pesticides, propoxur and chlorpyrifos, with similar use patterns and identical or similar formulations were used for estimating occupational exposure. The exposure estimates based on the chlorpyrifos data were an order of magnitude higher than the estimates based on the propoxur data. It is unknown if this difference is just due to the difference in the use patterns of the formulations or due to the physical/chemical properties of the two chemicals which may have been sufficiently different that it affected the amount of residue detected. Therefore, the occupational exposure estimated for one or two of the formulations may be overestimated or underestimated.

With acute exposure, it is preferable to give a range of exposure estimates from the mean to high-end estimates such as the 95th percentile to protect most of the exposed individuals. Insufficient information was available in the studies selected to calculate the 95th percentile. Consequently, the geometric mean or arithmetic mean was used for estimating a single day exposure. Therefore, the estimated MOEs for acute occupational and residential exposure may not cover those individuals at the upper end of the exposure distribution curve.

Two methods were used to estimate residential exposure, using different residue data and assumptions. With one method, the residential exposure for occupants was estimated using passive dosimetry during a 20-minute Jazzercise® routine in a treated room, assuming that one hour of extensive dermal contact during a Jazzercise® routine would provide as much dermal contact as 24 hours of normal daily activity. Without a comparison with monitoring over a 24-hour period, it is unknown if this assumption results in an over or underestimation of exposure. In another method, residential exposure was estimated assuming the dislodgeable residues in the carpet were in equilibrium with residues on the skin surface and that the total body surface area was exposed. The assumptions used with dislodgeable carpet residues should overestimate the exposure; however, the exposure estimates based on this method were lower than those based on the passive dosimetry. Either the assumptions used in extrapolating from the 1-hour Jazzercise® routine to 24 hours of normal daily activity overestimate the exposure or the dislodgeable carpet residues used with the equilibrium model were underestimated.

V. RISK APPRAISAL (cont.)

Risk Characterization

Generally, an MOE of at least 100 is considered sufficiently protective of human health when the NOEL for an adverse effect is derived from an animal study. The MOE of 100 allows for humans being 10 times more sensitive than animals and for the most sensitive human being 10 times more sensitive than the average human. However, a larger MOE may be preferable when the acute exposure estimate is based on average exposure rather than an upper end estimate. All the estimated MOEs for occupational and residential exposure were less than 200. The estimated acute MOEs for occupational exposure were less than 100 for applicators when using the 1% emulsifiable concentrate mix for soil injection, but greater than 100 for the 1% aerosol and the 1% ready-to-use trigger pump spray. The estimated acute MOEs for residential exposure were less than 100 for children using both the passive dosimetry and the dislodgeable carpet residues. For adults the acute MOE for residential exposure was less than 100 using the passive dosimetry, but was 122 using the dislodgeable carpet residues. The chronic MOEs for occupational exposure were less than 100 with all three formulations. The chronic MOEs for residential exposure were less than 100 for adults and children using passive dosimetry and for children using dislodgeable carpet residues, but was 147 for adults using dislodgeable carpet residues.

Dermal exposure to propetamphos was estimated to be 90 to 99% of the total exposure. However, no NOELs were established in acceptable acute or subchronic dermal studies. Therefore, the critical NOELs used in the calculation of the MOEs were based on animal studies in which the test material was administered orally. Because the peak blood levels would be lower with dermal exposure due to a slower absorption rate, even with the same percent absorption, the NOELs with acute and chronic dermal exposure would probably be higher and, thus, the MOEs would be higher.

Issues Related to the Food Quality Protection Act

Prenatal and Postnatal Sensitivity

Five developmental toxicity studies (2 with rats and 3 with rabbits) were available for propetamphos. No adverse developmental effects were found in any of the studies; however, only one rat and one rabbit study were acceptable based on FIFRA guidelines. Consequently, there does not appear to be any increased prenatal sensitivity to propetamphos; however, brain ChE activity was not analyzed in any of the developmental toxicity studies.

Four reproductive toxicity studies in rats were available for propetamphos with exposure ranging from one to three generations. Evidence of postnatal effects were observed in two studies, including increase pup mortality and reduced pup body weights. The lowest NOEL for these postnatal effects was 2.1 mg/kg/day. Adverse effects were also observed in adults in these studies, including tremors, hyperreflexia, exophthalmos, reduced body weights and food consumption, and brain ChE inhibition. The lowest parental NOEL in the reproductive studies was 0.3 mg/kg/day based on reduced body weights in females and brain ChE inhibition. There does not appear to be any increased postnatal sensitivity to propetamphos; however, brain ChE activity was not analyzed in any of the reproductive toxicity studies.

V. RISK APPRAISAL (cont.)

Endocrine Effects

Possible endocrine related effects were observed in several animal studies after exposure to propetamphos. Prolonged anestrus was observed in the 1-year dog study (Allen *et al.*, 1991). There were also reductions in fertility and mating indices in the rat reproduction studies which could be due to prolonged anestrus (Eschbach *et al.*, 1991a&b). However, in the main rat reproduction study the mating index increased from 72% to 83% when F₁ females at 75 ppm with negative vaginal smears were remated with proven males at 75 ppm. While this suggests male infertility may be contributing to the reduction in the mating index, the mating index was still slightly lower than the controls (92-96%) suggesting female infertility may have been a contributing factor. It is possible propetamphos is causing endocrine effects in both sexes. However, from the available data it is unclear if any of these effects are mediated through endocrine changes or some other mechanism. Regardless, the NOELs for these reproductive effects are equal to or greater than the NOELs for other endpoints in these studies and, consequently, a larger MOE is not needed to protect against these reproductive effects.

Cumulative Toxicity

There is a potential for cumulative toxicity between propetamphos and other organophosphates. U.S. EPA is currently in the process of developing the methodology to address this issue.

Aggregate Exposure

Since there was no dietary exposure assessment, there was also no analysis of combined dietary and residential or combined dietary and occupational exposure. While it is possible to do a combined occupational and residential exposure, this exposure scenario was considered remote and, therefore, was not analyzed.

VI. CONCLUSIONS

The risks for potential adverse human health effects with occupational and residential exposure to propetamphos were evaluated. The acute MOEs for occupational exposure were greater than 100 for the 1% aerosol and the 1% ready-to-use trigger pump spray, but less than 100 for the 1% emulsifiable concentrate mix for soil injection. The acute MOEs for residential exposure were less than 100 for children using either passive dosimetry or dislodgeable carpet residues. The acute MOEs for residential exposure were also less than 100 for adults using passive dosimetry, but greater than 100 using dislodgeable carpet residues. The chronic MOEs for occupational exposure were less than 100 for three formulations. The chronic MOEs for residential exposure were less than 100 for adults and children using passive dosimetry and for children using dislodgeable carpet residues, but greater than 100 for adults using dislodgeable carpet residues.

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APPENDIX

PEER REVIEW COMMENTS AND RESPONSES

Office of Environmental Health Hazard Assessment



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Pete Wilson
Governor

MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
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Department of Pesticide Regulation
1020 N Street
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FROM: Anna M. Fan, Ph.D., Chief
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DATE: August 27, 1998

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDE REGULATION'S
DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE
INGREDIENT PROPETAMPHOS

We have completed our review of the draft risk characterization for propetamphos submitted for our review under SB 950 by the Department of Pesticide Regulation (DPR). Propetamphos, (E)-1-methylethyl-3[[ethylamino) methoxyphosphinothioyl] oxy]-2-butenate, is an organophosphate insecticide used for controlling cockroaches, flies, ants, ticks, moth, fleas, and mosquitoes. Propetamphos is a high priority active ingredient under the Birth Defect Prevention Act of 1984 (**SB 950**).

We conclude from our review that the draft RCD for propetamphos requires significant revision. In general, the assumptions and conclusions stated in the draft risk characterization document require more scientific support, additional analysis, and more detailed discussion in order to provide a complete characterization of the risks posed by the use of propetamphos in California.

In reviewing the draft **RCD** for propetamphos, we considered the following information: 1) the draft propetamphos RCD (May 21, 1998); 2) the draft human exposure assessment for propetamphos prepared by the Worker Health and Safety Branch (August 9, 1996); 3) the

California Environmental Protection Agency



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Gary T. Patterson, Ph.D., Chief
August 27, 1998
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available toxicology summaries from **DPR**; 4) the analysis of acute exposure to propetamphos; 5) the analysis of chronic exposure to propetamphos; and 6) the results of our literature search.

Thank you for the opportunity to comment on the draft RCD for propetamphos. The comments are provided as follows. If you have any questions about our comments, please contact me or Dr. Michael J. DiBartolomeis at (510) 540-3063.

