

PROPOXUR

(BAYGON®)

RISK CHARACTERIZATION DOCUMENT

Medical Toxicology and Worker Health and Safety Branches

Department of Pesticide Regulation

California Environmental Protection Agency

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PROPOXUR

EXECUTIVE SUMMARY

INTRODUCTION

Propoxur is a carbamate insecticide developed by Bayer AG, Germany, and registered by the U.S. Environmental Protection Agency and by the State of California for use against ants, cockroaches, crickets, fleas, flies, mosquitoes, wasps, and ticks. It is not used on any food crops.

THE RISK ASSESSMENT PROCESS

Propoxur entered the risk assessment process because of oncogenic effects identified in chronic exposure studies. The risk assessment process consists of four aspects: hazard identification, dose response assessment, exposure evaluation, and risk characterization.

Hazard identification entails review and evaluation of the toxicological properties of each pesticide. The dose-response assessment then considers the toxicological properties and estimates the amount which could potentially cause an adverse effect. The amount which will not result in an observable or measurable effect is called the No-Observed-Effect Level, NOEL. A basic premise of toxicology is that at a high enough dose, virtually all substances will cause some toxic manifestation. Chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes. In reality, these terms describe chemicals which require low or high dosages, respectively, to cause toxic effects. Toxicological activity is determined in a battery of experimental studies which define the kinds of toxic effects which can be caused, and the exposure levels (doses) at which effects may be seen. State and federal testing requirements mandate that substances be tested at doses high enough to produce toxic effects, even if such testing involves chemical levels many times higher than those to which people might be exposed.

In addition to the intrinsic toxicological activity of the pesticide, the other parameters critical to determining risk are the exposure level, frequency and duration. The purpose of the exposure evaluation is to determine the potential exposure pathways and the amount of pesticide likely to be delivered through those routes.

The risk characterization then integrates the toxic effects observed in laboratory studies conducted with high dosages of pesticide, to potential human exposures at low dosages. The likelihood of potential, non-oncogenic adverse health effects in people is generally expressed as the margin of safety. A margin of safety is the ratio of the dosage which produced no effects in laboratory studies divided by the human exposure dosage. For oncogenic effects, the excess lifetime risk of cancer is determined by multiplying the cancer potency of the pesticide times the estimated exposure dosage.

TOXICOLOGY

Based on the currently available toxicity information, the Department of Pesticide Regulation (DPR) has concluded that acute exposure to propoxur resulted in clinical signs in both laboratory animals and humans due to inhibition of cholinesterase activity. Chronic exposure of laboratory animals to repeated doses of propoxur adversely affected the bladder epithelium of rats, causing hyperplasia, papillomas, and carcinomas. Likewise, repetitive dosing with propoxur resulted in hepatocellular adenomas in the livers of rats and mice. DPR has further concluded that, in the absence of additional data to the contrary, chronic exposure to propoxur has the potential to cause similar effects in humans.

WORKER EXPOSURE

Registrant supplied data was used to estimate potential exposure via dermal contact, and inhalation of pesticide control operators spraying propoxur in structural cracks and crevices. Non-occupational exposures to residents of treated buildings, and pet owners were also examined. Principal routes of exposure were dermal, through contact with treated surfaces, and inhalation.

CONCLUSIONS

Using current toxicity data and exposure data, the calculated margins of safety (MOSs) for potential acute and chronic occupational and non-occupational exposures to propoxur were greater than the values conventionally recommended to protect people from the toxic effects of a chemical. Maximum Likelihood Estimates (MLEs) of excess lifetime risks of cancer from occupational exposure to propoxur ranged from 1×10^{-6} to 6×10^{-6} . The upper-bound (95%) excess lifetime risks of cancer for occupational exposure to propoxur ranged from 2×10^{-6} to 9×10^{-6} . None of the MLEs for excess lifetime risks of cancer from potential non-occupational exposures to propoxur exceeded 1×10^{-6} . The upper-bound excess lifetime risks of cancer for potential non-occupational exposure to propoxur were not greater than 2×10^{-6} .

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SUMMARY

Propoxur [Trade name- Baygon®, 2(1-methylethoxy)phenol methyl carbamate] is a carbamate insecticide developed by Bayer AG, Germany, and registered by the U.S. Environmental Protection Agency and by the State of California for use against cockroaches, crickets, fleas, flies, mosquitoes, wasps, and ticks. It is not used on any food crops.

Illness Reports- Between the years 1982 to 1990, approximately 58 cases of occupational illness and 42 cases of non-occupational illness have been associated with propoxur.

Environmental Fate- The hydrolytic half-life of propoxur is 16 days at pH 8, but the half-life could not be determined at pH 7 as no hydrolysis occurred during the 107 day observation period. The photolytic half-life in neutral aqueous solution was approximately 10 days. Bacterial degradation of propoxur was the same under aerobic or anaerobic conditions, with half-lives ranging from 80 to 210 days (depending upon soil type). Propoxur leached readily from soils, moving with the water front. Based on these results, propoxur is unlikely to remain in the location where it is applied. However, because it is readily decomposed, propoxur is unlikely to become a persistent environmental contaminant.

Pharmacokinetics- Propoxur was readily absorbed by the gut of rats (approximately 100%), hamsters, and cattle. Less than 1% of radiolabel from an administered oral dose was found in the feces of these animals. Absorption across the gut in humans appeared to be approximately the same as laboratory animals. The principal route of excretion in laboratory animals and humans was through the urine, with up to 95% of the absorbed dose excreted within 48 hours by laboratory animals. Propoxur did not accumulate in any body tissues, with the exception of the kidney during the process of excretion. In cattle, less than 0.1% of the administered dose was found in the milk. The half-life of propoxur in humans following intravenous administration was 8 hours. The cumulative human dermal absorption for 24 hours was approximately 16%.

The major metabolites of propoxur in humans, hamsters and rats were 2-isopropoxyphenol, 2-isopropoxyphenyl-carbamic acid, 1,2-dihydroxybenzene, 2-hydroxyphenyl methylcarbamate, 2-isopropoxy-5-hydroxyphenyl methylcarbamate, and 2-isopropoxy-4(5)-methoxy-5(4)-hydroxyphenyl methylcarbamate. These metabolites were also conjugated to form O-glucuronides.

Acute Toxicity- The oral LD₅₀ for rats ranged from 40 to 150 mg/kg. In the rat, the No-Observed-Effect-Level (NOEL) for cholinergic signs (convulsions, reduced motility, apathy, bristling coat) from a single dose was 5 mg/kg. In humans, the Lowest-Observed-Effect-Level (LOEL) for cholinergic signs (stomach discomfort, blurred vision, moderate facial redness and sweating) was 0.36 mg/kg, and the 30-minute NOEL was 0.2 mg/kg.

Chronic Toxicity/Oncogenicity- The chronic NOEL for depression of body weight gain, and changes in blood parameters indicating hemolytic anemia was 7 mg/kg-day in the dog. In rats, the chronic NOEL for uroepithelial hyperplasia was 8.23 mg/kg-day in males and 11.02 mg/kg-day in females. Carcinogenicity was observed in the uroepithelium of bladders of both male and female Wistar rats during a chronic feeding study with propoxur. A second chronic feeding study with female Wistar rats indicated that hyperplasia of the bladder epithelium occurred as early as 4 weeks, and the earliest that carcinomas appeared was 78 weeks. Although female Sprague-Dawley rats did not develop bladder carcinomas in a subsequent 52

week study, their bladders developed bladder epithelial hyperplasia similar to that observed in treated Wistar rats. Wistar rats exposed to propoxur via whole-body inhalation developed treatment-related urinary bladder adenomas and carcinomas, as well as adenomas of the pituitary and liver.

No malignant tumors were observed in mice. However, male mice experienced a significant, dose-related increase in hepatocellular adenomas. Both male and female mice exhibited a significant, dose-related increase in hyperplasia of the bladder epithelium. The NOEL for epithelial hyperplasia of the urinary bladder (males and females), liver hepatocellular vacuolation (females), changes in clinical chemistry (males and females), ovarian hemorrhage and thrombus formation, and eosinophilic deposits in the kidneys (males) was 75 mg/kg-day.

Female hamsters, exposed to propoxur in the diet for one year, exhibited no histopathological effects in the bladder.

Genotoxicity- Propoxur, with or without activation, was not mutagenic in bacteria, yeast, or Chinese hamster ovary cells. However, a nitroso derivative of propoxur was mutagenic and produced mitotic gene conversion in bacteria, and caused DNA damage in human fibroblasts. Although propoxur did not cause chromosomal damage or unscheduled DNA synthesis in Chinese hamster tissue *in vitro*, propoxur did induce increased frequencies of sister chromatid exchanges and micronuclei in human lymphocyte cultures. Several major metabolites of propoxur, and the urine from rats treated with propoxur, were tested for mutagenicity and genotoxicity. With the possible exception of 2-isopropoxyphenylhydroxy methylcarbamate, no mutagenic effects of propoxur metabolites could be demonstrated in the Ames test. Consequently, the results of the genotoxicity studies on propoxur were equivocal.

Reproductive Toxicity- No adverse reproductive effects were noted in a two-generation rat reproduction study. The parental NOEL was 7.3 mg/kg-day for body weight gain decrement, and inhibition of brain and red blood cell cholinesterase activity. The developmental NOEL was 37 mg/kg-day for decrement in weight gain for pups after day 4.

Developmental Toxicity- Propoxur induced maternal toxicity in rats and rabbits. The 1-day NOEL for maternal toxicity in rats, based on cholinergic signs (chewing motions, teeth grinding, tremors), was 3 mg/kg-day. In rabbits, the 1-day maternal NOEL was 10 mg/kg-day, based on cholinergic signs (restlessness and dyspnea) and death. The developmental NOEL, based on vertebral malformations in rabbits was 10 mg/kg-day.

Neurotoxicity- The single dose LOEL in rats for cholinergic signs (excessive chewing and reclining posture) and significant inhibition of brain cholinesterase activity was 2 mg/kg. There was no NOEL.

Hazard Identification- Human volunteers (number unstated) were reported to have exhibited cholinergic signs (stomach discomfort, blurred vision, moderate facial redness and sweating) with a single oral dose of 0.36 mg/kg. Five individual doses of 0.2 mg/kg, administered at 30 minute intervals, produced no clinical signs, although red blood cell cholinesterase activity was depressed about 10%. Thus, the NOELs for clinical signs (specified amounts- up to 1 mg/kg- for specific lengths of time- up to 2 1/2 hours) were used to evaluate the health risks from potential acute exposures of different durations to propoxur.

The principal non-oncogenic chronic effects were depression of body weight, and changes in blood parameters indicating possible hemolytic anemia. The 1-year NOEL for hemolytic anemia in the dog, 7 mg/kg-day, was used to evaluate the health risks from potential annual exposures to propoxur. Two separate chronic feeding studies with Wistar rats have clearly demonstrated that propoxur causes bladder tumors. The combined incidence of benign and malignant bladder tumors in both male and female rats was used as the basis for calculating the potency of propoxur for humans (slope of the estimated risk/dose curve), using the Global 86 linear multistage model. An interspecies scaling factor, (body weight)^{3/4}, was used to adjust for species differences. The maximum likelihood estimate (MLE) for human cancer potency was 3×10^{-3} (mg/kg-day)⁻¹, with an upper bound (95% confidence level) of 4×10^{-3} (mg/kg-day)⁻¹.

Exposure- The mean absorbed dosages for Pest Control Operators (PCOs) per 2-hour cycle ranged from 0.16 to 1.5 $\mu\text{g}/\text{kg}\text{-cycle}$. The 95th percentile of the absorbed cycle dosage for PCOs ranged from 0.32 $\mu\text{g}/\text{kg}\text{-cycle}$ to 8.0 $\mu\text{g}/\text{kg}\text{-cycle}$. Annual average daily occupational dosages ranged from 4.5 to 14.6 $\mu\text{g}/\text{kg}\text{-day}$, and lifetime average daily dosages ranged from 0.5 to 2.0 $\mu\text{g}/\text{kg}\text{-day}$. Passive, non-occupational exposures ranged from absorbed daily dosages of 0.4 to 1.46 $\mu\text{g}/\text{kg}\text{-hr}$. The most exposed group was children, 1-5 years of age. The mean absorbed daily dosage for adults engaged in spraying two dogs per day for flea control was 10.3 $\mu\text{g}/\text{kg}\text{-day}$. The 95th percentile of the absorbed dosage for people spraying pets was 77.1 $\mu\text{g}/\text{kg}\text{-day}$. The annual average daily dosage was 0.75 $\mu\text{g}/\text{kg}\text{-day}$, and the lifetime daily dosage was 0.43 $\mu\text{g}/\text{kg}\text{-day}$.

Risk Characterization- Margins of Safety (MOSs) for mean acute occupational exposures, based on the 2-hour NOEL of 800 $\mu\text{g}/\text{kg}$ for cholinergic signs in humans, ranged from 544 (applicators handling 70WP) to 5,000 (applicators using 0.95% active ingredient in spray). The MOSs for the 95th percentile of the absorbed cycle dosages ranged from 100 (applicators handling 70WP) to 2,500 for spray applicators using 0.95% formulation. MOSs for potential chronic occupational exposure to propoxur ranged from 479 for aerosol applicators to 1,707 for 0.95% spray applicators. Maximum Likelihood Estimates (MLEs) of excess lifetime risks of cancer from occupational exposure to propoxur ranged from 1 to 6×10^{-6} . The upper-bound (95%) excess lifetime risks of cancer for theoretical occupational exposure to propoxur ranged from 2×10^{-6} to 9×10^{-6} .

MOSs for mean acute non-occupational exposures ranged from 97 for pet owner/groomers to 3,636 for adolescents at home after the house had undergone crack and crevice treatment with propoxur. The MOS for the 95th percentile of the absorbed cycle dosage for dog owner/groomers was 13. The MOSs for potential chronic exposure to propoxur, based on the NOEL of 7,000 $\mu\text{g}/\text{kg}$ for hemolytic anemia in dogs, ranged from 5,833 to 53,846, with children (ages 1-5 years) having the lowest MOS. None of the MLEs for excess lifetime risks of cancer from non-occupational exposures to propoxur exceeded 1×10^{-6} . The upper-bound (95%) excess lifetime risks of cancer for theoretical non-occupational exposure to propoxur were not greater than 2×10^{-6} .