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GENERAL COMMENTS

The draft risk characterization document for propetamphos includes summaries and critiques of the data available in DPR's registration database. There is a fair amount of repetition in summarizing the data, making the document unnecessarily hard to read. There are no appendices. The toxicological summary often included in RCDs was not appended to the draft propetamphos RCD. We found the inclusion of summary data tables helpful in accessing some of the more critical information.

Literature Search

It is not clear from reviewing the draft RCD whether there was a complete search of the open literature to identify relevant articles on the toxicology, mechanism of action, and pharmacokinetics of propetamphos and its major breakdown products. Pertinent information published in the open literature, but not submitted by the registrant, should be considered in preparing a risk assessment for any pesticide active ingredient. If a complete search was conducted, and no relevant data were identified, we recommend that this be made clear in the propetamphos RCD before it is finalized.

We conducted a literature search for propetamphos and its major breakdown products using the current 1998 on-line and CD-ROM based resources, including MedLine, ToxLine, BIOSIS, and the Integrated Risk Information System (IRIS). We would be happy to share the assembled information. In order to assist you in revising the draft RCD, we have cited selected published works at the end of this report that may be worth considering in your overall evaluation.

Biotransformation and Pharmacokinetics

The sections on biotransformation and pharmacokinetics of propetamphos are difficult to follow because the location of the radiolabel on the chemical is not specified. However, it appears that the chemical was probably labeled only on the side-chain leaving group. Thus the moiety being followed in the distribution and excretion sections would be only the inactive side chain, which is of little interest following the initial hydrolysis. A discussion of the pharmacokinetics of phosphorylation reactions, including inhibition and reactivation of cholinesterase by Propetamphos, would be more useful than a discussion of the rate of formation of CO₂ from the inactive side chain. We recommend that the revised RCD included a summary of the papers by Mason et al. (1993) and Dix et al. (1992) which address the aging of ChE and the pharmacokinetics of propetamphos. We also recommend including a discussion of the toxicodynamics of propetamphos, as well as the general principles applicable to organophosphate cholinesterase inhibitors in both the exposure assessment as well as the main risk characterization text.

Acute Toxicity

The draft RCD calculates margins of exposure (safety) well below 100 from exposure to propetamphos for both occupational and residential conditions, and for both adults and children. The draft exposure assessment utilizes average estimates for exposures. These margins of safety would be significantly smaller if upper-bound estimates for acute exposure were used as is scientifically valid and routinely done by risk assessors to obtain a range of exposure values inclusive of high-end exposures and to better characterize the uncertainty associated with using only mean estimates for exposure assessment. The draft RCD acknowledges that "the estimated MOEs for acute occupational exposures may not cover those individuals at the upper end of the exposure distribution curve." The same is true for the residential exposure estimates, and this should be stated also. We recommend including upper-bound estimates for acute exposures in addition to average estimates. If upper-bound estimates are not included, then an in-depth discussion of the quantitative impact of the use of average exposures rather than upper-bound exposures should be included in the uncertainty analysis section (see comment below on this issue). This approach and the results should also be discussed in the context of sensitive populations (see discussion of this issue below).

Selection of NOEL for Chronic Toxicity

From the one-year dog study a NOEL of 20 ppm (0.59 mg/kg-day) was identified and used in the draft propetamphos RCD for evaluating chronic occupational and residential exposure. According to the draft RCD, the NOEL is based on prolonged anestrus in females, reduced brain cholinesterase (ChE) activity, increased liver weights, and hepatic necrosis at the next higher dose of 100 ppm (3.03 mg/kg-day). However, we conclude that 0.59 mg/kg-day is a LO[A]EL, not a NOEL. Based on the scientific evidence, hepatotoxicity appears to be the critical toxic effect in this dog study; necrosis was observed at 3 mg/kg-day. At 0.59 mg/kg-day, significantly increased liver weights in male dogs were observed, establishing a dose-response for liver changes. In addition, inhibition of red blood cell ChE activity (55% and 71% of controls for males and females, respectively) was observed at 0.59 mg/kg-day. Furthermore, the revised October 31, 1995, version of the summary of toxicology data for propetamphos prepared by DPR (not included in the draft RCD) determined that the NOEL from this study is 4 ppm (0.13 mg/kg-day) propetamphos in the feed, presumably based on one or both of these endpoints. We determine that the NOAEL for this study is 0.13 mg/kg-day, in agreement with the DPR summary of toxicology data.

In another dog study (six month oral feeding), a NOEL of 0.09 mg/kg-day based on reduced brain ChE activity (64% of controls in male dogs) was identified. The two arguments (i.e., length of study and dose estimates not validated) for not selecting this lower NOEL for ChE inhibition for risk assessment were explained on page 37. The use of a six-month oral feeding study in dogs for chronic effects risk assessment can be scientifically justified. The fact that the concentrations of propetamphos in the feed cannot be confirmed is a concern, but not sufficient in itself to disregard the results. We conclude that 0.09 mg/kg-day is a scientifically acceptable NOEL to use for risk assessment.

After reviewing the available scientific information, we determine that 0.13 mg/kg-day is the most scientifically appropriate NOEL for the estimation of margins of safety for chronic exposure. This would agree with DPR's toxicological summary of October 31, 1995. The use of a NOEL of 0.59 mg/kg-day for reduced ChE activity rather than the NOEL of 0.13 mg/kg-day for the higher absolute and relative liver weights for the chronic exposure estimates underestimates risk by over four-fold. While the use of the NOEL of 0.09 mg/kg-day would result in lower margins of safety, the use of a slightly higher NOEL from a better-reported study would appear to be scientifically justified. Using the NOEL of 0.13 mg/kg-day, the lowest (mean) occupational MOE would be approximately 2 and the lowest (mean) residential exposure MOE for children would be approximately 10.

Sensitive Populations

No sensitive groups were identified in the draft RCD, although adverse reproductive effects were observed in a two-generation rat reproductive study at doses very close to the toxic threshold in dogs. In addition, the prolonged anestrus observed in the one-year dog study and the reduction in fertility and mating indices observed in the reproductive study may be related to endocrine effects. Increased sensitivity of females is further suggested by more pronounced inhibition of brain cholinesterase (ChE) in females than males in many of the subchronic experimental studies, and from the clinical differences in their susceptibility to propetamphos (Dix et al., 1992). We conclude based on the available scientific evidence that women should be considered a potential sensitive subgroup for this chemical, particularly during pregnancy. The observed endocrine effects are also likely to be more severe in the developing organism, and thus may require a higher margin of safety. We recommend consideration of this subpopulation in the risk appraisal in relation to the magnitude of risk in the general population, in relation to the use of averages for acute exposure (use of mean versus upper-bound exposure estimates), and with respect to the scientific uncertainty of evaluating exposure to only one organophosphate pesticide at a time.

Exposure Assessment

Level of Detail is Inadequate. The draft exposure assessment does not contain enough of the necessary scientific information to verify the results and assumptions made in deriving the potential exposure. For example, it is not possible to reproduce or confirm any of the calculations with the information provided. In addition, many exposure assumptions have not been justified (such as six hours of activity and 18 hours of rest per day for both adults and children, the adult inhalation rates, and the dislodgeable residue estimates). We recommend including scientific support for these assumptions when available, or when default assumptions are used, cite the risk assessment guidelines or other reference materials used as the source of the defaults.

One example where the science does not support the conclusions is related to the discussion of toxicity based on peak plasma levels of propetamphos following dermal and oral exposures. The draft RCD states that the use of an oral bolus administration is highly "conservative" for the estimation of exposure via the dermal route because the dermal dose acquired during a work-day would produce much lower peak plasma levels than the oral bolus,

and the toxicity would only occur when the plasma levels exceed critical levels in the target organs. When comparing dermal to oral absorption rates, it might be scientifically valid to apply a pharmacokinetically-derived correction factor to decrease the "apparent" toxicity when exposures are mainly dermal, when adequate data exist. However, this would not be based on the peak blood levels as indicated, because propetamphos is an irreversible cholinesterase inhibitor. The "plasma level" potency argument in the draft exposure assessment (pages 12 to 14) is not scientifically justified (nor scientifically valid). Another example is where the draft exposure assessment states that no aggregate exposure assessment (combined occupational and residential exposure) was carried out because "this exposure scenario was considered remote." This implies that no propetamphos applicators would have this termite treatment used in their own homes, which is still a possibility and worth consideration. A third example is the basis for assuming that one hour of extensive dermal contact during a Jazzercise® routine is equal to contact during a normal day's activities. This assumption has not been supported scientifically.

Discussion of Uncertainty. The draft exposure assessment "Exposure Appraisal" (page 12) states that "risk assessment is filled with uncertainty, and the risk assessor tends to be very conservative when making the numerous assumptions that are inherent in the process." The text continues by providing two examples of "the most important factors that produce overestimates." The overall conclusion of the draft exposure assessment is that the exposure estimates are overestimated by "several fold." First, while the draft exposure assessment was prepared to "openly and honestly discuss the sources of uncertainty so that the risk manager can put them in perspective," it has not included a discussion of the examples of the numerous assumptions used in the assessment that might underestimate the exposure levels. Secondly, while difficult to do, no attempt was made to quantify the level of uncertainty for any of the factors. Nevertheless, the assessment uses words like "grossly overestimates actual doses," "high degree of conservatism," and "several fold" when describing the level of uncertainty. This results in an emphasis on the potential overestimation, but is not balanced by a discussion of the potential underestimation.

The presentation of scientific support for the assumptions and concepts presented in this section is minimal and not quantifiable. As a result, this section describing uncertainty, which is an important component of a risk characterization, is not justified with a scientific analysis of the existing data and data gaps and may bias the "risk manager" into believing only one perspective. We recommend that this section be deleted from the draft exposure assessment and that a more inclusive and scientifically neutral discussion of uncertainty for the exposure and risk assessment be included in the main RCD where uncertainty is discussed (page 36).

Populations at Risk. The populations at risk are not adequately defined in the draft exposure assessment.

Illness Reports. The relationship of exposures, as estimated in the draft exposure assessment, and the illnesses as separately documented in DPR's pesticide illness surveillance program and reported on page four of the draft RCD, is not clear. Information given by Koehler and Moye (1995) on airborne insecticide residue may be of significance. We recommend reviewing this paper and including a discussion about the relationship between exposures and documented illness reports in the revised RCD.

SPECIFIC COMMENTS

Pages 3 and 7. On page 3 the draft RCD states that the registrant requested that "DPR assume 100% dermal absorption in lieu of [submitting] a dermal absorption study." On page 7 the draft RCD states that "no dermal absorption data were available for propetamphos, so a default assumption of 50% was used." These two statements are confusing and the rationale for selecting the 50% dermal absorption rate given on page 7 is misleading. The default assumption of 50% might be appropriate for propetamphos given its physical and chemical properties (which are derived from data). If so, this is the rationale for selecting the 50% absorption rate and not that the data were unavailable. It is misleading to support the decision to use a less than maximum default value by stating that data were unavailable when DPR has the authority to require the data, but waived it. This can be corrected by providing the scientific rationale for selecting the 50% default value on page 7 and not the maximum default of 100%, and then deleting the reference to the unavailability of data.

Pages 11 and 12. It would appear from the values for oral and dermal LD₅₀ in Tables 1 and 2 that the toxicity of propetamphos liquid concentrate is being reported in Table 2 in terms of the weight of formulation, not weight of the active ingredient. This should be made clear.

Page 20. The text identifies a NOEL of 0.59 mg/kg-day for ChE inhibition and increased liver weight (and other effects) from a one-year oral (feed) study in dogs. The October 31, 1995, summary of toxicological data for propetamphos identified a NOEL of 0.13 mg/kg-day for increased liver weight. As noted above, we conclude that the use of the lower NOEL is scientifically justified. Nevertheless, the inconsistency in the two reports with respect to this study needs to be resolved.

Page 20, Table 7. We recommend including the data for red blood cell and plasma ChE activities in the table, along with the brain ChE, because these values are discussed in the text and there were significant compound-related changes in these activities.

Page 27. In the acute inhalation study, the LOEL and LC₅₀ for the technical grade formulation appear high. According to the data presented, the concentrated product is less than one-tenth as toxic as the diluted product, the 18.9% liquid concentrate (Table 1 compared to Table 2), and the 50% emulsifiable concentrate (page 13, reference to Leuschner et al.). Similarly the concentrated formulation is less toxic than oral doses of the same technical grade product. Organophosphates are generally more potent by inhalation, not less potent. The obtained result is likely to be related to the difficulty of conducting inhalation exposures to a chemical at several thousand times its equilibrium vapor pressure (i.e., with aerosol droplets). For such studies, determination of the delivered concentration and dose is difficult. We recommend that the revised RCD include information on these aspects of the study to explain the apparent aberrant results rather than only presenting the data (Table 10)

Page 39, section V. It is appropriate that the risk characterization acknowledges that cumulative exposures to organophosphates that have similar mechanisms of action should be considered, but

that methodology for this is still under development. However, we recommend that a more prominent statement to this effect be included in the discussion on uncertainty as well as in the "Summary" and "Conclusions" as this is a major issue yet to be properly addressed.

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Gray Davis
Governor

MEMORANDUM

TO: Gary Patterson
Supervising Toxicologist

VIA: Keith Pfeifer
Senior Toxicologist

FROM: Carolyn Lewis
Associate Toxicologist

DATE: February 5, 1999

SUBJECT: Response to OEHHA's Comments Regarding the Risk
Characterization Document for Propetamphos

The following comments are in response to comments from OEHHA regarding the draft Risk Characterization Document for Propetamphos.

General Comments:

- ! DPR is perplexed by the comment on the amount of repetition in this document. There has always been a certain amount of repetition in these documents between the Toxicology Profile and the Hazard Identification section. The Toxicology Profile describes the findings in each study organized into sections based on the study type as defined by the FIFRA guidelines. There are short summaries at the beginning of each section of the Toxicology Profile which are meant to provide the reader with a brief overview of the effects seen, so that the reader does not have to read the whole section if he/she does not want to. On the other hand, the Hazard Identification summarizes the effects seen in the various types of studies by acute, subchronic and chronic exposure. Therefore, effects seen in an acute neurotoxicity study may be compared with effects seen in a developmental toxicity study in the process of selecting an acute NOEL. Similarly, the effects in a reproductive toxicity study may be compared with a subchronic

neurotoxicity study in selecting a subchronic NOEL. The organization used in this Risk Characterization Document is not unique to this document, although the summaries in the Toxicology Profile have only been used in the last few years.

- ! DPR no longer attaches the SB950 Toxicology Summary to the Risk Characterization Documents to keep the size of the documents as small as possible. The exposure assessment are now considered stand alone documents and, consequently, are not attached as an appendix. DPR also no longer attaches the printouts from TAS for the dietary exposure. The only other appendix that might be attached would be a printout from any modeling done for oncogenicity. Since there were no treatment-related increases in tumors for this compound, no modeling was done.

Literature Search:

- ! A literature search was done about 5 years ago when the risk assessment for propetamphos was first initiated. So few reports of any toxicological concern were found, that they were inadvertently forgotten. Since this literature search was done several years ago, another search was conducted. Twelve toxicologically relevant reports were found and have been incorporated in the risk assessment. The reports addressed mechanism of toxicity (Mason *et al.*, 1993), illness reports (Sherman, 1995), environmental fate (Jain *et al.*, 1987; Agnihotri *et al.*, 1987; Brüggemann and Halfon, 1990; Koehler and Moye, 1995), pharmacokinetics (Dix *et al.*, 1992; Wells *et al.*, 1986a&b), acute toxicity (Leber, 1972), genotoxicity (Kumari and Kristnamurthy, 1986) and delayed neurotoxicity (Abou-Donia and Wilmarth, 1995). None of the reports had a significant impact on the conclusions made in this document. A number of the studies that OEHHA included in their list of references for propetamphos were not considered relevant for our risk assessment since they either relate to uses that are not registered in California (Rammel and Bentley, 1989; Virtue and Clayton, 1997) or to its efficacy (Rettich, 1980) which DPR does not usually include in their risk assessments. It should be pointed out that DPR is not required under SB950 to do a literature search when conducting risk assessments, but has chosen to do so for completeness of our review. U.S. EPA does not

normally include studies from the open literature in the risk assessments they conduct for their Reregistration Eligibility Documents (RED's). Most of the time, studies in the open literature are less useful than the registrant studies because only summary information is provided.