Conclusions- Using current toxicity data and exposure data, the calculated margins of safety (MOSs) for potential acute occupational exposure of PCOs to propoxur were greater than 10, the value conventionally recommended to protect people from the toxic effects of a chemical determined in a human study. All MOSs for potential chronic occupational exposures to propoxur were greater than 100, the value conventionally recommended to protect people from the toxic effects of a chemical determined in a laboratory animal study. MOSs for potential acute or chronic passive non-occupational exposures to propoxur were greater than the values conventionally recommended to protect people from the toxic effects of a chemical. Maximum

Likelihood Estimates (MLE) of excess lifetime risks of cancer from occupational exposure to propoxur ranged from 1×10^{-6} to 6×10^{-6} . The upper-bound (95%) excess lifetime risks of cancer for theoretical occupational exposure to propoxur ranged from 2×10^{-6} to 9×10^{-6} . None of the MLE for excess lifetime risks of cancer from non-occupational exposures to propoxur exceeded 1×10^{-6} . The upper-bound excess lifetime risks of cancer for theoretical non-occupational exposure to propoxur were not greater than 2×10^{-6} .

I. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Propoxur [Trade name- Baygon®, 2(1-methylethoxy)phenol methyl carbamate]] is a carbamate insecticide developed by Bayer AG, Germany, and registered by the U.S. Environmental Protection Agency (USEPA) and by the State of California. Propoxur is not a restricted pesticide, and is contained in 148 products registered in California. It may be used as an emulsifiable concentrate, wettable powder, and dust on building exteriors, and interior crack and crevice treatments. Propoxur is also used alone, or in combination with other insecticides in room foggers, flea and tick spray, flea and tick collars, ant and cockroach traps, insecticide tapes, ant and cockroach sprays, wasp, bee and hornet spray, and in flea and tick dips for pets. Although propoxur is used on buildings where food is stored or prepared, it is not used on food crops.

B. BIOLOGICAL CHARACTERISTICS

The primary biological activity of propoxur is through carbamylation of cholinesterase (ChE) enzymes, resulting in inhibition. 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. Inhibition of AChE leads to accumulation of acetylcholine in the synaptic cleft which results in over stimulation of the nerves followed by depression or paralysis of the cholinergic nerves throughout the central and peripheral nervous system. AChE is highly selective, although not exclusively, for acetyl esters as substrates (Brimijoin, 1992). Another form of cholinesterase, butyrylcholinesterase (BuChE), preferentially hydrolyzes butyryl and propionyl esters, depending on the species; however, it will hydrolyze a wider range of esters, including acetylcholine (Brimijoin, 1992). Unlike AChE, the physiological function of BuChE is not known. Although AChE and BuChE are found in most tissues, their ratio varies from one tissue to another and from one species to another. In rats, AChE is the predominant form of ChE in the central nervous system and in the neuromuscular junctions of peripheral tissues such as the diaphragm, skeletal muscle, heart, and spleen (Gupta *et al.*, 1991; Mendoza, 1976). AChE and BuChE are present in roughly equal proportions in the liver and kidney. Non-synaptic AChE is also present to a lesser extent in peripheral tissues, however, its function is not known (Brimijoin, 1992). Non-synaptic AChE is essentially the only ChE present in erythrocytes of higher animals. BuChE is the predominant form of ChE in the plasma of humans, however, the ratio of AChE to BuChE varies greatly from species to species and between sexes. For example, the AChE:BuChE ratio in human plasma is approximately 1:1000, but closer to 1:2 in female rats and 3:1 in male rats.

In acutely toxic episodes, muscarinic, and nicotinic receptors are stimulated by acetylcholine with characteristic signs and signs occurring throughout the peripheral and central nervous systems (Murphy, 1986). Peripheral muscarinic effects can include increased intestinal motility, bronchial constriction and increased bronchial secretions, bladder contraction, miosis, secretory gland stimulation and bradycardia. Peripheral nicotinic effects include muscle weakness, twitching, cramps and general fasciculations. Stimulation of muscarinic and nicotinic receptors in the central nervous system can cause headache, restlessness, insomnia, anxiety, slurred speech, tremors, ataxia, convulsions, depression of respiratory and circulatory centers,

and coma. Death, which occurs in the worst circumstances, is usually due to respiratory failure from a combination of peripheral and central effects.

In the case of propoxur, spontaneous hydrolysis of the carbamate-cholinesterase complex occurs *in vivo*, usually leading to the disappearance of clinical signs within 24 hours (Ellenhorn and Barceloux, 1988).

C. TECHNICAL AND PRODUCT FORMULATIONS

Propoxur is contained in 117 products actively registered in California. Approximately 22,483 lbs of propoxur were sold in the state of California in 1993 (DPR, 1995). The concentration of propoxur in the various formulations ranges from 0.95% in sprays to 70% in wettable powder.

D. REGULATORY HISTORY

The USEPA Office of Pesticide Programs established a Reference Dose (RfD) for propoxur of 0.004 mg/kg-day, based on a NOEL of 4 mg/kg-day for decreased red blood cell cholinesterase activity seen in a subchronic dog dietary study (USEPA, 1994). In 1987, the Office of Pesticide Programs, Health Effects Division, of the USEPA classified propoxur as a probable (B2) human carcinogen. At the same time, the USEPA Carcinogen Assessment Group of the Office of Research and Development classified propoxur as a possible (C) human carcinogen. The current upper bound human-equivalent potency is 3.7×10^{-3} [mg/kg-day]⁻¹ (USEPA, 1992a).

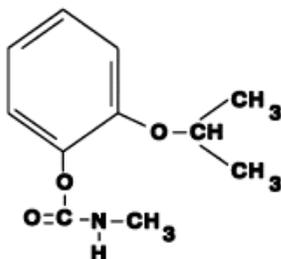
The American Conference of Governmental Industrial Hygienists has given propoxur a Threshold Limit Value (TLV) of 0.5 mg/m³, as a time-weighted average (ACGIH, 1986).

E. ILLNESS REPORTS

Between the years 1982 to 1990, approximately 58 cases of occupational illness and 42 cases of non-occupational illness have been associated with propoxur (Sanborn, 1995).

F. CHEMICAL/PHYSICAL CHARACTERISTICS¹

Chemical Name:	2-(1-methylethoxy)phenol methyl carbamate
Common Name:	propoxur
CAS Number	114-26-1
Empirical Formula:	C ₁₁ H ₁₅ NO ₃
Chemical Structure:	



Molecular Weight:	209.2
Melting Point:	85.5°C
Vapor Pressure:	3.75E-5 mm Hg at 28.9°C
Henry's Law Constant:	7.2E-10 (Atm.m ³ mol ⁻¹) at 20°
Solubility (20°C)	C 1.859 g/L (water)
Octanol:Water Partition Coefficient	36 at 20°C

^{1/} References: Mobay, 1984; Bowman and Sans, 1983a; Bowman and Sans, 1983b; Mobay, 1986.

G. ENVIRONMENTAL FATE

Summary- The hydrolytic half-life of propoxur is 16 days at pH 8, but the half-life could not be determined at pH7 as no hydrolysis occurred during the 107 day observation period. The photolytic half-life in neutral aqueous solution is approximately 10 days. Bacterial degradation of propoxur was the same under aerobic or anaerobic conditions, with half-lives ranging from 80 to 210 days (depending upon soil type). Propoxur leached readily from soils, moving with the water front. Based on these results, propoxur is unlikely to remain in the location where it is applied. However, because it is readily decomposed, propoxur is unlikely to become a persistent environmental contaminant.

Hydrolysis

The hydrolysis studies submitted to the Department of Pesticide Regulation (DPR) by the registrant were reviewed and judged unacceptable because: a) data for the concentrations of propoxur and its products as a function of time were not included, b) a material balance was not provided, c) some details of the analytical method were omitted, and d) the study was conducted at 30°C and 50°C rather than 25°C. (Leffingwell, 1987). A published report indicates that the half-life of propoxur in water is 16 days at pH 8; however, at pH 7 it did not hydrolyze during the 107 day observation period (Aly and El-Dib, 1971).

Photodegradation

Aqueous solutions (pH 7) containing 5 ppm ¹⁴C-UL-ring-propoxur without a photosensitizer were subjected to constant irradiation with artificial light. The half-life under continuous illumination was approximately 10 days (Gronberg and Pither, 1977).

Soil Metabolism

Propoxur was found to degrade in silty loam and sandy loam soil following incubation under aerobic conditions ($T_{1/2} = 80$ and 210 days, respectively)(Gronberg *et al.*, 1981). In silty loam soil, the rate of breakdown was the same under either aerobic or anaerobic conditions. Following application of propoxur, no significant extractable radiolabelled metabolite residue could be detected for up to 1 year. Residual radiolabel was either bound to the soil matrix or characterized as carbon dioxide.

Soil Mobility

Propoxur weakly adsorbed to sandy loam, silty clay loam, and high organic silty clay loam soils with respective dissociation constant (K_d) values of 0.49, 0.62, and 1.12 (Flint and Shaw, 1971). When spray concentrate was applied to freshly tilled soil, irrigation produced residues in runoff water. Propoxur leached readily in soil columns, moving with the water front passing through the column.

II. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Summary: Propoxur was readily absorbed by the gut of rats (approximately 100%), hamsters, and cattle. Less than 1% of radiolabel from an administered oral dose was found in the feces of these animals. Absorption across the gut in humans appeared to be approximately the same as laboratory animals. The principal route of excretion in laboratory animals and humans was through the urine, with up to 95% of the absorbed dose excreted within 48 hours by laboratory animals. Propoxur did not accumulate in any body tissues, with the exception of the kidney, during the process of excretion. In cattle, less than 0.1% of the administered dose was found in the milk. The half-life of propoxur in humans following intravenous administration was 8 hours. The cumulative human dermal absorption for 24 hours was approximately 16%.

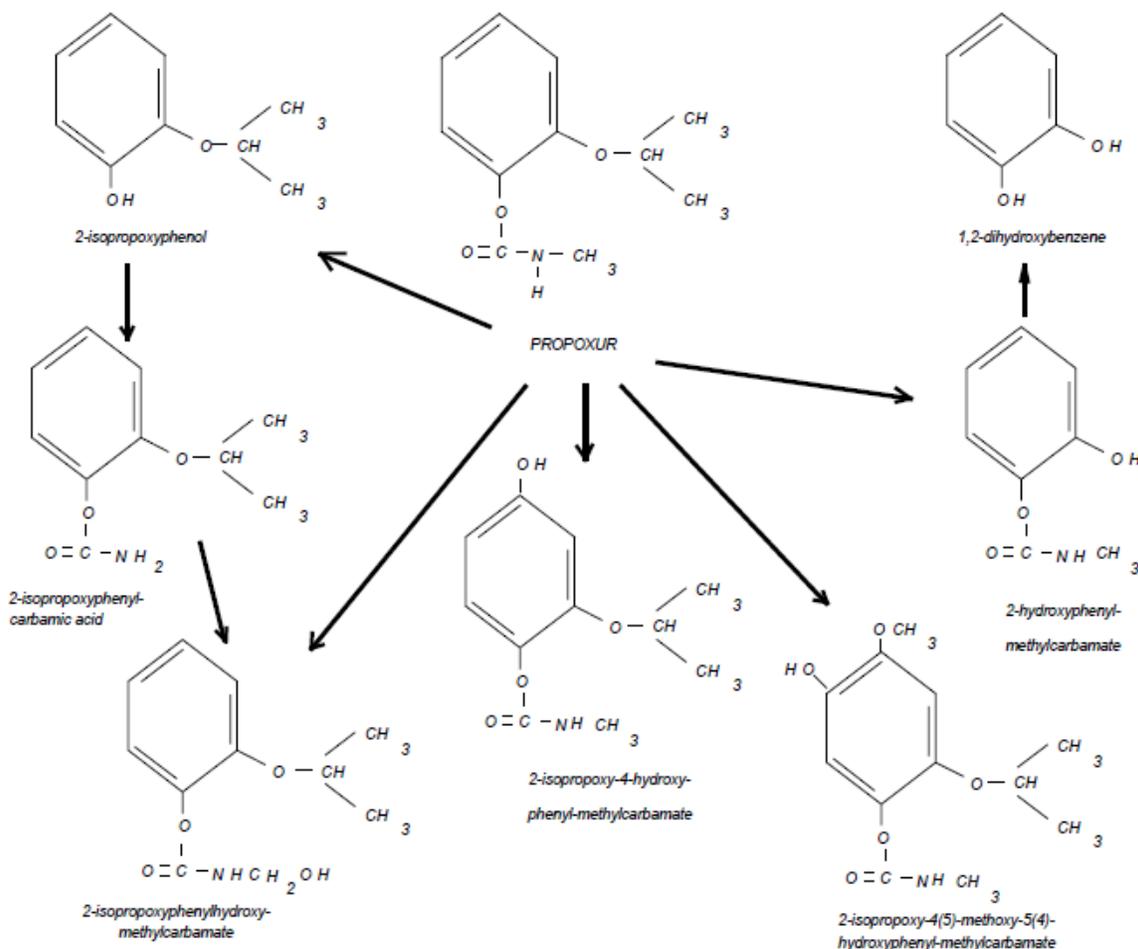
The major metabolites of propoxur in humans, hamsters and rats were 2-isopropoxyphenol, 2-isopropoxyphenyl-carbamic acid, 1,2-dihydroxybenzene, 2-hydroxyphenyl methylcarbamate, 2-isopropoxy-5-hydroxyphenyl methylcarbamate, and 2-isopropoxy-4(5)-methoxy-5(4)-hydroxyphenyl methylcarbamate (Figure 1). These metabolites were also conjugated to form O-glucuronides.

Oral- Rat

Rats (strain unspecified) were dosed with carbonyl-¹⁴C, 1,3-isopropyl-¹⁴C, or 1,3-isopropyl-³H propoxur by gavage (Everett and Gronberg, 1971). At 16 hours, 90% of the radiolabel had been excreted- 5% in the feces, 25% as volatile compounds and 60% in the urine as conjugates. The major routes of metabolism were: depropylation to 2-hydroxyphenyl-N-methyl carbamate, and hydrolysis of the carbamate to yield isopropoxy phenol. Additional hydroxylation occurred at the 5 position of the ring, with secondary hydroxylation of the 2'-carbon of the isopropoxy group as well as N-methyl hydroxylation. Metabolites containing a 5-hydroxy group formed O-glucuronides.