Biotransformation and Pharmacokinetics

- ! The location of the radiolabel has been added to the Pharmacokinetics section. The ^{14}C label was on the 1 and 3 position of the butenoic acid moiety. The label positions in the registrant's pharmacokinetic studies (Bhuta, 1979; Patel *et al.*, 1982; Patel and Winkler, 1982) are identical to the label positions used in the article by Dix *et al.* (1992) probably because they obtained the labeled and unlabeled propetamphos from the same registrant that did the pharmacokinetics study submitted to DPR. This was also the same radiolabel position in the studies conducted by Wells *et al.* (1986a&b). It is unclear why the reviewer considered the leaving group to be any less active than the methyl ester or amido side groups since any reaction which removes these side groups from propetamphos produces metabolites that no longer inhibit cholinesterase (Mason *et al.*, 1993). The best radiolabel position for organophosphates would be on the phosphorus, but that is seldom done. Despite the label positions used, the investigators were able to isolate metabolites showing the O-demethylation of the methyl ester side group.
- ! The phosphorylation of cholinesterase by propetamphos was not considered a form of biotransformation since this has to do with its mechanism of toxicity, rather than its activation and detoxification. However, a few additional sentences have been added to the Chemical Identification section in the Introduction describing the phosphorylation and aging reaction in more detail.

Acute Toxicity

- ! The statement in the risk appraisal section was revised to "Therefore, estimated MOEs for acute occupational *and residential* exposure may not cover those individuals at the upper end of the exposure distribution curve".

As stated in this section upper end estimates for exposure could not be calculate due to insufficient information from available studies. It is not possible to quantitate the impact of using the average exposure if one doesn't know where the extremes are.

Selection of NOEL for Chronic Toxicity

- ! In reevaluating the increased liver weights, we found that they did not correlate with the hepatic necrosis at 100 ppm. The dog with the highest liver weight was did not have elevated liver enzymes or hepatic necrosis and the dog with the most severe hepatic necrosis had a *reduced* liver weight. It is logical that the liver weight would decrease if there is necrosis. However, we also looked for possible histopathological lesions that might logically be associated with an increased liver weight such as fatty liver or inflammation. Focal inflammation of the liver was observed in all groups, including the control group; however, the incidence was lowest at 100 ppm. There was no evidence of fatty liver either from histopathological examination or in the clinical chemistry values (i.e., cholesterol, total lipids, triglycerides). The most probable explanation for the increased liver weights is microsomal induction. There was no histological evidence to confirm this possibility; however, microsomal induction is not easily detected with histopathological examination unless it is marked. Without any evidence correlating the increased liver weights to adverse pathological changes, DPR assumed this increase in liver weights was due to microsomal induction. Although microsomal induction is a treatment-related effect, DPR considers it an adaptive response, not an adverse effect. Therefore, the NOEL was set at 20 ppm even though there were increased liver weights at this dose level. The lack of correlation of the increased liver weights with pathological findings was added to the RCD. In addition, the NOEL in the SB-950 Toxicology Summary has been revised to 20 ppm after discussion of this issue with the toxicologist that initially reviewed the study.

- ! The NOEL from the 6-month dog study was not rejected because of its length of study, but because findings in the study were confounded by changes in the dose levels in two groups during the study and no analysis of feed to verify propetamphos concentration. Errors in calculations or

weighing during feed preparation or improper mixing can result in either lower or higher concentrations of the test compound in the feed than intended, possibly by orders of magnitude. Since a NOEL was established for the same endpoint in a longer study in the same species which met FIFRA guidelines (including analysis of test article for purity and concentration in the diet), greater weight was given to this study when selecting a NOEL for chronic toxicity.

Sensitive Population

- ! As discussed in the Risk Appraisal section under FQPA issues, there was not any evidence increased pre- or postnatal sensitivity to propetamphos based on the available developmental and reproductive toxicity studies. Therefore, pregnant and lactating women would not be considered a sensitive subpopulation. There was evidence of reproductive effects in the dog study (prolonged anestrous) and the rat reproductive toxicity study (reduced mating index); however, the NOEL for these reproductive effects was equal to or higher than the NOEL for other toxic endpoints in these studies. Therefore, a larger margin of exposure is not needed to protect for these reproductive effects. A sentence has been added to the discussion of endocrine effects under the FQPA section in the Risk Appraisal to indicate that the NOELs for the reproductive effects were equal to or higher than the NOEL for other toxic endpoints which was not mentioned in the previous draft.

Exposure Assessment

- ! Response to the comments on the exposure assessment document will be addressed by the Worker Health and Safety Branch in a separate memorandum.

Specific Comments

- ! At the time the registrant opted not to conduct a dermal absorption study, 100% was the default value that DPR used when there was no dermal absorption study. Subsequently, the Worker Health and Safety Branch of

DPR switched to using 50% as the default value after reviewing the dermal absorption data for 40 pesticides in rats. So the sentence on p. 3 is correct, albeit confusing after reading the statement in the summary on p. 7 that a default of 50% was used. To avoid confusion, the statement on p. 3 was revised so there is no specific mention of the default value to be used. The scientific rationale for the use of 50% dermal absorption as a default value was previously explained in the risk appraisal under the exposure assessment section. Since the reviewer apparently did not notice this, it was moved into the pharmacokinetics section under absorption. The lack of dermal absorption data was the reason for using a default value, so this was left in. The reason 50% was used instead of 100% is due to a science policy decision of the Worker Health and Safety Branch.

- ! Units were inadvertently omitted from both Table 1 and 2. The units in Table 2 are expressed as mg formulation for clarity.
- ! As mentioned previously under the selection of the chronic NOEL, the SB950 Toxicology Summary was revised to be consistent with the RCD.
- ! The red blood cell and plasma ChE activities were discussed in the text because they were considered indicators of exposure; however, they were not included in Table 7 because reductions in their activity are not considered adverse in the absence of clinical signs. There were also transient effects seen in this study that were discussed in the text, but not included in Table 7. The purpose of Table 7 is not to show every effect seen in the study, but to show those effects which we considered toxicologically significant when selecting a chronic NOEL for this study.
- ! The inhalation LC₅₀ study for the formulation was actually based on a study using a 50% emulsifiable concentrate. Rather than conduct another inhalation study, the registrant opted to use this study to fill the data requirement for the lower concentration formulation. A sentence was added to the discussion of the acute toxicity data for the formulation to indicate that the inhalation study for the formulation was actually for a higher concentration formulation. Comparing the LC₅₀ values for the technical grade material and the formulation is not very meaningful given the poor

quality of the LC₅₀ study for the technical material. The study for the technical material was conducted in 1974 before the FIFRA guidelines existed and consequently lacked any chamber measurements and details on the conduct and findings of the study. Since there was no analysis of chamber concentrations the LC₅₀ value for the technical grade material was expressed as a nominal concentration whereas the LC₅₀ value for the formulation is expressed as the analytical concentration which is more meaningful. This information has been added as a footnote to the tables. The particle size was also not measured in the study for the technical material so it is also possible much of the aerosol in the study for the technical material was not respirable.

- ! The possible cumulative exposure to organophosphates was discussed in the Risk Appraisal section along with all the other uncertainties associated with this risk assessment. The uncertainties in our risk assessments are not usually mentioned in the Summary and Conclusions for the purposes of brevity. Since there are so many uncertainties involved in the risk assessment it would be difficult to decide which ones warranted discussion in the Summary and Conclusions.

Additional Changes Made Not Related to OEHHA's Comments

Several changes were made to the document not due to any comments from OEHHA, but due to additional information that became available after the last draft.

- ! A new registrant metabolism study that recently became available was added to the Pharmacokinetics section.
- ! U.S. EPA recently made available on the internet, several documents related to the draft RED for propetamphos. Since U.S. EPA selected different studies to evaluate dietary, residential, and occupational exposure, we included a discussion of these studies and why DPR did not use them. U.S. EPA also discussed a questionable increase in pancreatic tumors in female rats which they did not consider sufficient evidence to calculate a cancer potency factor. DPR had not originally discussed this tumor incidence in

Keith Pfeifer
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the RCD since there was no significant trend or significant increase at the high dose. However, since U.S. EPA mentioned it in their evaluation, DPR added a discussion of this tumor incidence in the Toxicology Profile and Hazard Identification.

ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA
TO PESTICIDE PRODUCTS THAT CONTAIN
PROPETAMPHOS

BY

Tareq A. Formoli, Associate Environmental Research Scientist

HS-1731, August 9, 1996

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ABSTRACT

Propetamphos is an organophosphate insecticide that is registered in California primarily for structural pest control. A total of 371 illnesses associated with the use of propetamphos alone or in combination with other pesticides have been reported in California from 1982 to 1993. The reported illnesses were predominantly for non-pesticide handlers, involving mostly office workers, restaurant workers, and residents reentering treated areas. The number of illness reports appears to be in decline since 1988. Propetamphos was extensively absorbed and rapidly eliminated when administered orally to laboratory animals. The major nonconjugated and conjugated metabolites were volatiles consisting of acetone- and acetate-type compounds. In the absence of any dermal absorption data, a dermal absorption rate of 50% was assumed in this document to estimate human absorbed dosage. The workers with potential exposure are the structural pest control operators (PCO) handling propetamphos-containing products. The estimates of absorbed daily dosage (ADD) for PCOs were based on surrogate data and ranged from 13 to 110 $\mu\text{g}/\text{kg}/\text{day}$. Occupants and residents entering treated structures could be exposed to propetamphos residues. The estimates of ADD for children and adults reentering a treated resident were 44 and 28 $\mu\text{g}/\text{kg}/\text{day}$, respectively.

DPR is currently preparing a risk characterization document for propetamphos because it can cause cholinesterase inhibition in laboratory animals at low dosages. This human exposure assessment document was prepared to be incorporated into the risk characterization document for propetamphos.

Department of Pesticide Regulation
Worker Health and Safety Branch

Human Exposure Assessment

Propetamphos

August 9, 1996

INTRODUCTION

Propetamphos is an insecticide that is registered in California mainly for indoor structural uses. It is an organophosphate pesticide that can cause cholinesterase inhibition in mammals. In March 1990, the Department of Pesticide Regulation (DPR) (then a division within the California Department of Food and Agriculture) placed propetamphos into the reevaluation process because of the increasing number of reported illnesses associated with its use. In September of the same year, the DPR requested additional data from the registrant on dermal sensitization, odor threshold, indoor exposure, and dermal absorption. The requested data, except for dermal absorption, have been submitted to the DPR. Propetamphos is on the list of the first 200 pesticides to be reviewed under the Senate Bill 950 (SB 950), the Birth Defect Prevention Act of 1984. The DPR is currently preparing a risk characterization document for propetamphos because animal toxicity studies have shown that it can cause cholinesterase inhibition at low dosages.

Human exposure assessment is essential for the assessment of risk to those that are potentially exposed and is an integral part of the risk assessment process. This human exposure assessment document was prepared to be incorporated into the risk characterization document for propetamphos. It will also serve as a basis for developing mitigation strategies if exposure is found to cause excessive theoretical risk. A propetamphos human exposure study was used to estimate human nonoccupational exposure. Occupational exposure was estimated using propoxur and chlorpyrifos exposure information as surrogates.

CHEMICAL/PHYSICAL PROPERTIES

Propetamphos (CAS # 31218-83-4) is the common name for (E)-1-methylethyl 3-[[[(ethylamino) methoxyphos-phinothioyl]oxy]-2-butenate. The trade name is Safrotin . Its empirical formula is $C_{10}H_{20}NO_4PS$ with the molecular weight of 281.3. Propetamphos is a light brown, oily liquid that boils at approximately 88 °C. It is soluble in organic solvents such as xylene, hexane, and acetone. Its water solubility is 110 mg/L at 24 °C. Its half-life in a buffered aqueous solution is 37 to 47 days at 20 °C. It photodecomposes in aqueous media with a $t_{1/2}$ of 5 days. It has a vapor pressure of 8.1×10^{-5} mm Hg @ 25 °C (Sandoz, 1978).

FORMULATION AND USAGE

Propetamphos (Safrotin) is not registered for use on any agricultural commodity nor is it to be used on pets. It is an insecticide currently registered for institutional, industrial, home, and structural uses, both indoors and outdoors. According to the California Pesticide Use Report, 24,235 lb, 23,804 lb, and 38,307 lb of propetamphos were used in 1992, 1993, and 1994, respectively (DPR, 1994; DPR, 1995a; DPR, 1996). The use was almost entirely for structural pest control. Currently, there are two propetamphos-containing products registered in California: one is a pressurized liquid and the other is a liquid concentrate for home and institutional uses. Propetamphos is to be applied as spot, surface, crack & crevice, and injection treatments via low pressure spray. Injection applications are for termites. The application rates are shown in Table 1.

Table 1: Application Rates for Different Formulations of Propetamphos

Formulation	Application Rate (a.i.)*		
	surface application	spot, crack & crevice	injection
ready-to-use (RTU) aerosol	1%	1%	not on label
liquid concentrate	12.1 - 24.3 $\mu\text{g}/\text{cm}^2$	0.5 - 1.0%	1.0%

* - active ingredient

LABEL PRECAUTIONS

The liquid concentrate formulation contains 18.9% a.i., showing the signal word WARNING on the label with respect to acute oral toxicity. The liquid concentrate formulation is a Toxicity Category III for acute inhalation, acute dermal toxicity and skin and eye irritation (Sandoz Agro, Inc., 1994). The aerosol formulation contains 1% a.i., showing the signal word CAUTION on the label. The aerosol formulation is a Toxicity Category III with respect to acute oral, acute dermal, acute inhalation and skin & eye irritation (Zoecon Corporation, 1989).

No personal protective equipment (PPE) or engineering controls are required or shown on the label for the aerosol or the liquid concentrate formulation.

ILLNESSES/INJURIES

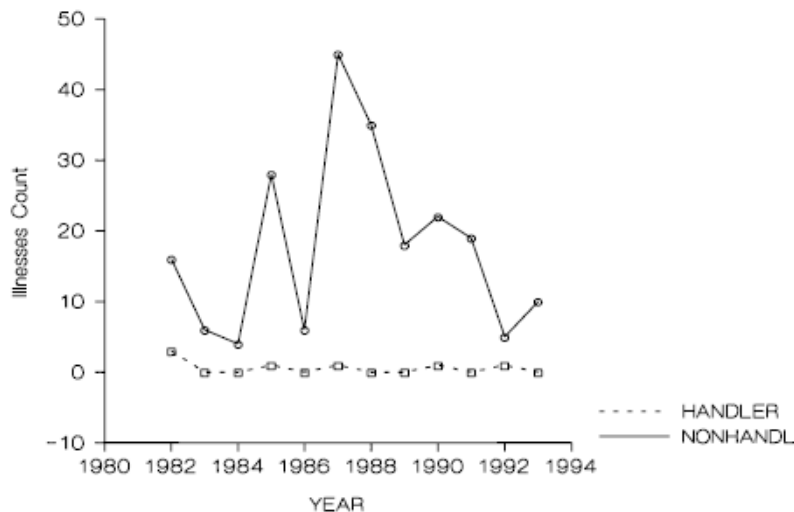
A total of 371 incidents were reported for the 12 year period of 1982 through 1993 (DPR, 1995b). These incidents include illnesses and injuries that were related to the exposure of propetamphos alone or to propetamphos in combination with other pesticides. There was one reported hospitalization and 86 cases involving disability that ranged from 1 to 36 days (DPR, 1995b). The population most adversely affected was the non-pesticide handlers, such as office workers, teachers, restaurant workers, and residents (Fig. 1). Of the 371 cases, 93% (346 cases) were structural residue related (Table 2 & Fig. 1). Twenty-five (7%) of the 371 incidents occurred during application. The most frequent comment given by the injured persons was the detection of an "odor"; and the available cholinesterase data were inconclusive (DPR, 1995b).

Of the non-pesticide handler-related cases due to only propetamphos, 56% (124 cases) were classified as definite/probable systemic incidents and 38% (84 cases) were determined to be possible systemic incidents. Of the residue related cases due to propetamphos plus other pesticides, 56% (84 cases) were classified as definite/probable systemic incidents and 24% (36 cases) were classified as possible systemic incidents. The 12 non-systemic cases were mostly skin-related injuries (9 cases: 4 definite & 5 possible), and the remaining 3 cases involving eye exposure were definite non-systemic.

Of the 25 handler illnesses, only 28% (7 cases) were due to exposure to propetamphos alone while 72% (18 cases) were due to exposure to propetamphos plus other pesticides in the same mix.

Of this 12-year period, illnesses/injuries reported by gender includes only the years 1989 through 1993. During this 5-year period, 164 incidents were reported. Of these 164 incidents, 132 (80%) cases involved adult females. All of the incidents involving adult females were structural residue related. Thirty-two (20%) of the 164 incidents involved males. One of the 32 incidents involved a male child. Of the 31 incidents involving adult males, 21 were structural residue related and 11 occurred during application.

Fig. 1: Reported Illnesses Related to Handler and Non-Pesticide Handler Exposures to Propetamphos: 1982 - 1993.