Metabolites were extracted and identified from the urine of male Wistar rats, fed on a diet containing propoxur (8,000 ppm) for 13 weeks (Eben *et al.*, 1985a). The major metabolites are shown in Figure 1. Several additional metabolites were characterized from the urine including: 2-isopropoxy-4-hydroxyphenyl methylcarbamate, 2-isopropoxy-5-hydroxyphenyl-hydroxymethylcarbamate, 2,5-dihydroxyphenyl-methylcarbamate, 2-isopropoxy-3-hydroxyphenyl-methylcarbamate, 1,3-dihydroxy-2-isopropoxy benzene, 2-isopropoxy-5-hydroxyphenyl carbamic acid, 1,5-dihydroxy-2-isopropoxy benzene, 1,5-dihydro-2-isopropoxy-(α -methyl)-benzyl urea, 1-hydroxy-2-isopropoxy-4-nitrobenzene, 2,4-dihydro-5-isopropoxy-4'-hydroxy-3'-isopropoxy-diphenylmethane, 2,4-dihydro-5-isopropoxy-3'-hydroxy-4'-isopropoxy-diphenylmethane, 2-isopropoxyphenylhydroxy-methylcarbamate mercaptouric acid, and 2-isopropoxyphenol sulfate.

Figure 1. Principal metabolites of ^{14}C -propoxur (2-isopropoxyphenyl-N-methyl carbamate) found in the urine of mammals following oral administration of the insecticide. Arrows indicate suggested metabolic pathways (Eben *et al.*, 1985a).



Female Wistar rats, pretreated for 13 weeks with 8000 ppm propoxur in the diet, were given a dose of ^{14}C -UL-ring-propoxur (Weber, 1986). Within 48 hours of administration, independent of whether casein was present in the diet, 95.6% of the recovered radioactivity was present in the urine.

Intraperitoneal- Rat

Sprague-Dawley rats were injected intraperitoneally with ^{14}C -carbonyl labeled propoxur (Krishna and Casida, 1966). The bulk of the radioactivity (93%) was eliminated within 48 hr (60% in the urine and 1.2% in the feces, 31% expired as CO_2). When rats were dosed orally with ^{14}C -methyl- or ^{14}C -isopropyl labeled propoxur, 94% of the applied dose of radioactivity was eliminated within 48 hr (64% in urine, 26% respired as CO_2 , and 4% in the feces).

Oral- Hamster

Female Syrian golden hamsters were fed a diet containing 8000 ppm propoxur for a period of 12 months (Eben *et al.*, 1986). At the end of that time the urine was collected over a 48 hour period, and analyzed for the presence of propoxur metabolites. The major metabolites are shown in Figure 1, and the minor metabolites were: 2-isopropoxy-4-hydroxyphenyl-

methylcarbamate, 1,5-dihydroxy-2-isopropoxy benzene, 2-isopropoxy-3-hydroxyphenyl methylcarbamate, 1-hydroxy-2-isopropoxy-4-nitrobenzene, 2-isopropoxyphenylhydroxy methylcarbamate mercaptouric acid, 2,4-dihydroxy-5-isopropoxy-4'-hydroxy-3'-isopropoxy-diphenylmethane, and 2,4-dihydroxy-5-isopropoxy-3'-hydroxy-4'-isopropoxydiphenylmethane.

Oral- Cow

¹⁴C-Propoxur (0.21 mg/kg) was administered orally in capsular form to a lactating dairy cow (Bell and Gronberg, 1975). Within 12 hours, 95% of the label had been excreted in the urine. Less than 1% was excreted in the feces. Total ¹⁴C in the blood peaked at 1 hour, and maximal milk residues (0.007 ppm) occurred at 8 hours. Repetition of the dosing, followed by sacrifice of the cow at 2.5 hours, indicated that the label was evenly distributed throughout the body, with the exception of the kidneys, which had levels 18 times higher than other tissues.

Oral- Human

The urine from an individual who attempted suicide by ingesting a "large" amount of propoxur was analyzed for metabolites (Eben *et al.*, 1985b). The principal degradation products identified in the urine indicated a metabolic pathway similar to that of the rat: depropylation, O-hydrolysis, N-demethylation and ring hydroxylation at the 5 position (Figure 1). Some metabolites were present in free and conjugated forms, others only as conjugates. Two additional compounds, alpha-methyl-benzyl urea and 2-isopropoxyphenol, were present in very low concentrations. Propoxur and metabolites found in the urine were not quantified in this report.

Three male subjects (body weights unknown) were given single oral doses of 50 mg propoxur. Approximately 27.4% of orally administered propoxur was excreted as 2-isopropoxyphenol in the urine by 8 hours (Dawson *et al.*, 1964). By 24 hours, the percentage of the dose of propoxur recovered in urine as 2-isopropoxyphenol had increased to 29.7%.

A male subject was given a single oral dose of propoxur at 1.5 mg/kg (Vandekar *et al.*, 1971). Over a 24 hour period, approximately 45% of the administered dose was excreted in the urine as the 2-isopropoxyphenol metabolite. As abundant vomiting started 23 minutes after ingestion, it may be assumed that much of the propoxur was not available for absorption.

Intravenous- Human

Six male volunteers were given 1 μ Ci of ¹⁴C-propoxur in the antecubital vein (Feldman and Maibach, 1974). The cumulative rate of label excretion in the urine was as follows: after 4 hours- 41.4%; 8 hours- 70.6%; 12 hours- 76.5%; 24 hours- 78.8%; 48 hours- 80.3%. The half-life of propoxur was stated to be 8 hours.

Dermal- Human

A total of 4 μ g ¹⁴C-propoxur was applied per cm² of skin of six human volunteers to obtain an applied dose of 1 μ Ci (Feldman and Maibach, 1974). The cumulative rate of label excretion in the urine was as follows: after 4 hours- 1.4%; 8 hours- 4.2%; 12 hours- 9.0%; 24 hours- 15.5%; 48 hours- 17.7%. After 5 days, approximately 20% of the applied radioactive dose had been detected in the urine.

Inhalation- Human

Four human volunteers were subjected to a 4 hour atmospheric exposure of 3 mg/m³ propoxur (Machemer *et al.*, 1982). Neither plasma nor red blood cell cholinesterase activities were affected. No cholinergic signs were reported. Between 2 and 4 mg of 2-isopropoxyphenol were detected in the urine of the subjects during the 24 hours following exposure.

Dermal- In vitro

[C¹⁴]-Propoxur (99.6% purity; 37.66 mCi/mmol) was applied to rabbit, pig, and human skin *in vitro* at 25, 100, or 200 $\mu\text{g}/\text{cm}^2$ for a period of six hours (van de Sandt *et al.*, 1993). At the end of the experiments, 90% of total radioactivity was recovered. Approximately 50% of the label was at the site of the application at the end of the experiment, while $2.0 \pm 0.3\%$ of the label penetrated human skin, $2.7 \pm 0.6\%$ penetrated rabbit skin, and $4.2 \pm$ penetrated pig skin. The permeation rates were linear with time, and in humans were 9.2 ± 4.7 ng/cm²-hr (25 $\mu\text{g}/\text{cm}^2$), 40.7 ± 11.4 ng/cm²-hr (100 $\mu\text{g}/\text{cm}^2$), and 56.6 ± 20.6 ng/cm²-hr (200 $\mu\text{g}/\text{cm}^2$).

B. ACUTE TOXICITY

In acute exposures to propoxur, carbamylation of cholinesterase produces accumulation of acetylcholine, resulting in both muscarinic (diarrhea, urination, miosis, bradycardia, bronchorrhea, emesis, lacrimation, sweating) and nicotinic (fasciculations, weakness, paralysis) effects. Spontaneous hydrolysis of the carbamate-cholinesterase complex occurs *in vivo* leading to the disappearance of clinical signs within 24 hours (Ellenhorn and Barceloux, 1988). The acute toxic effects of propoxur are shown in Table 1. A single dermal dose of 2,000 mg/kg caused clinical signs (fasciculations, decreased motor activity, hyper-reactivity) in rabbits (Sheets, 1988). A single dermal dose of 1,000 mg/kg did not cause clinical signs in rats (Bocker, 1961).

Table 1. The Acute Toxicity of Technical Propoxur

Test/Species	Sex	Dose	References ^a
TECHNICAL GRADE (98-99%)			
<u>Oral LD₅₀</u>			
Rat	M/F	83 mg/kg	1
	M	60-150 mg/kg	2,3
	F	40-110 mg/kg	2,3
Guinea Pig	M/F	40 mg/kg	2,4
Mouse	M/F	100-109 mg/kg	5
<u>Inhalation LC₅₀</u>			
Rat	M/F	12.6 mg/L (4 hr)	6
<u>Dermal LD₅₀</u>			
Rat	M/F	>2,400 mg/kg	1
Rat	M/F	4,000 mg/kg	7
Rabbit	M/F	>2,000 mg/kg	8
<u>Dermal Sensitization</u>			
Guinea Pig	M/F	None Observed	9
<u>Dermal Irritation</u>			
Rabbit	M/F	no irritation	10
<u>Eye Irritation</u>			
Rabbit	M/F	mild irritation	10

^{a/} References: 1. Dubois, 1961; 2. Mobay, 1963; 3. Mobay, 1974; 4. Gaines, 1969; 5. WHO, 1986; 6. Pauluhn, 1988; 7. Mobay, 1966; 8. Sheets, 1988; 9. Heimann, 1982a; 10. Crawford and Anderson, 1971.

Oral- Human

A single oral dose of 0.36 mg/kg of propoxur ingested by an unstated number of human volunteers produced a rapid fall in red blood cell cholinesterase activity to 57% of control levels within 10 minutes, then returned to red control levels by 3 hours (Vandekar *et al.*, 1971). At 15 to 20 minutes the subjects experienced short-lasting stomach discomfort, blurred vision, moderate facial redness and sweating. When propoxur was given as 5 oral doses of 0.2 mg/kg at half-hourly intervals, there were no cholinergic signs. Red blood cell cholinesterase activity was depressed to a minimum of 60% of control levels, returning to control levels within 2 hours. The acute no-observed-effect-level (NOEL) in humans for cholinergic signs arising from a single bolus dose of propoxur was 0.2 mg/kg. The 150 minute NOEL for cholinergic signs in humans from repeated bolus doses was 1.0 mg/kg.

Oral- rat

Male and female Wistar rats (5/sex/group) were given single oral doses of propoxur (99.2% purity) at 0, 1, 5 or 25 mg/kg and sampled for plasma and red blood cell cholinesterase activity at 0, 30, 60 min, 3, 5, 24 hr, and 3 days (Heimann, 1982b). No effect on cholinesterase activities was seen. However, the assay technique used (Ellman) was relatively insensitive for carbamates. Animals in the high dose group (25 mg/kg) exhibited cholinergic signs (convulsions, reduced motility, apathy, bristling coat) for several hours up to two days. The NOEL for cholinergic signs from a single dose was 5 mg/kg.

The LD₅₀ (oral) for the metabolite, 2-isopropoxyphenyl hydroxymethylcarbamate in rats was 1100 mg/kg (Dubois, 1966). *In vitro* anticholinesterase activities of 2-isopropoxy-5-hydroxyphenyl methylcarbamate and 2-isopropoxy-4-hydroxyphenyl methylcarbamate were greater than propoxur (Oonnithan and Casida, 1968). *In vitro*, 2-isopropoxyphenyl 1,4-bis(N-methylcarbamate) had the same anticholinesterase activity as propoxur, and 2-hydroxyphenyl methylcarbamate, 3-isopropoxy-4-hydroxyphenyl methylcarbamate, 2-isopropoxyphenol, 2-isopropoxyphenyl carbamate, and 2-isopropoxyphenyl N-hydroxymethylcarbamate had less anticholinesterase activity than propoxur.

Oral- dog

Technical propoxur (purity unknown) was given to beagle dogs in a single oral dose in capsules at 1 (1 Male), 3 (4M, 5 Female), 4 (4M, 5F), 5 (2M, 3F), 6 (4M, 3F), 10 (4M, 3F), 13 (2M), 15 (4M, 5F), 18 (4M, 5F), 20 (1F), and 40 mg/kg (1F) (Crawford and Nelson, 1970). Cholinergic signs (muscle fasciculations, ptyalism, emesis, mild ataxia, and frequent defecation) were observed with increasing frequency and severity in dogs dosed with 5 mg/kg or more. The single dose NOEL for cholinergic signs in dogs was 4 mg/kg.

The acute toxicity data for propoxur formulations are contained in Table 2. The extreme range of toxicities presented in the table are probably the result of considering a large number of products with wide-ranging concentrations of the active ingredient.

Table 2. The Acute Toxicity of Propoxur Formulations

Test/Species	Sex	Dose	References ^a
LIQUID CONCENTRATES (1-50%)			
<u>Oral LD₅₀</u>			
Rat	M	100-18,000 mg/kg	1-10
Rat	F	141-11,750 mg/kg	1-10
Sheep	M/F	40 mg/kg	11
<u>Inhalation LC₅₀</u>			
Rat	M/F	0.93 - >20 mg/L (1-4 hr)	12-14
Mouse	M/F	0.612 mg/L (1 hr)	12
<u>Dermal LD₅₀</u>			
Rat	M/F	>4,000 mg/kg	15
Rabbit	M/F	900 mg/kg	16
<u>Dermal Irritation</u>			
Rabbit	M/F	moderate irritation	17
POWDERS (1-70%)			
<u>Oral LD₅₀</u>			
Rat	M	11-1,640 mg/kg	3,15,18-23
Rat	F	61-1,340 mg/kg	3,15,18-23
<u>Dermal Irritation</u>			
Rabbit	M/F	no irritation	28
SPRAYS AND FOGGERS (0.5-15.8%)			
<u>Oral LD₅₀</u>			
Rat	M	100-3,400 mg/kg	3,24-26
Rat	F	87-2,811 mg/kg	3,24-26
<u>Dermal LD₅₀</u>			
Rat	M/F	7,410 mg/kg	27

a/ References: 1. Lamb and Matzkanin, 1976a; 2. Lamb and Matzkanin, 1978; 3. Mobay, 1963; 4. Mobay, 1974; 5. Moreno and Moreno, 1983; 6. Wolf *et al.*, 1984; 7. Harrison, 1976; 8. Dubois and Kinoshita, 1970; 9. Dubois and Kinoshita, 1971; 10. Shapiro, 1989a; 11. Cox, 1963; 12. Dubois and Kinoshita, 1969; 13. Nelson and Armstrong, 1978; 14. Shapiro, 1989c; 15. Crawford, 1971; 16. Shapiro, 1989b; 17. Shapiro, 1989d; 18. Lamb and Matzkanin, 1976b; 19. Costello and Moore, 1986; 20. Costello and Murray, 1986; 21. Nelson and Euell, 1978; 22. Nelson, 1971; 23. Flucke, 1971; 24. Beck and Hewett, 1980a; 25. Rosenfeld, 1985; 26. Murchison and Keefe, 1987; 27. Beck and Hewett, 1980b; 28. Crawford and Anderson, 1971.