HANDLER means a person's work tasks require the handling of pesticides.
 NONHANDL means non-pesticide handler. Non-pesticide handler means a person's work tasks do not require the handling of pesticides. Such people are office workers, patients, teachers, nurses, *et cetera*.

Table 2: Handler vs. Non-Pesticide Handler Illnesses/Injuries Related to Propetamphos

	Handler ^(a)			Non-pesticide handler ^(b)			Total
	systemic ^(c)	non-systemic ^(d)	subtotal	systemic ^(c)	non-systemic ^(d)	subtotal	
Propetamphos	2	5	7	208	6	214	221
Propetamphos + other pesticides	16	2	18	120	12	132	150
Total			25			346	371

^(a) Work tasks requiring the handling of pesticides.

^(b) Office workers, patients, teachers, nurses, bar employees, *et cetera*.

^(c) Symptoms compatible but may or may not be specific to cholinesterase inhibition.

^(d) Eye, skin, or both.

DERMAL SENSITIZATION

No dermal sensitization studies involving human subjects were noted in the public domain literature. The animal model studies indicate the formulated products, up to 75% AI, were not skin sensitizers (Beck, 1984; Braun, 1985; Sandoz Ltd. Agro Development, 1980; Wilkinson and Singer, 1990).

DERMAL ABSORPTION

No dermal absorption data were reported. Worker Health & Safety will evaluate the exposure assessment assuming a 50% dermal absorption (Donahue, 1996).

DISLODGEABLE FOLIAR RESIDUES

Since there are no crop uses, dislodgeable foliar residue is not expected. The presence of dislodgeable residues following indoor structural applications is discussed in the exposure section.

METABOLISM

Female Wistar rats (10/dose) were administered a single oral dose of ¹⁴C-labeled propetamphos at 0.6, 6, or 16 mg/kg and placed in metabolism cages for 96 hours while urine and feces were collected (Bhuta, 1979). Additional female rats (4/dose) were placed in metabolism cages for 7 or 48 hours to collect CO₂. The estimates of excretion as ¹⁴CO₂ during the first 7 hours were 80, 60, and 40% at 0.6, 6, and 16 mg/kg, respectively. Approximately 12, 20, and 38% of the radioactivity was excreted in the urine at the respective dosages. Fecal excretion was less than 3% of the administered dose. Greater than 95% of the administered dose was excreted within the

first 24 hours, indicating that when administered orally, propetamphos is extensively absorbed and rapidly eliminated.

In the same study (Bhuta, 1979), another three female rats/time/dose were administered labeled propetamphos at 0.6 and 6 mg/kg and were sacrificed at 1, 2, 4, 8, 24, 72, or 96 hours for blood and tissue distribution analyses. At 0.6 mg/kg dose, the radioactivity in blood showed a monophasic elimination pattern with an estimated half-life of 60 hours. At 6 mg/kg dose, the elimination followed a biphasic pattern with estimated half-lives of 12 and 110 hours. The investigator suggested that these long half-lives do not indicate bioaccumulation but rather reflect the distribution and incorporation of the radiolabeled metabolites into natural constituents in tissues through the carbon pool. Blood and tissue radioactivity analyses within one hour of administration showed that the blood levels were lower than most surrounding tissues. The bone marrow and reproductive organs had the highest levels. In a separate study, when rats were given multiple oral doses, the highest tissue levels were in the lung, skin, and fat (Patel, *et al.*, 1982). The investigators suggested that the difference in the tissue residues with single and multiple doses may be due to an increased metabolism rate in the steady state condition.

The analysis of urine collected by Bhuta (1979) showed that the major non-conjugated and conjugated metabolites were volatiles consisting of acetone- and acetate-type compounds (Patel and Winkler, 1982). Minor non-volatile metabolites were desmethyl, desisopropyl, and desmethyl-desisopropyl propetamphos. The investigators proposed that propetamphos is metabolized by hydrolytic reactions, breaking the P-O-vinyl bond to form an acetoacetate moiety which decarboxylates to acetone and CO₂ after ester hydrolysis.

HUMAN EXPOSURE

Propetamphos uses are limited to indoor structural pest control in California. The workers with potential exposure are the structural pest control operators (PCO) handling the product. The exposure to individuals applying propetamphos in homes and institutions is shorter in duration and frequency when compared to PCOs. Occupants and residents entering treated structures could be exposed to propetamphos residues. Children and adults of residential structures who spend much of their time indoors and have movements that result in greater contact with treated areas may be the subgroup with the greatest potential of exposure to residues.

Worker Exposure (Mixer/Loader/Applicator for Indoor Applications)

There are no studies available that monitored the exposure of structural pest control operators during indoor application of propetamphos to carpets. Pesticide handlers exposure database (PHED) may not be an ideal surrogate to estimate the exposure of PCOs or others workers handling propetamphos for indoor home use. The closest exposure data in the PHED are greenhouse applicators, farm house applicators, and painters. The estimates of exposure of propoxur applicators were used as surrogate to estimate the exposure of applicators using identical or similar formulations of propetamphos. In the DPR exposure assessment document for propoxur, four propoxur exposure monitoring studies were reviewed (Sanborn, 1995). The

estimates of exposure were made for applicators using an aerosol (1%), a bait (2%), a ready-to-use spray (0.95%), and a 1% spray mix prepared from a wettable powder formulation. The percent of a.i. in the aerosol and ready-to-use formulations are identical to those of propetamphos. The exposure information for these two formulations was used as surrogate data for propetamphos. There are no wettable powder or bait formulations of propetamphos. Propoxur applicators wore cotton coveralls, baseball caps and chemical resistant gloves in addition to or in place of normal work clothing (long-sleeved shirt, long pants). Dermal exposure was monitored using patch dosimetry according to Durham and Wolfe (1962). Dermal exposure was calculated using patches attached under a layer of clothing. Hand washes were collected to estimate the exposure to hands. Inhalation exposure was monitored by collecting air samples from the breathing areas of applicators, using personal air pumps equipped with quartz microfiber air filters. More than 80% of the patches were below the limit of detection for applicators using the aerosol, bait, and ready-to-use formulations. In estimating the exposure, samples below the limit of detection were assumed to contain residues at one-half of the limit of detection. The estimates of absorbed daily dosage (ADD) and annual average daily dosage (AADD) of propetamphos applicators using aerosol or ready-to-use formulations are provided in Table 3.

Table 3: Estimate of ADD and AADD for Applicators Handling Different Formulations of Propetamphos Based on Surrogate Data

Formulation (n)	Dermal exposure (ug/application)	Inhalation exposure (ug/application)	Duration of application (hour)	ADD ^a (ug/kg/day)	AADD ^b (ug/kg/day)
1% aerosol (32)	390 (2.1)*	40 (2.0)*	0.41	13.8	8.8
1% RTU trigger pump spray (32)	260 (1.8)*	2 (1.8)*	0.27	12.8	8.2
1% E.C. mix for soil injection (8)	16500**	130**	2.8	109.6 ^c	69.9

a - Based on dermal absorption of 50% (see dermal absorption section), inhalation uptake of 50% (Raabe, 1988), adjusted for 2 hours of actual application time and male body weight of 75.9 kg (Thongsinthusak, *et al.*, 1993a).

The propetamphos product labels have no specific PPE statements. Workers were assumed to wear work clothing and gloves based on dermal hazards shown on the product labels and as a common practice.

b - An average of 233 days of work per year (Munro, 1992).

c - PCOs worked an average of 7 hours per day, 2.8 hours of actual application and the rest for site preparation.

* - Geometric mean (geometric standard deviation) adapted from Sanborn, 1995.

** - Arithmetic mean adapted from Thongsinthusak *et al.*, 1993.

(n) = number of replicates

RTU - Ready-to-use

In the chlorpyrifos exposure assessment document, an estimate of exposure of PCOs using chlorpyrifos for termite control was made based on an exposure study that monitored dermal and inhalation exposure of PCOs during chlorpyrifos sub-slab and soil injection (Thongsinthusak, *et al.*, 1993). This estimate of exposure was used as a surrogate to estimate the exposure of applicators using propetamphos for the same purpose. An emulsifiable concentrate formulation of chlorpyrifos was mixed with water to make a 1% solution. Dermal exposure was measured

using gauze patches and hand washes. Patches were placed outside the work clothing at the neck, chest and both shoulders to measure exposure to the head and neck. Additional patches were placed underneath the work clothing at the forearms, and upper and lower legs to measure exposure to protected areas of the body. The exposure to torso was estimated using patches placed outside the work clothing and assuming the work clothing provided 90% exposure protection. Inhalation exposure was determined using personal air pumps equipped with glass fiber filters. The PPE worn by the workers was not standardized and workers did not wear gloves during most of the work period. Six of the eight workers rolled up their sleeves, exposing the forearm patches. Most of the exposure occurred to upper and lower legs (51%) and forearms (34%). The estimate of exposure of applicators applying propetamphos as soil injection for termite control is also shown in Table 3.

Residential Exposure

Since the predominant use of propetamphos is for indoor structural pest control, there is a potential for exposure of occupants entering treated structures. The potential exposure of residents, particularly children, entering treated homes is a primary concern since they spend more time indoors and, therefore, have the greatest potential exposure. In order to evaluate the indoor exposure of residents, a study was conducted to monitor the potential dermal and inhalation exposure of human volunteers entering carpeted rooms treated with propetamphos (Rosenheck and Hudlow, 1993). The study was conducted in February of 1993 in Fresno, using vacated and cleaned hotel rooms. The study was conducted in compliance with the US EPA Good Laboratory Practice standards except for collection, handling, and analysis of blood cholinesterase samples.

A 0.5 percent propetamphos solution was applied to the 100 percent nylon carpet at the label-recommended rate of one gallon of product per 1,500 square feet by a licensed PCO as a broadcast spray. The exposure of five human volunteers (2 males, 3 females) was monitored at 3, 6, and 9 hours after application. The volunteers wore a full-body dermal dosimeter (long underwear, athletic socks, and gloves, all made of 100 percent cotton) and entered hotel rooms treated with propetamphos at the above intervals. Two rooms were used for each reentry interval resulting in ten replicates for each reentry interval. The volunteers performed a set of Jazzercise routines in each room for approximately 20 minutes. The Jazzercise routines allowed maximum body contact with the treated carpet. Face and neck wipes were collected to estimate dermal exposure to uncovered areas of the body. Hand rinses were collected in 300 mL of a 0.01 percent v/v sodium dioctyl sulfosuccinate solution to remove any residues that may have passed through the gloves. Full-body dosimeters were cut into three sections (arms, upper body, lower body) after collection. Inhalation exposures for children and adults were estimated from propetamphos residues in the air samples taken from the center of each room at the height of 6 and 36 inches, respectively.

Air samples were taken at the rate of 1.5 liter/minute using a cassette equipped with a glass fiber filter (1 μ m pore size) and polyurethane foam plug. Air sampling began when the volunteers entered the room and continued for approximately 4 hours. Dislodgeable residue samples were collected at each reentry interval by rolling a swivel handled roller weighing 17 kg over four

0.165 m² cotton cloths. The roller moved back and forth ten times over the cloth that was placed over the treated carpet. The level of propetamphos applied to the carpet was determined by analysis of four 0.165 m² cotton cloth samples with impervious backing that were placed in each room prior to application and were collected 15 minutes after application. The level of residues on the carpet was also determined by theoretical calculation of the amount of product sprayed in each room.

All collected samples were stored on dry ice in an ice chest. Samples were delivered the next day to a walk-in freezer until transported to the analytical laboratory five days later where they were kept at or below 0°C until analysis. Spike and control samples were taken on the day of monitoring in the same hotel but in separate rooms. Two samples of each matrix were spiked, one at 5.1 µg/matrix and the other at 102 µg/matrix. All spiked matrices except for face and neck wipes, hand wash solutions, and air samples, were kept exposed to the environment for 20 minutes before storage in an ice chest containing dry ice. Air samples remained exposed to the environment for 40 minutes. Average field recovery for all matrices ranged from 75 percent (hand washes) to 89 percent (full-body dosimeters). Samples below the minimum quantifiable level (MQL) were assumed to contain residues half the MQL. These samples were not corrected for field recoveries. All other samples were corrected for average field recovery for that specific matrix.

Table 4. Total and Dislodgeable Residues of Propetamphos on the Carpet and Air Residues Following Carpet Treatment

Post application reentry (hours)	Total carpet residue (µg/cm ²)	Dislodgeable residue (roller) (µg/cm ²)	Transfer to roller (%)	Air residue at 6 inches (µg/m ³)	Air residue at 36 inches (µg/m ³)
3	16.3	0.079	0.49	6.05	8.41
6	21.1	0.074	0.35	6.36	6.88
9	17.2	0.112	0.65	9.83	12.90
Average	18.2	0.088	0.50	7.41	9.73

The amount of a.i. used in each room was approximately 2.9 grams. The calculated target value for total deposition on each cloth was 23.0 mg/cloth or 13.9 µg/cm². The actual level of total residues on the deposition cloths that were placed on the carpet prior to application was between 99 and 162% of the calculated value. The mean residue found on the carpet was 30.0 mg/cloth or 18.2 µg/cm².

Plasma and RBC cholinesterase levels of volunteers were determined before and after the exposure. Volunteers were observed up to two weeks following the exposure. None exhibited any symptoms of discomfort or toxicity. Their cholinesterase levels tested 24 and 72 hours after the exposure remained within ±15 percent of the pre-exposure range.

Table 5. Dermal Exposure of Volunteers Performing Jazzercise® on Carpets Treated with Propetamphos

Reentry post application (hours)	Duration of Exposure (hour)	Head exposure (µg/person)	Body exposure (µg/person)	Hand exposure (µg/person)	Dermal exposure (µg/person/0.33 hour)	Dermal Exposure (µg/person/hour)
3	0.308	1.3	979	162	1,143	3,711
6	0.275	1.2	768	140	909	3,305
9	0.308	1.0	1,188	183	1,371	4,451
Average	0.297	1.2	978	162	1,141	3,822

% of total		0.10	85.7	14.2	100	
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Dermal exposure to head, body, and hands of volunteers at various times of reentry is shown in Table 5. The daily exposure to residents reentering a house three hours after propetamphos application was estimated with the following assumptions: occupants with no clothing, one hour of extensive dermal contact (Jazzercise®) with the treated area would provide as much dermal contact as a daily normal activity, and 6 hours of activity and 18 hours of rest for inhalation exposure. Daily dermal exposure was calculated as follows:

Daily dermal exposure:

$$\text{Adults} = (3,822 \text{ } \mu\text{g/person/day})/70.9 \text{ kg} = 53.9 \text{ } \mu\text{g/kg/day}$$

$$\text{Children} = [(3,822 \text{ } \mu\text{g/person/day}) \times (3,925 \text{ cm}^2/17,900 \text{ cm}^2)]/10.5 \text{ kg} = 79.8 \text{ } \mu\text{g/kg/day}$$

Based on adult body weight of the study participants, adult body surface area from Thongsinthusak, *et al.*, 1993a (average of 2 males and 3 females), and child body surface area and body weight from Snyder, *et al.*, 1974.

Oral exposure was estimated as a fraction of hand exposure, assuming 5% and 50% of hand exposure would be ingested by adults and children, respectively (Ross, *et al.*, 1992). Since hand exposure constituted 14% of total dermal exposure (Table 5), oral exposure was estimated as follows:

Daily oral exposure:

$$\text{Adults} = (53.9 \text{ } \mu\text{g/kg/day} \times 14\%) \times 5\% = 0.4 \text{ } \mu\text{g/kg/day}$$

$$\text{Children} = (79.8 \text{ } \mu\text{g/kg/day} \times 14\%) \times 50\% = 5.6 \text{ } \mu\text{g/kg/day}$$

The estimates of ADD for indoor occupants are shown in Table 6. Since the oral contribution is derived from the total dermal exposure, dermal exposure in Table 6 was corrected for the fraction of hand exposure that will be ingested.

Table 6. Estimates of ADD and AADD for Occupants Entering Carpeted Rooms Treated with Propetamphos

Indoor Occupant	Body weight (kg)	Inhalation rate (m ³ /hour)		Exposure (µg/kg/day)			ADD ^d (µg/kg/day)	AADD ^e (µg/kg/day)
		activity	rest	Dermal	Oral	Inhalation ^c	Total	Total
Adult ^a	70.9	0.66	0.50	53.5	0.4	2.2	28.3	9.3
Child ^b	10.5	0.25	0.09	74.2	5.6	2.6	44.0	14.5

a - Inhalation rates from Thongsinthusak, *et al.*, 1993a (weighted average for 3 female and 2 male study participants). Average body weight of the study participants.

b - Body weight, body surface area, and inhalation rates from Snyder, *et al.*, 1974.

c - The first 6 hours of exposure is based on average of 3 to 9 hours post-application air residues measured at 6 and 36 inches for children and adults, respectively, and the last 18 hours of exposure is based on 9 hours post-application air residues at 6 and 36 inches for children and adults, respectively.

d - Based on dermal absorption of 50% (see dermal absorption section), inhalation uptake of 50% (Raabe, 1988), and oral absorption of 100%.

e - A total of 24 applications in a year as label recommends bimonthly maintenance, and 5 days of exposure following each application.