C. SUBCHRONIC TOXICITY

Summary- Because of initial indications of oncogenicity, several short-term studies were begun to determine whether the effect was species specific, and/or diet specific. None of the studies were run long enough, nor, in some cases, with sufficient numbers of animals, to draw any conclusions.

Dietary- Rat

Female Wistar (Bor strain: WISW) rats (50/group), controls and one test group, were fed on a diet containing propoxur (99.9% purity) at 8000 ppm (850 mg/kg-day) for 14 weeks (Hahnemann, 1988d). The food consisted of "a semi-synthetic basal diet with no vitamin C supplement". Toxicity at 850 mg/kg-day was indicated by a 27% decrement in weight gain compared to controls over the 14 week period. Examination of the urinary bladders, kidneys, and livers at 4 weeks (5 rats/group), 8 weeks (5 rats/group) and 14 weeks (40 rats/group) revealed no chemical related histopathological changes. No other parameters were examined. The study was considered an ancillary study.

Gavage- Monkey

Three rhesus monkeys/sex were given propoxur (99.6% pure, 40 mg/kg-day) by gavage in tylose (methyl cellulose) suspension for a period of 13 weeks (Hoffmann and Ruehl, 1985). No controls were used. Transient inhibition of plasma cholinesterase activity was observed, with the inhibition reaching as high as 50% one hour after dosing on weeks 12 and 13. Transient signs, such as excessive salivation, were commonly seen for a few minutes after dosing. However, there were no other distinctive cholinergic signs, changes in blood chemistry, or hematological effects. Microscopic examination of the urinary bladder as well as histopathology of other body organs did not indicate any effects of propoxur.

Dermal- Rabbit

New Zealand White rabbits (10/sex/dose) were dosed with propoxur (100% purity) in Cremophor EL (2% v/v) at 0, 50, 250 or 1000 mg/kg-day 6 hours/day, 5 days a week for 13 weeks (Diesing and Flucke, 1989). No treatment related cholinergic signs were observed. The clinicochemical, hematological, and gravimetric investigations and macroscopic and microscopic examinations of the internal organs provided no evidence of treatment related effects or damage.

D. CHRONIC TOXICITY/ONCOGENICITY

Summary: In the dog, the chronic NOEL for depression of body weight gain, and changes in blood parameters indicating hemolytic anemia was 7 mg/kg-day. In the rat, the chronic NOEL for uroepithelial hyperplasia was 8.23 mg/kg-day in males and 11.02 mg/kg-day in females. Carcinogenicity was observed in the uroepithelium of bladders of both male and female Wistar rats during a chronic feeding study with propoxur. A second chronic feeding study with female Wistar rats indicated that hyperplasia of the bladder epithelium may occur as early as 4 weeks, and the earliest that carcinoma of the bladder uroepithelium appeared was 78 weeks. Although female Sprague-Dawley rats did not develop bladder carcinomas in a subsequent 52 week study, their bladders developed bladder epithelial hyperplasia similar to that observed in treated Wistar rats. Wistar rats exposed to propoxur via whole-body inhalation developed treatment-related urinary bladder adenomas and carcinomas, as well as adenomas of the pituitary and liver.

No malignant tumors were observed in mice. However, male mice experienced a significant, dose-related increase in hepatocellular adenomas. Both male and female mice exhibited a significant, dose-related increase in hyperplasia of the bladder epithelium. The NOEL for epithelial hyperplasia of the urinary bladder (males and females), liver hepatocellular vacuolation (females), changes in clinical chemistry (males and females), ovarian hemorrhage and thrombus formation, and eosinophilic deposits in the kidneys (males) was 75 mg/kg-day.

Female hamsters, exposed to propoxur in the diet for one year, exhibited no chemical related histopathological changes.

Dietary- Rat

Male and female rats (BOR:WISW, SPF Cpb) (50/sex/dose) were fed a diet containing propoxur (99.4% pure) at 0, 200, 1000, or 5000 ppm (approximately 0, 8.23, 42.03, or 222.3 mg/kg-day for males and 0, 11.02, 56.16, 292.79 for females from consumption data) for 106 weeks (Suberg *et al.*, 1984). Additional groups of 10 rats/sex/group were included for an interim sacrifice at the end of the first year. A statistically significant ($P < 0.05$) depression in weight gain was seen between weeks 1 and 20 in the 1000 and 5000 ppm groups. At the one year interim sacrifice, high dose males exhibited bladder papillomas (2/10), but neither females at high dose, or males and females at any other dose exhibited papillomas. Bladder hyperplasia was evident in all male and female high dose animals at one year, and in 4/10 of the males and 1/10 of the females at the mid dose (1000 ppm). No incidences of epithelial hyperplasia or papillomas were observed in the low dose group at the 1 year point. The 1-year systemic NOEL was 200 ppm (8.23 mg/kg-day in males and 11.02 mg/kg-day in females) for uroepithelial hyperplasia. Carcinoma of the bladder epithelium was first observed in male rats at week 78. By the end of the experiment, both bladder papillomas and carcinomas were present in high dose males and females (Table 3). Bladder epithelial hyperplasia was also observed in the mid and high dose males and females. The incidence of uterine carcinomas was slightly increased in the high dose females, but the results were not statistically significant by Fisher's Exact Test at the 0.05 level (0 ppm: 3/48; 200 ppm: 4/48; 1000 ppm: 4/47; 5000 ppm: 8/48). The incidence of uterine carcinomas at the high dose was within the range of the historical controls (0 to 22%), but greater than the mean (9.4%) (Bomhard, 1980, 1982; Mobay, 1986b; Karbe, 1992). The study was acceptable to DPR under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) guidelines (USEPA, 1984).

Table 3- Incidence of bladder lesions in Wistar rats fed for 24 months on a diet containing propoxur (Suberg *et al.*, 1984)^a.

Lesion type	Males				Females			
	Dietary conc. of propoxur (ppm)				Dietary conc. of propoxur (ppm)			
	0	200	1000	5000	0	200	1000	5000
Bladder Papillomas	0/49+++ (0%)	0/50 (0%)	1/50 (2%)	25/49*** (51%)	0/49+++ (0%)	0/46 (0%)	0/49 (0%)	28/48*** (58%)
Bladder Carcinomas	0/49+++ (0%)	0/50 (0%)	0/50 (0%)	8/49** (16%)	0/49+++ (0%)	0/46 (0%)	0/49 (0%)	5/48* (10%)
Combined	0/49+++ (0%)	0/50 (0%)	1/50 (2%)	33/49*** (67%)	0/49+++ (0%)	0/46 (0%)	0/49 (0%)	33/48*** (69%)
Bladder Hyperplasia	1/49+++ (2%)	1/50 (2%)	10/50** (20%)	44/49*** (90%)	0/49+++ (0%)	0/46 (0%)	5/49* (10%)	48/48*** (100%)

^a/ The incidence is expressed as the number of animals bearing bladder lesions per number of animals at risk (Those animals surviving 78 weeks or more). The number in parentheses represents the incidence percentage.

* Significantly (P<.05) different from the control group based on the Fisher's exact test.

** Significantly (P<.01) different from the control group based on the Fisher's exact test.

*** Significantly (P<.001) different from the control group based on the Fisher's exact test.

+++ Significant (P<.001) trend based on a dose-weighted chi-square trend test.

Sprague-Dawley rats (50/group; female only) were fed on a diet of Altromin 1321 Mehl containing propoxur (99.6-99.9% purity) at 0, 3000 or 8000 ppm (approximately 0, 247.9 or 722.4 mg/kg-day) (Hahnemann, 1988a). Scheduled killings per group were at 4 wk (5); 9 wk (5); 12 wk (10); 27 wk (10); and 52 wk (20). Reduced body weight gain was statistically significant (P<.01 by Student's t test) in both treatment groups, and related to the dose (P<.05, trend test). Hyperplasia of the urinary bladder uroepithelium was time and dose-related (Table 4). The study was considered an ancillary study to the data base for propoxur.

Table 4. Time-related incidence of bladder hyperplasia in female Sprague-Dawley rats fed on a diet containing propoxur for up to 52 weeks (Hahnemann, 1988a).^a

Week of Sacrifice	Dietary concentration of propoxur (ppm)		
	0	3000	8000
4	0/5+++	3/5** (60%)	4/5*** (80%)
9	0/5+++	0/5	3/5*** (60%)
12	0/10+++	5/10** (50%)	8/10*** (80%)
27	0/10++	3/10* (30%)	10/10*** (100%)
52	0/20+++	14/20** (70%)	20/20*** (100%)

^{a/} The incidence is expressed as the number of animals bearing bladder hyperplasia per number of animals at each time point. The number in parentheses represents the incidence percentage.

* Significantly (P<.05) different from the control group based on the Fisher's exact test.

** Significantly (P<.01) different from the control group based on the Fisher's exact test.

*** Significantly (P<.001) different from the control group based on the Fisher's exact test.

++ Significant (P<.01) trend based on a dose-weighted chi-square trend test.

+++ Significant (P<.001) trend based on a dose-weighted chi-square trend test.

A two-year feeding study was conducted in female Wistar rats in order to determine the dose-effect-time relationship for the production of bladder lesions (Hahnemann and Ruehl-Fehlert, 1988a). The rats were dosed with 0, 50, 250, 1000, 3000, 5000 or 8000 ppm (approximately 0, 2.8, 14, 58, 184, 348, or 639 mg/kg-day based on dietary consumption) propoxur (99.4% pure), and killed at weeks 4, 7, 12, 26, 53, 78, and 104. Treatment related signs of bladder hyperplasia were noted at 58 mg/kg-day and above (Figure 2). The incidence and severity of uroepithelial bladder hyperplasia increased with dose. The earliest appearance of uroepithelial hyperplasia (4 weeks) was at the highest dose (639 mg/kg-day). At a given dose (at 58 mg/kg-day or greater), uroepithelial hyperplasia increased in severity (from simple hyperplasia to nodular hyperplasia) with continued dosing. Papillomas were observed at doses of 184 mg/kg-day or greater, and both papillomas and carcinomas were observed at 348 and 639 mg/kg-day (Figure 3). The incidence of bladder carcinomas was 9% at 348 mg/kg-day and 20% at 639 mg/kg-day. It appeared as though there were a progression from uroepithelial hyperplasia to papillomas to carcinomas. The percentage of animals with uroepithelial hyperplasia appeared to peak at 80 to 90% at 53 weeks. Then, the percentage with hyperplasia declined as the incidence of first papillomas, and next, carcinomas increased. The percentage of animals with bladder lesions remained at between 80 and 90% at the high doses. No evidence of increased mortality, significant cholinergic signs or indices were found in any of the dose groups. Historical data supplied by the registrant on bladder lesions in Wistar rats indicated a very low incidence of bladder uroepithelial papillomas and carcinomas. In one group of 21 studies completed between 1975 and 1983, only 3 spontaneous papillomas and

carcinomas were found in 2406 control rats, a rate of 0.1% (Mobay, 1986b). A second group of 11 studies involving the same strain of Wistar rat used in the above experiments, indicated no spontaneous papillomas or carcinomas in 978 rats- (Bomhard, 1980). A third set of data involving historical records from 8 studies using Wistar rats indicated 1 spontaneous papilloma in 1041 animals- a rate of 0.1% (Bomhard, 1982). Animals in the 348 mg/kg-day and 639 mg/kg-day dose groups did exhibit significant body weight losses (> 15%). The Maximum Tolerated Dose (MTD) was, therefore, estimated to lie somewhere between 184 and 348 mg/kg-day. This indicated that the development of bladder lesions began at a dose below the MTD. The study was considered ancillary.

Figure 2. Incidence of uroepithelial hyperplasia in female rat bladders. The percentage of lesions are plotted against the dose of propoxur and the week in which the lesion appeared (Hahnemann and Ruehl-Fehlert, 1988a).