Based on an equilibrium model, the dislodgeable residue data collected by the roller can also be used to estimate dermal exposure. This model assumes that during the period of contact of the body with the treated surface, the concentration on the body will come into equilibrium with the dislodgeable residue concentration on the surface. It also assumes that the total human body surface area will come in contact with the treated carpet. Therefore, the exposure to the skin surface area in contact with the treated carpet will be equivalent to the residues found in sampling cotton cloths pressed against the treated carpet (dislodgeable residues). Table 7 shows dermal exposure estimates based on dislodgeable residue rate of 0.088 µg/cm², using the equilibrium model. Inhalation exposure was assumed to be the same as shown in Table 6. Oral exposure was calculated the same manner as was described previously.

Table 7. Estimate of ADD and AADD Based on Equilibrium Model for Occupants Entering Carpeted Rooms Treated with Propetamphos

Indoor Occupant	Body weight (kg)	Body surface area (cm ²)	Dislodgeable residues (µg/cm ²)	Exposure (µg/kg/day)			ADD ^b (µg/kg/day)	AADD ^c (µg/kg/day)
				Dermal	Oral	Inhalation ^a	Total	
Adult	70.9	17,900	0.088	22.0	0.2	2.2	12.3	4.0
Child	10.5	3,925	0.088	30.6	2.3	2.6	18.9	6.2

a - From Table 6.

b - Based on dermal absorption of 50% (see dermal absorption section), inhalation uptake of 50% (Raabe, 1988), and oral absorption of 100%.

c - A total of 24 applications in a year as label recommends bimonthly maintenance, and 5 days of exposure following each application.

This study indicates that dermal exposure was the primary route of exposure and occurred mainly to upper and lower parts of the body. Hand exposure, which includes the oral exposure, accounted for 14.2% of the total dermal exposure. Exposure to the head was minor. The roller method indicated that only 0.5% of residues on the carpet is dislodgeable (Table 4). Based on the dislodgeable residue values in Table 4 and dermal exposure values in Table 5, an average dermal transfer factor of 43,800 cm²/hour can be obtained. None of the actual carpet residues, dislodgeable residues, or dermal exposure values shown in Tables 4 and 5 exhibit a declining pattern over the time period of monitoring. This is consistent with a propetamphos dislodgeability study, indicating almost no residue dissipation over four weeks following the application (Zoecon, 1988). In this study, however, dislodgeable residues showed a slow and gradual decline over the same period, indicating approximately 50% decline in 5 days. Assuming that the exposure would decline parallel to the reduction in dislodgeable residues, the AADD in Tables 6 and 7 were calculated based on average 5 days of exposure after each application and two applications each month.

EXPOSURE APPRAISAL

The science of risk assessment is filled with uncertainty, and the risk assessor tends to be very conservative when making the numerous assumptions that are inherent in the process. It is incumbent upon the risk assessor to openly and honestly discuss the sources of uncertainty so that the risk manager can put them in perspective. The best risk estimates are made with adequate high quality data. Unfortunately, for many chemicals such data are lacking.

There are several factors in most exposure assessments that make them very conservative. Even with "reasonable" input parameters for exposure calculation, there is a high degree of conservatism (tendency to overestimate exposure) not immediately apparent. These factors are very real, but typically hidden and therefore not acknowledged. Below is a brief narrative on the most important factors that produce overestimates.

Dermal versus Oral Plasma Levels

Dosage is expressed as a single static value both in worker exposure and animal toxicology studies. The rate of dermal absorption is always lower than the rate of oral absorption in animals used for toxicology testing. Adverse effects occur when plasma levels in the target organ exceed a critical level. However, dermal acquisition occurs over the entire workday, and because dermal absorption is slower than oral, plasma levels for the same total absorbed dosage will not be nearly as high for a dermal versus oral exposure. A dermal dose acquired over the entire workday produces peak plasma levels much lower than the bolus oral feeding dosage acquired by animals in seconds to minutes. Because the effect is highly dependent on plasma level, treating an eight-hour dermal acquisition as a bolus is so conservative that it outweighs any other perceived source of underestimating exposure. The net effect of assuming instantaneous dermal dose acquisition and absorption is an overestimate of peak plasma concentration compared to the oral route by several fold for the same absorbed dose (Table 8). Note that the lower the dose, the

more pronounced this difference becomes. This difference is particularly pertinent when comparing the doses used in a toxicology study to those to which a human would be exposed.

Table 8. Peak Plasma Levels in Man After Oral and Dermal Exposure to Fluazifop-Butyl^a, Normalized for Total Absorbed Dose

Applied Dose (mg)	Route of Exposure	Absorption (% of Applied) ^b	Peak Level (µg/L/mg) ^c	Ratio of Levels Oral vs. Dermal
6.1	oral	100.0	100.0 (3 h)	-
200.0	dermal	1.5	73.3 (22 h)	1.4
20.0	dermal	3.4	32.4 (22 h)	3.1
2.0	dermal	8.0	12.5 (22 h)	8.0

^a adapted from Auton *et al.* (1993).

^b *in vivo* absorption as measured by Auton *et al.* (1993), except for oral; note that the peak plasma concentration ratios between dermal and oral administration would have been (proportionally) higher, if a value lower than the default of 100% were used for oral absorption of this pesticide.

^c normalized for total absorbed dose; in parentheses are the intervals between the time of dosing and the time at which the peak plasma level occurred.

Lower urinary metabolite concentrations (an indication of lower peak plasma concentrations) are also seen with dermally applied pesticides when compared with the urinary metabolite concentration observed following oral dosing (Krieger *et al.*, 1993).

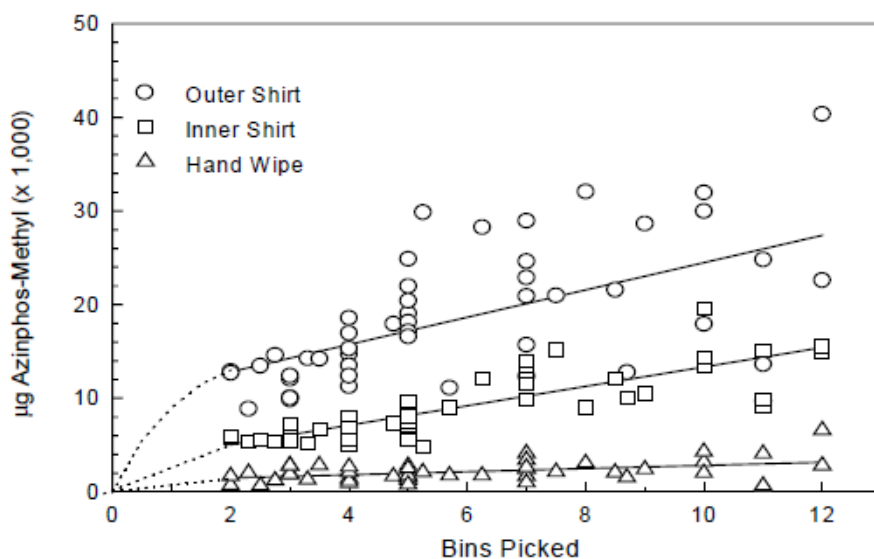
Short Workday Exposure Monitoring Overestimates Full Day

Another source of overestimated dose comes from partial-day monitoring. Figure 2 shows that if an estimate of full-day exposure were extrapolated from 1/3 day (four bins picked) the exposure would be overestimated by more than 50 - 80% and from 1/2 day (six bins picked) 20 - 40%. Shorter monitoring periods are encouraged because it allows an investigator to obtain two or more replicates per individual per day of monitoring. Note that hand residues remain virtually constant indicating that they rapidly come into equilibrium with their environment. Thus summing hand washes taken throughout the day grossly overestimates actual dose. This same principle is operative for pesticide handler exposure monitoring studies.

Conclusion About Exposure Estimates

These factors are operating in the vast majority of exposure estimates and because they are multiplicative, result in overestimates of several fold. The concern that the maximally exposed individual is not adequately represented by mean estimates of exposure is not well founded when considering all the "hidden" conservatism built into all estimates of exposure resulting from the dermal route.

Figure 2. Dermal Monitoring Residues vs. Peach Production, Sutter County, 1989^a



^a adapted from Spencer *et al.* (1995).

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