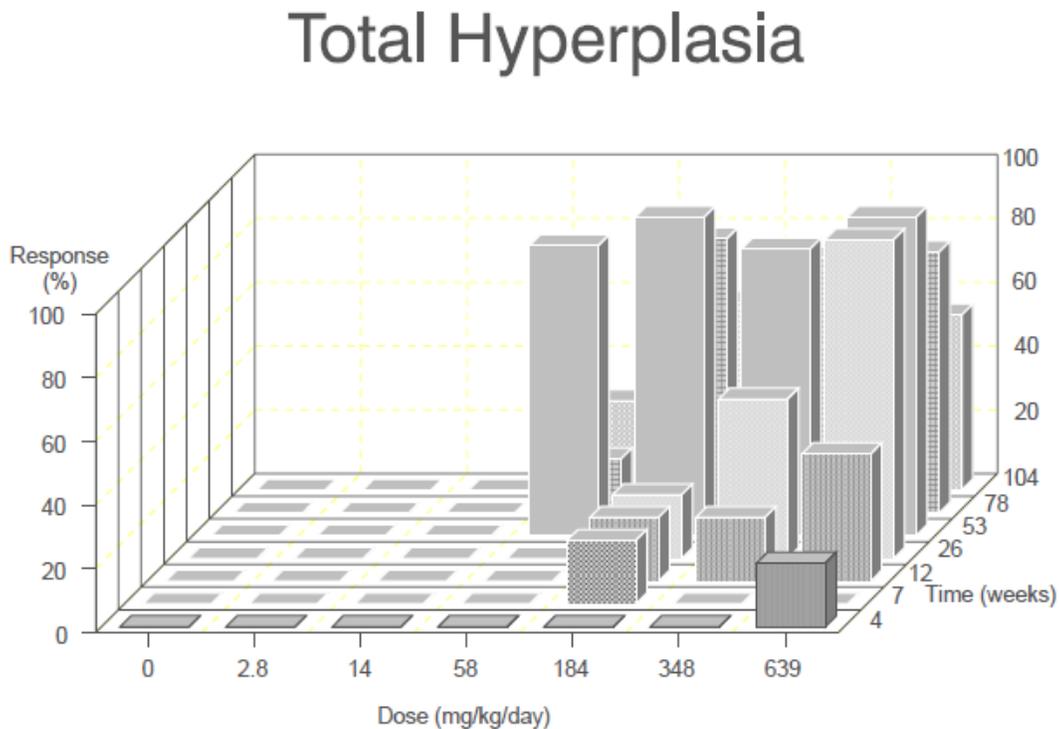
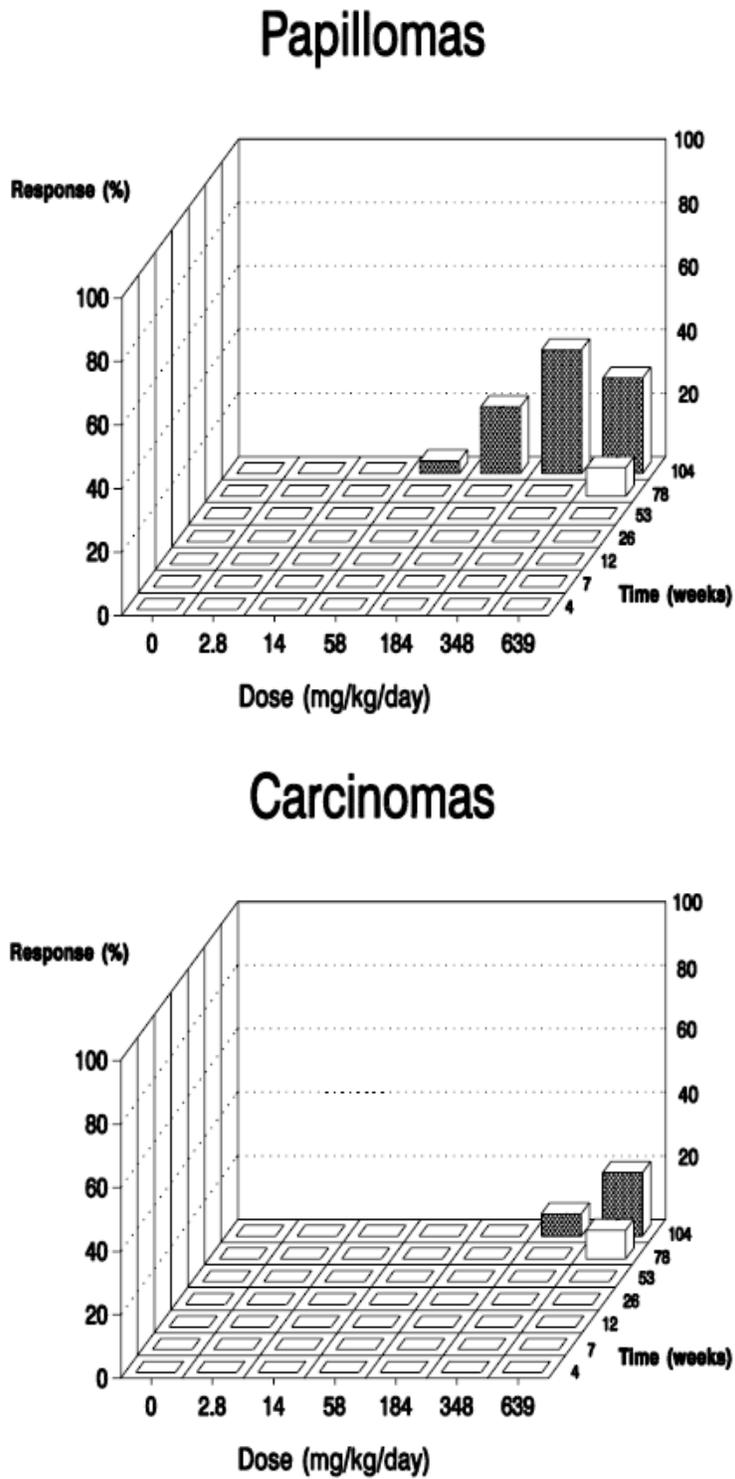


Figure 3. Incidence of papillomas, and carcinomas of the uroepithelium in female rat bladders. The percentage of lesions are plotted against the dose of propoxur and the week in which the neoplasm appeared (Hahnemann and Ruehl-Fehlert, 1988a).



In an effort to test the hypothesis that neoplastic lesions of the bladder uroepithelium were due to acidic conditions in the bladder, propoxur (99% purity) at 0, 3000, or 8000 ppm (approximately 212 and 609 mg/kg-day by consumption data) was administered in a semi-synthetic diet without vitamin C supplement to female Wistar rats (50/dose) for up to 100 weeks (Hahnemann and Ruehl-Fehlert, 1988b). Five rats/dose were necropsied at 2, 4 and 8 weeks, and 10 rats/dose were necropsied at 14 and 26 weeks. The remainder were terminated at 100 weeks. There were no reported histopathological changes in the bladder uroepithelium. The study was considered supplemental.

Female Wistar rats (50/dose) received technical propoxur (99% purity) at 0, 1000, 3000, or 8000 ppm in the Altromin® diet with or without 1% L-(+) ascorbic acid for up to 50 weeks (Hahnemann and Ruehl-Fehlert, 1988c). Five animals per group were necropsied at 4, 8, 12, and 26 weeks. The remainder were terminated at 48 or 50 weeks. The dosages, based on consumption data, were 82.6, 253.7 and 794.7 mg/kg-day without ascorbic acid, and 81.8, 286.8, 844.3 with ascorbic acid for 1000, 3000, and 8000 ppm, respectively. The appearance of urinary bladder hyperplasia was dose-related and independent of the presence of dietary ascorbic acid (Table 5). Papillomas were noted at 844.3 mg/kg-day (1/30) with and 794.7 mg/kg-day (1/30) without ascorbic acid. Carcinomas of the uroepithelium were noted at dosages of 253.7 mg/kg-day (1/30) and 794.7 mg/kg-day (2/30) without ascorbic acid.

Table 5. Effect of propoxur on the incidence of hyperplasia of the uroepithelium in female rat bladders, with or without ascorbic acid in the diet (Hahnemann and Ruehl-Fehlert, 1988c).

Dosage (mg/kg-day)	<u>Week No.</u>				
	4	9	12	26	50
No Ascorbic Acid					
0	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/30 (0%)
82.6	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/30 (0%)
253.7	4/5* (80%)	2/5* (40%)	4/5* (80%)	4/5* (80%)	28/30* (93%)
794.7	3/5* (60%)	5/5* (100%)	4/5* (80%)	5/5* (100%)	17/30* (57%)
Ascorbic Acid					
0	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/30 (0%)
81.8	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/30 (0%)
286.8	0/5 (0%)	4/5* (80%)	5/5* (100%)	5/5* (100%)	27/30* (90%)
844.3	5/5* (100%)	3/5* (60%)	5/5* (100%)	5/5* (100%)	30/30* (100%)

* Significantly ($P < .05$) different from the control group based on the Fisher's exact test.

Inhalation- rat

Wistar rats (60/sex/dose) were exposed to propoxur (99% purity) via whole-body inhalation for 6.3 hr/day, 5 days/wk at 0 (1:1 blend of ethanol and polyethylene glycol; mean PEG = 410 mg/m³), 2.2, 10.4 or 50.5 mg/m³ propoxur (Pauluhn, 1992). Five rats per sex per group were killed at 51, 77, and 102 weeks. The remainder were kept on treatment for 102 weeks, then taken off treatment 20 weeks before termination. Assuming all propoxur entered through the inhalation route, and using default inhalation values (Zielhuis and van der Kreek, 1979), the nominal absorbed dosages were 0, 0.6, 2.6, or 12.7 mg/kg-day. However, the conversion of air concentrations of propoxur to absorbed dosages using default inhalation values may not be accurate because an unquantified amount of chemical is likely to be taken up orally through grooming behavior (Blair *et al.*, 1974; Langard and Nordhagen, 1980; Wolff *et al.*, 1982; Iwasaki *et al.*, 1987; Hext, 1991; Jaskot and Costa, 1994; Tyl *et al.*, 1995). At 51 weeks (1 year), there was no NOEL for inhibition of red blood cell cholinesterase activity (Table 6). The 1-year NOEL for inhibition of plasma and brain cholinesterase activities was 0.6 mg/kg-day. Increased lymphocyte infiltration in the interstitial cells of the lungs was observed in

males (16/50) at 12.7 mg/kg-day compared to controls (5/46 males; 10/47 females). Males (12/50) and females (11/47) at 12.7 mg/kg-day had increased cell proliferation in the Harderian gland compared to controls (0/47 males; 2/47 females). Also, both males (21/50) and females (25/47) exhibited an increase in sinus catarrh in mandibular lymph nodes compared to controls (11/47 males; 10/47 females).

Table 6. Effect of propoxur exposure via whole-body inhalation on cholinesterase activity in the rat at different time points (Pauluhn, 1992).

Red Blood Cell Cholinesterase Activity, % Inhibition^a				
Study Duration		Nominal Dose (mg/kg-day)		
Sex	(wks.)	0.6	2.6	12.7
<u>Male</u>	51	15*	21**	27**
	77	0	0	15**
	102	0	0	8*
<u>Female</u>	51	9*	19**	27**
	77	0	0	12**
	102	0	7	7*
Plasma Cholinesterase Activity, % Inhibition				
Study Duration		Nominal Dose (mg/kg-day)		
Sex	(wks.)	0.6	2.6	12.7
<u>Male</u>	51	0	20**	23**
	77	0	15	11
	102	0	0	19
<u>Female</u>	51	0	1	1
	77	0	4	0
	102	10	12	11
Brain Cholinesterase Activity, % Inhibition				
Study Duration		Nominal Dose (mg/kg-day)		
Sex	(wks.)	0.6	2.6	12.7
<u>Male</u>	51	20	29**	50**
	77	0	0	11
	102	0	25**	29*
<u>Female</u>	51	0	6	24
	77	0	0	51**
	102	9	0	27**

a/ Expressed as percent inhibition of concurrent control

* Significantly ($p < 0.05$) different from control by Fisher's Exact Test.

** Significantly ($p < 0.01$) different from control by Fisher's Exact Test.

Based on previous results, it was expected that there would be a dose-dependent increase in uroepithelial hyperplasia, papillomas, and carcinomas in the bladder. Instead, no chemical related histopathological changes were noted in the bladder. An increase in hepatocellular adenomas at the high dose (6/60) was not significantly different from the incidence in controls (2/60). A significant ($P < 0.05$; Fisher's Exact test) increase in pituitary adenomas, compared to concomitant controls, was observed in male rats at the high dose (Table 7). This resulted in a positive trend test ($P < 0.05$). However, the incidence of pituitary adenomas (15%) at the high dose was not above the average level (26%) found in contemporary historical controls (Bomhard, 1992a). Thus, the indications of tumorigenic response in the pituitary may not be treatment-related. The study was considered acceptable by DPR under FIFRA testing guidelines.

Table 7. Incidence of tumors in Wistar rats exposed to propoxur via whole-body inhalation (Pauluhn, 1992).

Lesion	Nominal Male Dose (mg/kg-day)				Nominal Female Dose (mg/kg-day)			
	0	0.6	2.6	12.7	0	0.6	2.6	12.7
Pituitary								
- adenoma	+2/57 (3%)	4/60 (7%)	4/57 (7%)	9/59* (15%)	19/58 (33%)	18/58 (31%)	14/58 (24%)	19/57 (33%)
- carcinoma	0/57 (0%)	1/60 (2%)	0/57 (0%)	0/59 (0%)	0/58 (0%)	1/58 (2%)	0/58 (0%)	1/57 (2%)
- combined	+2/57 (3%)	5/60 (8%)	4/57 (7%)	9/59* (15%)	19/58 (33%)	19/58 (33%)	14/58 (24%)	20/57 (35%)

* Significantly ($P < .05$) different from the control group by Fisher's exact test.

+ Significant ($P < .05$) trend based on a dose-weighted chi-square trend test.

Dietary- Dog

Beagles (6/sex/dose) were given propoxur (99.4% pure) in the diet at 0, 200, 600, or 1800/3600/5400 ppm (approximately 0, 7, 23, or 69/142/220 mg/kg-day) for 1 year (Hoffmann and Groning, 1984). The dose was increased from 1800 to 3600 ppm at the end of week 40, and again from 3600 to 5400 ppm after week 44. The intent was to produce a clearly toxic effect. At the high dose of 5400 ppm, both males and females exhibited cholinergic signs (salivation, spasms, uncertain gait). No cholinergic signs were observable at any other dosage. Propoxur had no effect on red blood cell or brain cholinesterase activity. Plasma cholinesterase activity in both males and females was significantly reduced (34% and 38%, respectively) from week 45 to week 52. At 40 weeks, there was no effect on mean body weights at any dosage. However, at 52 weeks measurements of both male and female dogs at the highest dosage (5400 ppm) indicated a decreased mean body weight gain (24% and 16%, respectively), increased mean relative liver weight (132% and 158%, respectively), increased mean cholesterol levels (140% and 146%, respectively), and changes in blood parameters indicating possible hemolytic anemia. Specifically, a rising trend in thrombocyte and reticulocyte counts after dosage was increased above 1800 ppm; a rising trend in leukocyte count at 5400 ppm, and an increased incidence of Heinz' inclusion bodies in red blood cells as a sign of toxic

damage at 5400 ppm. Blood chemistry parameters, except for cholesterol, were within the normal range. At 600 ppm, only a significant ($P < 0.05$) elevation of cholesterol levels (130% and 141% for males and females, respectively) was noted. Therefore the NOEL for systemic effects was 600 ppm (approximately 23 mg/kg-day). The study was considered acceptable by DPR under FIFRA testing guidelines.

Propoxur (99.8% pure) was administered to beagles (4/sex/dose) in the diet at 0, 100, 250, 750 or 2000 ppm (0, 19.2, 50.2, 151.1 or 377.1 mg/kg-day for males; 0, 17.6, 49.8, 128.6 or 90.6 mg/kg-day for females from consumption data) for two years (Loser, 1968). At the high dose, all dogs exhibited subdued behavior, weakness, spasms and quivering. Increased mortality (1/4 males, 4/4 females) was observed at the high dose, along with decrements in mean body weight (28% in males) and mean food consumption (60% in females). The time of death was not reported. The NOEL for mortality and decrement in mean body weight gain was approximately 151.1 mg/kg-day. The study was acceptable to DPR under FIFRA testing guidelines even though no analysis of the diet was provided with the study.

Dietary- Mouse

B6C3F1 (SPF-Han) mice (50/sex/group) were fed on a diet containing propoxur (99.6% purity) at 0, 500, 2000, or 8000 ppm for two years (Bomhard, 1992b). Ten additional mice/sex/group were utilized as a 1 year interim sacrifice group. Dosing due to dietary consumption could not be precisely ascertained, as there were indications of spillage. The dosages were estimated by the study's author to be 0, 114.3, 472.4 or 2080.6 mg/kg-day for males and 0, 150.4, 591.4 or 2671.1 mg/kg-day for females. There was a significant ($P < 0.01$) decrement in mean body weight gain at 8000 ppm in both males (8%) and females (16%). Females at 2000 and 8000 ppm had statistically significant ($P < 0.01$) increases in mean hemoglobin (3 and 7%, respectively) and mean hematocrit (3 and 6%, respectively) at one year. Both females and males exhibited significant ($P < 0.01$) increases in mean hemoglobin concentration (7 and 18%, respectively) at two years. There were several statistically significant changes in blood chemistry which probably reflected liver toxicity. Alkaline phosphatase and alanine amino transferase were significantly ($P < 0.05$) elevated in both males and females at 8000 ppm at 52, 77, and 103 weeks. Serum protein and serum albumin concentrations were significantly ($P < 0.05$) reduced in both males and females at 2000 and 8000 ppm at 52 weeks. Phosphate levels were significantly ($P < 0.01$) reduced in females at 2000 and 8000 ppm at 103 weeks.

Histopathological findings are summarized in Table 8. A dose-related, statistically significant ($P < 0.05$) increase in hepatocellular adenomas was observed in male mice. No increase in hepatocellular carcinomas in males or females were reported. The combined incidence of hepatocellular carcinomas and adenomas was significantly greater at 8000 ppm than in the controls. Hepatocellular vacuolation was observed in female mice at 2000 ppm. Both male and female mice exhibited statistically significant ($P < 0.01$) epithelial hyperplasia of the bladder at 8000 ppm. As the decrement in body weight gain in male mice was not large (8%), and longevity was not affected, it did not appear that the maximum tolerated dose was exceeded. The NOEL for epithelial hyperplasia of the urinary bladder (males and females), increased alkaline phosphatase and alanine amino transferase (males and females), hemorrhage and thrombus formation (females), and eosinophilic deposits in the kidneys (males) was 2000 ppm (approximately 472 mg/kg-day). The study was considered acceptable to DPR under FIFRA testing guidelines.

Table 8. Histopathological findings in mice fed on a diet containing propoxur for up to 103 weeks (Bomhard, 1992b).

	Males (ppm)				Females (ppm)			
	0	500	2000	8000	0	500	2000	8000
Hepatocellular Adenomas	10/50 (20%)	10/51 (20%)	15/49 (31%)	21/50* (42%)	9/50 (18%)	4/49 (12%)	3/51 (6%)	7/50 (14%)
Carcinomas	5/50 (10%)	6/51 (12%)	8/49 (16%)	5/50 (10%)	1/50 (2%)	1/49 (2%)	1/51 (2%)	1/50 (2%)
Combined	15/50 (30%)	16/51 (31%)	23/49 (47%)	26/50* (52%)	10/50 (20%)	5/49 (10%)	4/51 (8%)	8/50 (16%)
Hepatocellular Vacuolation	0/49 (0%)	1/49 (0%)	1/49 (2%)	2/48 (2%)	0/48 (4%)	9/47* (0%)	5/48 (19%)	10/48 (10%)
Bladder Hyperplasia	2/49 (4%)	2/49 (4%)	5/49 (10%)	20/50** (40%)	1/48 (2%)	1/48 (2%)	6/47 (13%)	31/48** (65%)
Kidney Eosinophilic deposits	1/50 (2%)	0/51 (0%)	1/49 (2%)	6/50 (12%)	5/48 (10%)	2/48 (4%)	1/47 (2%)	7/48 (15%)
Ovarian Hemorrhage					1/48 (2%)	1/48 (2%)	1/47 (2%)	6/48 (13%)
Ovarian Thrombi					0/48 (0%)	0/48 (0%)	0/47 (0%)	6/48* (13%)

* Significantly different (P<0.05) from the control by Fisher's exact test.

** Significantly different (P<0.01) from the control by Fisher's exact test.

Propoxur (99.6% pure) was added to the diet and fed to 50/sex/group of CF1/W 74 mice at 0, 700, 2000 or 6000 ppm daily for 2 years (Bomhard and Loser, 1981). No oncogenicity was demonstrated. However, the study was considered unacceptable under FIFRA because excessive mortality and tissue autolysis compromised the results; no justification for dose selection; and no analysis of the diet were provided.

Female NMRI mice (50/group) were fed on a diet containing propoxur at 0, 3000 and 8000 ppm for varying lengths of time (Hahnemann, 1988b). Animals were killed for tissue analysis at 4 wk (5), 9 wk (5), 12 wk (10), 27 wk (10), and 1 yr (20). In contrast to the earlier study in mice, neither hyperplasia of the urinary bladder, nor other toxicity in the uroepithelium was observed. However, as fatty deposits appeared in the liver at both treatment levels, there was no NOEL. The study did not follow FIFRA testing guidelines, but was considered ancillary data in an attempt to test the hypothesis that propoxur has adverse effects on the uroepithelium of the bladder.

Dietary- Hamster

Female hamsters (50/group) were fed propoxur (99.6-99.9% pure) in a fixed-formula standard diet at 0, 3000 or 8000 ppm (equivalent to 0, 351 or 985 mg/kg-day from food consumption data)(Hahnemann, 1988c). Animals were killed for tissue analysis at 4 wk (5), 9 wk (5), 12 wk (10), 27 wk (10), and 1 yr (20). There were no adverse histopathological findings. Decreased mean body weight gain (11%) at the high dose, and cholinergic signs observed at both doses during the course of the study were apparently substance related. The study was considered ancillary in an attempt to test the hypothesis that propoxur has adverse effects on the uroepithelium of the bladder.

E. GENOTOXICITY

Summary. Propoxur, with or without activation, was not mutagenic in bacteria, yeast, or Chinese hamster ovary cells. However, a metabolite, a nitroso derivative of propoxur, was mutagenic and produced mitotic gene conversion in bacteria, and caused DNA damage in human fibroblasts. Although propoxur did not cause chromosomal damage or unscheduled DNA synthesis in Chinese hamster tissue *in vitro*, propoxur did induce increased frequencies of sister chromatid exchanges and micronuclei in human lymphocyte cultures. Several major metabolites of propoxur, and the urine from rats treated with propoxur, were tested for mutagenicity and genotoxicity. With the possible exception of 2-isopropoxyphenylhydroxy methylcarbamate, no mutagenic effects of propoxur metabolites could be demonstrated in the Ames test. Consequently, the results of the genotoxicity studies on propoxur are equivocal.

Gene Mutation

A mixture of technical propoxur from 5 batches (98.6% purity) was tested with *Salmonella* strains TA1535, TA1537, TA98, and TA100, with and without rat liver activation; tested at 0, 20, 100, 500, 2,500 and 5,000 $\mu\text{g}/\text{plate}$ (trial 1), and at 0, 750, 1,500, 3,000, 6,000 and 12,000 $\mu\text{g}/\text{plate}$ (trial 2) with four plates per concentration (Herbold, 1982). No evidence of reversion was reported. This study was acceptable to DPR. The acceptability of the genotoxicity studies to DPR was based on the Toxic Substances Control Act guidelines (Federal Register, 1985).

Propoxur (99.8% purity) in DMSO was added to suspension cultures of *S. cerevisiae* D7 for 16 hours at 37°C with and without activation at concentrations of 75 to 10000 $\mu\text{g}/\text{ml}$ in three tests (Herbold, 1985a). Aliquots of the suspension were plated on growth agar, and other selective agars. Decreased survival was observed at the highest dose, but no mutagenic effects were observed. This study was acceptable to DPR.

Propoxur (99.6% purity) was tested with Chinese hamster ovary cells (CHO-K1-BH4) with and without activation (Lehn, 1988). Cells were incubated for 5 hours at 0 (negative and DMSO vehicle), 25, 50, 75, 100, or 125 $\mu\text{g}/\text{ml}$ without activation (duplicate cultures, two trials), and at 0, 600, 800, 900, 1000, or 1500 $\mu\text{g}/\text{ml}$ with activation. No mutagenic effects were noted. This study was acceptable to DPR.

Propoxur (98.0% purity) was tested in *Salmonella* strains TA1535, TA1537, TA98 and TA100 with activation at 0, 0.1, 10 or 1000 $\mu\text{g}/\text{plate}$, and without activation at 1000 $\mu\text{g}/\text{plate}$ (Inukai and Iyatomi, 1978). There was no evidence of a mutagenic effect. The study was not acceptable to DPR because there was no justification of the highest concentration, only single plates were used, no repeat trials, no evidence of cytotoxicity, and a minimal protocol.

Propoxur (98% purity) was tested with *Salmonella* strains TA1535, TA1537, TA1538, TA98 and TA100, and *E. coli* strain WP2, with and without activation, at 0, 10, 50, 100, 500, 1000 or 5000 $\mu\text{g}/\text{plate}$ (Shirasu *et al.*, 1979). There was no evidence of an increased reversion rate. The study was unacceptable to DPR because there was no repeat trial.

Propoxur (98% purity) was tested in *Salmonella* strains TA1535, TA1537, TA1538, TA98, and TA100 with and without rat liver activation, also *E. coli* WP2 strain, tested at 0, 500, 1000, 2500, 5000, 10000, or 25000 $\mu\text{g}/\text{plate}$ (Ohta and Moriya, 1983). The study was unacceptable to DPR because there was no repeat trial.

Propoxur metabolite, THS 1241b batch 17101983 (2-isopropoxyphenyl-hydroxymethylcarbamate; no purity stated), was tested with *Salmonella* strains TA1535, TA1537, TA1538, TA98 and TA100, with and without activation at 0 to 8748 $\mu\text{g}/\text{plate}$, 4 plates per strain and concentration (Herbold, 1984d). In almost every trial with TA1535, one or more concentrations with or without S9 activation showed at least a doubling of the spontaneous mutation rate. The actual values, however, were quite low. The study was acceptable to DPR as a mutagenicity test for a metabolite of propoxur.

Brenzcatechin (1,2-dihydroxy benzene; a possible metabolite of propoxur, no purity stated) was tested with *Salmonella* strains TA1535, TA1537, TA98 and TA100, with and without activation, by plate incorporation procedure with 4 plates per concentration at 0, 20, 100, 500, 2500 or 12500 $\mu\text{g}/\text{plate}$ in trial 1 and 0, 625, 1250, 2500, 5000 or 10000 $\mu\text{g}/\text{plate}$ in trial two (Herbold, 1983a). The metabolite was cytotoxic at concentrations greater than 2500 $\mu\text{g}/\text{plate}$. No increase in the reversion rate was seen. *Escherichia coli* strains (K12)p 3478 (repair deficient) and W 3110 (pol A+) were incubated in the presence of brenzcatechin with and without rat liver activation. In the first trial the test article was placed on the filter disk at 0, 625, 1250, 2500, 5000, or 10,000 $\mu\text{g}/\text{plate}$; in the second trial, at 0, 1200, 1800, 2700, 4050, and 6075 $\mu\text{g}/\text{plate}$; and in the third trial at 0, 800, 1200, 1800, 2700, 4050 $\mu\text{g}/\text{plate}$. There were four plates per concentration with water as the vehicle. No genotoxic effects were reported at or below concentrations which were cytotoxic. The study was acceptable to DPR as an ancillary report.

THS2490 (no purity stated), a metabolite of propoxur, was tested with *Salmonella* strains TA1535, TA1537, TA1538, TA98 and TA100, with and without activation (Herbold, 1984a). Four plates were used per concentration. The concentrations were 0, 312.5, 625, 1250, 2500 or 5000 $\mu\text{g}/\text{plate}$. No increase in the reversion rate was reported. The study was acceptable as ancillary information.

Isopropoxyphenol (no purity stated), a metabolite of propoxur, was tested with *Salmonella* strains TA1535, TA1537, TA98 and TA100, with and without activation, four plates per strain, at concentrations of 0, 20, 100, 500, 2500 or 12,500 $\mu\text{g}/\text{plate}$ (trial 1), and 0, 625, 1250, 2500, 5000, or 10,000 $\mu\text{g}/\text{plate}$ (trial 2) (Herbold, 1983b). No increase in the reversion rate was reported. The study was acceptable to DPR as ancillary information.

Urine from rats treated with propoxur (0 or 8000 ppm) was processed and extracted for testing with *Salmonella* strains TA1535, TA1537, TA98 and TA100, with and without activation, four plates per strain, at concentrations of 0, 14.5, 29 or 58 μl propoxur origin urine (where 58 μl is equivalent to 1.42 ml urine) (Herbold, 1985c). The extracted urine was bacteriostatic at the highest amount. There was no indication of mutagenicity. The study was considered supplemental information.

Urine from rats fed 8000 ppm propoxur was processed and extracted before testing for mutagenicity in *Salmonella* strains TA1535, TA1537, TA98 and TA100, with and without activation (Herbold, 1985d). Freeze dried urine equivalent to 767 μ l per plate did not produce any evidence of reversion. The study was considered supplemental.

Structural Chromosomal Aberration

Propoxur (99.6% purity) was given in a single oral dose to 5 Chinese hamsters/sex/group at 0, 14.5, 75 or 150 mg/kg (Herbold, 1985b). The animals were killed 24 hours after dosing. There was no evidence of sister chromatid exchange in the 20 metaphases/animal examined. This study was acceptable to DPR.

Propoxur (97.8% purity) was tested with CHO cells for chromosome aberration induction (Putman and Morris, 1988). Cells without activation were incubated at 0 (negative and DMSO), 157, 313, 625 or 1250 μ g/ml for an 18 hour incubation and a 20 hour harvest time. Cells with activation were incubated at 0, 625, 1250, 2500 or 5000 μ g/ml for a 2 hours exposure with 10 hour harvest. Duplicate cultures were used for each concentration, and 50 cells per culture were scored. There was no evidence of increased chromosomal aberrations. This study was acceptable to DPR.

Propoxur (99.5% purity) was given to Chinese hamsters in a single oral gavage dose at 0 (vehicle, 0.5% Cremophor) or 150 mg/kg with 5/sex treated with propoxur killed at 6, 24 or 48 hours (Herbold, 1988). In a second test, doses of 0, 75, 150 or 300 mg/kg were given to 5/sex/group and killed at 48 hours. A marginal increase in aberrations (excluding gaps) which had been seen at 48 hours in the first run at 150 mg/kg was not confirmed in the re-run at 150 mg/kg or at 300 mg/kg. Cyclophosphamide was used as the positive control. No DNA damage or chromosomal aberrations were seen. This study was acceptable to DPR.

Propoxur (99.6% purity), suspended in 0.5% aqueous Cremophor emulsion, was given orally to 10 male Chinese hamsters/dose at 0, 75 or 150 mg/kg (Herbold, 1986). The hamsters were dosed intraperitoneally with colcemid (3.3 mg/kg) 5.5 hours before being killed at 24 hours after dosing. The metaphase spermatogonial chromosomes were examined microscopically. No dose-related clinical abnormalities were seen in the hamsters. No dose-related cytogenetic abnormalities were seen in the metaphase chromosomes. The study was considered supplemental information.

Propoxur (99.2% purity) was given by oral gavage in a single dose at 0 or 10 mg/kg to 50 NMRI males per group, which were mated 1:1 with females for 12 matings of four days duration (Herbold, 1980). There was no evidence of chromosomal aberrations. The study was considered unacceptable because only a single dose (which caused no toxic effects) was used; there was no positive concurrent control or acceptable historical positive control data.

Propoxur (99.6-100% purity) in DMSO was added to cultures of PHA stimulated human lymphocytes (2 cultures/sex/group) for 2.5 hours with activation (22.5 hr recovery) at 250, 500, and 1000 μ g/ml (Herbold, 1985e). Dosing without activation was 125, 250 and 500 μ g/ml. Cultures were harvested by standard procedures, and twenty metaphases/culture were examined. The mitotic index decreased, but no structural aberrations or sister chromatid exchanges were induced by propoxur. The positive control (Mitomycin C) failed to induce a two-fold increase in the background levels of SCE in 3/4 of the cultures without activation, and cyclophosphamide failed in 1/2 the cultures. The positive controls had no effect on structural aberrations, and a variable effect on the mitotic index. The study was unacceptable because

the lack of a clear effect by positive controls precluded an evaluation for adverse effects from the test substance.

Other Genotoxic Effects

Technical propoxur (98.5% purity) was tested with primary rat hepatocytes from male Fisher 344 rats for 18-20 hours at 0, 1.5, 5.0, 15, 50, 150, 500, or 1000 $\mu\text{g/ml}$ in the presence of 3H-thymidine (Curren, 1989). Cells were fixed with ethanol-glacial acetic acid, and fifty cells/plate were scored for 3H-thymidine incorporation by autoradiograph. Cytotoxicity and precipitation were seen at 500 and 1000 $\mu\text{g/ml}$. Treatment related increases in nuclear grain counts were not seen. Cytotoxicity was evaluated in a parallel trial by measuring lactate dehydrogenase release into the medium. No adverse effects were noted. The study was acceptable to DPR.

Propoxur (99.4-99.8% purity) was given by oral gavage to Chinese hamsters (10/sex/dose) at 0 (0.5% Cremophor), 75, 150 or 300 mg/kg in a single dose (Herbold, 1991). Five/sex were killed at 6 and 24 hours post-treatment, and 100 metaphases were scored per animal. Cyclophosphamide was used as a positive control. There was no evidence of cytogenetic effects caused by propoxur. This was considered a supplementary study.

Propoxur (no purity stated) at 0 or 8000 ppm was fed in the diet to female BOR:WISW rats (Klein, 1986). Two diets were used: Altromin and Basal Diet No. 531. In the first part of the study, rats (10 females/group/dose) were fed for 24 hours or 7 days. The epithelial cells of the urinary bladders were isolated and put into culture. The cells were incubated with ^3H -thymidine for two hours, washed and prepared for autoradiography. In the second part, 6 rats/group/dose were fed 0, 40, 200 or 1000 ppm for 7 days. Positive controls were methyl methane sulfonate and o-phenylphenol. Slides were scored for percentage of cells in S phase and for UDS induction. No adverse effect was indicated. The study was unacceptable to DPR because the purity of the material was not described, dietary analyses were not provided, and there was no justification for using only females.

Propoxur (98.0% purity) was used with *B. subtilis* strains NIG17 and NIG45 in the *rec+/-* test (Inukai and Iyatomi, 1978). The doses used were 0, 3, 30 or 300 $\mu\text{g/disc}$ with no activation. The study was considered unacceptable as the dose was not justified, there was no activation, a single plate per dose, and no measurable cytotoxicity.

Propoxur (no purity stated) and three metabolites (THS2490, THS1240, THS1241b) in 10% ethanol were given at 10 mg/kg by gavage to 24 male Wistar rats/compound (Klein, 1983). After 24 hours, the rats were killed and spleen cell suspensions were prepared to measure programmed DNA synthesis, suppressed programmed DNA synthesis, unprogrammed DNA synthesis, and nucleoid sedimentation. THS2490 and 1241b decreased programmed DNA synthesis, but propoxur and THS1240 had no effect. No effect of any test substance was seen on unprogrammed DNA synthesis, nucleoid sedimentation, or DNA binding. No adverse effect was indicated. The study was unacceptable because of a lack of rationale for the dosing vehicle, dose level, dose and route of exposure of the positive control, use of spleen cells for the *in vivo* assays, and the lack of a metabolic activating system for the *in vitro* binding assay.

Isopropoxyphenol (no purity stated; a metabolite of propoxur) was tested with *Saccharomyces cerevisiae* diploid strain D7 for mitotic crossing-over and mitotic gene conversion with and without activation (Herbold, 1984b). Cultures were incubated for 16 hours with 0, 625, 1250, 2500, 5000 or 10000 $\mu\text{g/ml}$ in test 1; with 0, 187.5, 375, 750, 1500 or 3000 $\mu\text{g/ml}$ in test 2; and 0, 185.9, 260.3, 364.4, 510.2, 714.3 or 1000 $\mu\text{g/ml}$ in trial 3. The substance

was cytotoxic at concentrations greater than 750 $\mu\text{g/ml}$. There was no evidence for genotoxicity in either mitotic gene conversion or mitotic crossing-over. The study was acceptable to DPR.

F. REPRODUCTIVE TOXICITY

Summary- No adverse reproductive effects were noted in a two-generation rat reproduction study. The parental NOEL was 7.3 mg/kg-day for body weight gain decrement, and inhibition of brain and red blood cell cholinesterase activity. The developmental NOEL was 37 mg/kg-day for decrement in body weight gain for pups after day 4.

Dietary- Rat

Wistar rats (25/sex/group) were treated with 0, 100, 500, or 2500 ppm propoxur in the diet for 2 generations, one litter per generation (Suter *et al.*, 1990). Statistically significant ($P < 0.05$) decrements in body weight gain (approximately 7%) were noted at the high dose for all parental stock in both the F_0 and F_1 generations. Females in the F_1 generation exhibited a statistically significant ($P < 0.05$), 6% and 17% weight gain decrements at the two highest doses, respectively. Statistically significant inhibition of plasma, red blood cell, and brain cholinesterase activities were also observed in the two highest treatment groups (Table 9). Both male (2/25 and 8/25) and female rats (6/25 and 7/25) in the F_0 and F_1 generations, respectively, exhibited uroepithelial hyperplasia at the highest dose. The parental NOEL was 7.3 mg/kg-day (based on consumption data) for decrement in body weight gain and a statistically significant ($P < 0.05$), 20% or greater inhibition of brain cholinesterase activity. The developmental NOEL was 37 mg/kg-day for decrement (17%) in weight gain for pups after day 4. The study was acceptable to DPR under FIFRA guidelines.

An earlier study on reproduction in rats was unacceptable to DPR under FIFRA guideline requirements as the registrant failed to make clinical observations or analyze the diet; no necropsies were performed; and mating was mixed (Loser, 1973).

Table 9. Mean Percent Cholinesterase Inhibition in Wistar Rats Exposed to Propoxur in Their Diet (Suter *et al.*, 1990).

<u>Plasma Cholinesterase Activity^a</u>			
Dose (ppm)			
Sex	100	500	2500
F ₀ Male	0	6	0
F ₀ Female	0	0	15
F ₁ Male	0	0	0
F ₁ Female	0	22*	22*
<u>Red Blood Cell Cholinesterase Activity^a</u>			
Dose (ppm)			
Sex	100	500	2500
F ₀ Male	11*	41*	44*
F ₀ Female	0	26*	45*
F ₁ Male	11	23*	35*
F ₁ Female	6	26*	27*
<u>Brain Cholinesterase Activity^a</u>			
Dose (ppm)			
Sex	100	500	2500
F ₀ Male	0	14*	14*
F ₀ Female	0	0	14*
F ₁ Male	0	0	17*
F ₁ Female	12*	20*	25*

a/ Expressed as mean percent inhibition of concurrent control, N = 25.

* Significantly different from control by Dunnett's Test, p<0.05

In a range-finding study, Wistar/HAN rats (10/sex/group) were fed on a diet containing propoxur (99.3% purity) at 0, 200, 1000, or 5000 ppm for one generation (Suter *et al.*, 1991). Rats were treated from 3 weeks prior to mating until after lactation in a single mating trial. An additional five rats per sex per group were allocated for assay of cholinesterase activities. The parental NOEL was 200 ppm (approximately 17 mg/kg-day from consumption data) for significant (P<0.05) mean decrement in weight gain (10% at 1000 ppm and 22% at 5000 ppm) and reduced food intake. At 5000 ppm there were indications of a reduction in the average number of implantation sites (10.3 compared to 14.3 in controls), and an increase in post-implantation loss (14.6% compared to 8.8% in controls). The developmental NOEL was also 200 ppm for significant (P<0.05) decrement in birth weight (9% at 1000 ppm and 14% at 5000 ppm). The study was considered supplemental information.

G. DEVELOPMENTAL TOXICITY

Summary- Propoxur induced maternal toxicity in rats and rabbits. The 1-day NOEL for maternal toxicity in rats, based on cholinergic signs (chewing motions, teeth grinding, tremors), was 3 mg/kg-day. In rabbits, the 1-day maternal NOEL was 10 mg/kg-day, based on cholinergic signs (restlessness and dyspnea) and death. The developmental NOEL, based on vertebral malformations in rabbits was 10 mg/kg-day.

Gavage- Rat

Wistar rats were dosed by gavage with propoxur (99.4% pure) on days 6-15 of gestation with 0, 3, 9, or 27 mg/kg-day (Becker *et al.*, 1989a). The NOEL for maternal toxicity, cholinergic signs (chewing motions, teeth grinding, tremors) which lasted 1-2 hours after dosing on day one, was 3 mg/kg-day. No developmental toxicity was seen at any dose. The study was acceptable to DPR under FIFRA testing guidelines.

Propoxur (98.4% purity) was fed in the diet at 0, 1000, 3000, or 10,000 ppm to FB 30 rats (10/group) during the entire gestation period (Lorke, 1970). The NOEL for maternal toxicity, decrement in body weight (40 and 55% at the two highest doses, respectively), was 1000 ppm. The developmental NOEL was 1000 ppm for decrement in fetal weight and increased numbers of resorptions at the two highest doses. The study was unacceptable to DPR under FIFRA guidelines because of inadequate numbers of rats, treatment of entire gestation period, no individual body weights, and no clinical observations.

Gavage- Rabbit

Chinchilla rabbits were given propoxur (99.4% pure) at 0, 3, 10 or 30 mg/kg-day by gavage in 0.5% Cremophor aqueous suspension on days 6-18 post coitum (Becker *et al.*, 1989b). At 30 mg/kg-day there were 3 maternal deaths (two on day 2; one on day 6), temporary restlessness and dyspnea following treatment in 8/16 animals, and a transient reduction in food consumption. The maternal NOEL was 10 mg/kg-day. Offspring in the 30 mg/kg-day group exhibited an increased incidence (3/79) of abnormally ossified or fused sternbrae compared to controls (1/124), and slight ossification delays in some phalanges. The developmental NOEL was thus 10 mg/kg-day. The study was acceptable to DPR under FIFRA testing guidelines.

In an earlier developmental study, Himalayan CHBB:HM rabbits (15/group) were given 0, 1, 3 or 10 mg/kg-day of propoxur on days 6-18 of gestation (Schluter, 1981). No effects were seen, and both the maternal and the developmental NOELs were \geq 10 mg/kg-day. The study was unacceptable to DPR under FIFRA guideline requirements because of an inadequate high dose, no corpora lutea counted, no food consumption data, and no purity given for the test article.

H. NEUROTOXICITY

Summary- The single dose LOEL for cholinergic signs (excessive chewing and reclining posture) and significant inhibition of brain cholinesterase activity in rats was 2 mg/kg. There was no NOEL established for neurotoxicity from the four studies.

Chickens- oral

Propoxur (no purity stated) was fed for 30 days to chickens at 0, 300, 1500, 3000, or 4500 ppm (Hobik, 1967). Three chickens per group were terminated immediately at the end of dosing. Two to three chickens were terminated after a 28 day observation period. This study was unacceptable to DPR under FIFRA guidelines as there was no positive control, no basis for the dose levels, and the protocol was inappropriate.

Propoxur (no purity stated) was administered to chickens in a single oral application of 100, 200, 500, or 1000 mg/kg and observed for 6 weeks, or a single intraperitoneal injection of 25, 37.5, 50 or 100 mg/kg (Kimmerle, 1966). Some deaths and acute toxicological effects were observed, but no neurotoxic damage was evidenced. The study was considered unacceptable by DPR as being scientifically invalid. The figures and tables of results were missing; there was no positive control, no analysis of the dosing material, and missing data.

Rats- oral

In a neurobehavioral study in which rats were exposed for 50 days to propoxur (purity unspecified) at 0, 25 and 50 ppm (approximately 0, 1.25 and 2.5 mg/kg-day) in the diet, neurobehavioral effects were observed, with a LOEL of 1.25 mg/kg-day (Desi *et al.*, 1974). The study was considered supplemental.

Wistar rats (12/sex/dose) were fasted for 15 hours prior to administration of a single oral dose of propoxur (99.4% purity) at 0 (polyethylene glycol 400), 2, 10 or 25 mg/kg (Dreist and Popp, 1994). A variety of cholinergic signs were noted in rats dosed with 10 and 25 mg/kg (Table 11). Body temperatures were significantly reduced in both males and females dosed with 10 or 25 mg/kg. Male rats dosed with 10 or 25 mg/kg exhibited significantly ($P < 0.05$; ANOVA) reduced grip strength, while only females dosed with 25 mg/kg exhibited reduced grip strength. Significant ($P < 0.01$) inhibition of brain cholinesterase activity was observed at all doses (Table 12). There was no NOEL for cholinergic signs (repetitive chewing and reclining posture), or inhibition of brain cholinesterase activity. The study was not acceptable to DPR under FIFRA guidelines because it lacked a cited report verifying analytical capabilities of the test lab, and some details or clarifications of the histopathology.

Table 11- Cholinergic signs induced in Wistar rats by a single oral dose of propoxur (Dreist and Popp, 1994)

Parameter	Dose			
	0 mg/kg	2 mg/kg	10 mg/kg	25 mg/kg
<u>Males</u>				
Gait abnormalities	1/12	0/12	8/12	12/12
Involuntary motor activity (clonic)	0/12	0/12	9/12	12/12
Sitting or lying normally	0/12	6/12	9/12	12/12
<u>Females</u>				
Gait abnormalities	0/12	0/12	8/12	12/12
Involuntary motor activity (clonic)	0/12	2/12	11/12	12/12
Abnormal righting reflex	0/12	0/12	1/12	6/12
Sitting or lying normally	1/12	1/12	5/12	12/12

Table 12 - Inhibition of cholinesterase activity in Wistar rats exposed to a single dose of propoxur by gavage (Dreist and Popp, 1994)^a.

Parameter	Dose		
	2 mg/kg	10 mg/kg	25 mg/kg
<u>Males</u>			
Plasma ChE	11	46**	54**
RBC ChE	19	72**	83**
Brain ChE	18**	47**	61**
<u>Females</u>			
Plasma ChE	20	9	36*
RBC ChE	16*	63**	88**
Brain ChE	21**	49**	59**

^{a/} Expressed as mean percent inhibition of control value. Six animals were used at all doses except in males at 25 mg/kg where N=2.

* Statistically significant (P<0.05) by Dunnett's test.

** Statistically significant (P<0.01) by Dunnett's test.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

The principal acute effects of propoxur were primarily related to its inhibition of cholinesterase activity. In acutely toxic episodes, muscarinic and nicotinic receptors are stimulated by acetylcholine with characteristic signs occurring throughout the peripheral and central nervous systems (Murphy, 1986). However, spontaneous hydrolysis of the carbamate-cholinesterase complex occurs *in vivo*, leading to the disappearance of clinical signs within a very short period of time (Ellenhorn and Barceloux, 1988). Repetitive dosing with propoxur over a lifetime produced oncogenic effects. A summary of selected toxicity studies presented in this document on the effects of propoxur is contained in Table 13.

Acute Toxicity

The principal route of exposure for most pesticide applicators using propoxur, occupationally or non-occupationally, was through the skin (Appendix A). Consequently, it would appear to be preferable to use the dose-response of adverse effects observed in short-term dermal toxicity studies as the basis for calculating margins of safety for workers with short-term exposure to propoxur. Such studies were available in the database for propoxur.

A single dermal dose of 2,000 mg/kg caused clinical signs (fasciculations, decreased motor activity, hyper-reactivity) in rabbits (Sheets, 1988). The single-dose dermal NOEL for clinical signs was 1,000 mg/kg in both rabbits (Diesing and Flucke, 1989) and rats (Bocker, 1961). These single dose dermal NOELs for clinical signs were considerably greater than the oral NOELs in the same species. In a rabbit developmental study, the maternal NOEL (1-day) was 10 mg/kg-day, based on cholinergic signs and death at 30 mg/kg (Becker *et al.*, 1989b). In the rat, the LOEL (30-min) for cholinergic signs (convulsions, reduced motility, apathy, bristling coat) from a single dose was 25 mg/kg with a NOEL of 5 mg/kg (Heimann, 1982b). The LOEL for maternal toxicity (cholinergic signs) in a rat developmental study was 9 mg/kg-day, with a 1-day NOEL of 3 mg/kg-day (Becker *et al.*, 1989a). A single oral dose of 5 mg/kg resulted in cholinergic signs (muscle fasciculations) in dogs, but a dose of 4 mg/kg did not produce any signs (Crawford and Nelson, 1970). In a single oral dose, neurotoxicity study, the LOEL for cholinergic signs (excessive chewing and reclining posture) and significant brain cholinesterase inhibition was 2 mg/kg-day (Dreist and Popp, 1994). Differences in the effective dose were due to the slower and reduced percentage of dermal absorption compared to oral absorption (Everett and Gronberg, 1971; Feldman and Maibach, 1974; Eben *et al.*, 1985b). Despite the fact that dermal dosing is more germane to human exposure scenarios, the dermal NOELs, 1000 mg/kg for clinical signs in rats and rabbits, were not used as the basis for assessing the risks from acute exposure to propoxur. Nor were oral NOELs for clinical signs in laboratory animals used as the basis for risk characterization.

The toxicological basis for characterizing the risk from acute exposure to propoxur was an oral NOEL from a human study (Vandekar *et al.*, 1971). The human oral NOEL was used because 1) the use of human dose-response data eliminates the uncertainty associated with extrapolating to humans from laboratory animal studies, and 2) the quality of the clinical observations in the dermal toxicity studies (Bocker, 1961; Diesing and Flucke, 1989) was not comparable to the clinical observations in the human study. In the human study, volunteers (number unstated) were reported to have exhibited cholinergic signs (stomach discomfort, blurred vision, moderate facial redness and sweating) after a single bolus oral dose of 0.36 mg/kg (Vandekar *et al.*, 1971). Doses of 0.2 mg/kg administered every half hour for up to 2 1/2

hours (a total of 1 mg/kg) produced no cholinergic signs. Thus, the 30 minute NOEL for cholinergic signs in humans following a single bolus dose was 0.2 mg/kg. In the same study, red blood cell cholinesterase activity was depressed about 2% after the first dose, and 10% after a total of 5 doses. This indicated a cumulative inhibitory effect on cholinesterase activity by multiple doses of propoxur. Depression of plasma or red blood cell cholinesterase activities is generally used as an indication of exposure to a neurotoxic substance, but the toxicological significance is controversial (USEPA, 1988, 1990a, 1993). Consequently, inhibition of red blood cell cholinesterase activity, as reported in the study (Vandekar *et al.*, 1971), was not used to characterize the potential risk to human health. The NOELs for clinical signs (specified amounts- up to 1 mg/kg- for specific lengths of time- up to 2 1/2 hours) from the Vandekar *et al* study (1971) were used to evaluate the health risks from potential acute exposures of different durations to propoxur.

Chronic Toxicity- The principal non-oncogenic effects of chronic exposure to propoxur in the diet were depression of body weight, bladder hyperplasia in the rat (Hahnemann and Ruehl-Fehlert, 1988a), and changes in blood parameters indicating possible hemolytic anemia in the dog (Hoffmann and Groning, 1984). The 1-year NOEL for uroepithelial hyperplasia in rats was 14 mg/kg-day (Hahnemann and Ruehl-Fehlert, 1988a). The 1-year NOEL for hemolytic anemia in the dog, 7 mg/kg-day (Hoffmann and Groning, 1984), was used to evaluate the health risks from potential annual exposures to propoxur.

Oncogenic Effects- Two separate chronic feeding studies with Wistar rats have clearly demonstrated that propoxur caused tumors of the bladder uroepithelium (Hahnemann and Ruehl-Fehlert, 1988; Suberg *et al.*, 1984). Chronic feeding studies using other strains of rats were of insufficient duration to be considered conclusive (Hahnemann, 1988a,b,c,d; Hoffmann and Groning, 1984). Despite the one year limitation of a study involving Sprague-Dawley rats (Hahnemann, 1988a), propoxur did induce lesions of the uroepithelium that were similar in type and frequency compared to those seen in Wistar rats in the same time frame.

Both male and female Wistar rats exposed to propoxur via whole body inhalation for 30 months developed adenomas and carcinomas of the bladder epithelium, and male rats developed hepatocellular adenomas and carcinomas (Pauluhn, 1992). Male Wistar rats also had a significantly ($P < 0.05$) greater incidence of pituitary adenomas. It was suggested that propoxur-induced bladder tumor development was limited to rats (Machemer and Schmidt, 1988).

Although mice exposed to propoxur in the diet did not develop bladder tumors, they did exhibit a significant, dose-related increase in hepatocellular adenomas and hyperplasia of the urinary bladder epithelium (Bomhard, 1992a). These data are considered to be supportive of the tumorigenic effect associated with propoxur exposure. Another hypothesis suggested that the tumorigenicity of propoxur was related to the acidity of the urine as a result of diet (Machemer and Schmidt, 1988). However, not all dietary studies gave results consistent with this hypothesis (Hahnemann and Ruehl-Fehlert, 1988b; Hahnemann and Ruehl-Fehlert, 1988c).

It is clear that the urinary tract is the principal route of excretion of propoxur and its metabolites (Krishna and Casida, 1966; Everett and Gronberg, 1971; Bell and Gronberg, 1975; Weber, 1986). Daily dietary dosages resulting in oncogenicity in the mouse or rat exceeded the oral LD₅₀ from a single bolus dose for the respective species by three to twenty-fold (Hahnemann and Ruehl-Fehlert, 1988; Suberg *et al.*, 1984; Bomhard, 1992a), consequently substantial amounts of propoxur and metabolites accumulated in the bladders of these animals. Some factors suggest that the onset of oncogenicity in the bladder uroepithelium may have a

threshold. In particular, daily oral dosages of propoxur, which caused oncogenicity in female Wistar rats, induced hyperplasia in the bladder uroepithelium as early as four weeks (Figure 2; Hahnemann and Ruehl-Fehlert, 1988). As the oncogenic effects, which occur later in life (not before week 69- Hahnemann and Ruehl-Fehlert, 1988; Suberg *et al.*, 1984; Pauluhn, 1992), were preceded by a long period of bladder hyperplasia, dosages which do not cause hyperplasia of the bladder uroepithelium appear to be unlikely to induce uroepithelial tumors (Figures 2 and 3).

Results of studies on the direct effects of propoxur on the genome were equivocal. Although mutagenicity studies in bacteria were negative, no studies contradicted the finding that propoxur caused formation of micronuclei in cultured human lymphocytes (Gonzalez-Cid *et al.*, 1990). Consequently, propoxur must be considered potentially genotoxic.

The weight of evidence in laboratory animal studies is sufficient to consider propoxur a potential human carcinogen: 1) The incidence of uroepithelial carcinoma in rats was both substance-related, and dose-related. 2) Dietary exposure to propoxur induced uroepithelial carcinoma in both male and female Wistar rats. 3) A second study, examining the time course of bladder oncogenicity in female Wistar rats, was also positive. 4) The incidence of uroepithelial carcinoma was extremely rare in historical controls. 5) Sprague-Dawley rats, in an abbreviated study, developed lesions of the uroepithelium similar to those seen in Wistar rats in the same time frame. 6) Both male and female Wistar rats in a two-generation rat reproduction study also developed uroepithelial lesions with dietary exposure to propoxur. 7) The tumorigenic effect was present at doses below the maximum tolerated dose. 8) Propoxur was demonstrated to be tumorigenic in mice and caused hyperplasia of the mouse urinary bladder epithelium. 9) Propoxur was tumorigenic through both the oral and inhalation routes.

Because the data indicate propoxur is potentially genotoxic, it is assumed that a tumorigenic threshold does not exist, in the absence of pharmacokinetic data to the contrary. Under this assumption, the linearized multistage model was used for determining the carcinogenic potency of propoxur in the low dose range. Although Wistar rats exposed to propoxur via whole body inhalation for 24 months developed hepatocellular adenomas (Pauluhn, 1992), no chemical related histopathological changes were noted in the bladder. The incidence of pituitary adenomas (15%) in male rats at the high dose, was significantly greater than concurrent controls (3%), but it was not above the average level (26%) [range, 6% to 46%] found in contemporary historical controls in 7 studies (Bomhard, 1992a). Thus, the indication of tumorigenic response in the pituitary of male rats was probably not treatment-related.

Only two studies had data adequate to allow a quantitative risk assessment (Suberg *et al.*, 1984, and Hahnemann and Ruehl-Fehlert, 1988). In the former study, used by USEPA to develop their potency factor (USEPA, 1992a), both male and female rats developed uroepithelial carcinomas. Following National Toxicology Program guidelines (McConnell *et al.*, 1986), the combined incidence of benign and malignant bladder tumors in both male and female rats from the Suberg *et al.* (1984) study were used to calculate a potency. The potency of propoxur for humans was calculated using the Global 86 linear multistage model (Howe *et al.*, 1986) for males (separately), females (separately), and both sexes combined. The Maximum Likelihood Estimates (MLEs) of the potency slopes were effectively zero. The upper bound (95% confidence limit) potency slopes were calculated in each instance. The major disparities between the MLEs and the upper bound potency estimates were illustrative of the limitation of the Global 86 linear multistage model in the analyses of the data to quantitatively present a range of potencies. The upper bound estimates did not reflect the dose-response relationship of the experimental data, but, rather indicated the influence of the response at the

high dose. As a consequence, a realistic estimate of the overall oncogenic risk could not be generated from this study.

The second study utilized only female rats and examined the chronological appearance of the uroepithelial tumors (Hahnemann and Ruehl-Fehlert, 1988). Consequently, the potency estimate in the second study was derived from MultiWeibel time to tumor analysis (Krewski *et al.*, 1983), as well as from the Global 86 linear multistage model (Appendix B). The best fit of the data to the models from the various analyses was obtained from the Hahnemann and Ruehl-Fehlert study (1988) using the linear multistage model. An interspecies scaling factor, (body weight)^{3/4}, was used to adjust for species differences. The maximum likelihood estimate (MLE) for human cancer potency was $3 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$, with an upper bound (95% confidence level) of $4 \times 10^{-3} \text{ (mg/kg-day)}^{-1}$. The USEPA's current upper bound human-equivalent potency is $3.7 \times 10^{-3} \text{ [mg/kg-day]}^{-1}$ (USEPA, 1992a).

Table 13 - Summary of Selected Propoxur Toxicity Studies

<u>STUDY</u>	<u>SPECIES</u>	<u>ROUTE</u>	<u>EFFECT</u>	<u>LOEL NOEL</u> <u>(mg/kg-day)</u>		<u>GENOTOXIC</u>	<u>REF^a</u>
acute (30 min)	human	oral	cholinergic signs	0.36	0.2		1
acute (30 min)	rat	oral	cholinergic signs	25	5		2
acute (1d)	dog	oral	cholinergic signs	5	4		3
neurotox.(1d)	rat	oral	cholinergic signs	2	-		4
combined	rat	diet	uroepithelial hyperplasia	58	14		5
combined	rat	diet	uroepithelial carcinoma				5
combined	rat	diet	dec. weight gain	42	8.2		6*
combined	rat	diet	uroepithelial carcinoma				6*
chronic	dog	oral	hemolytic anemia	23	7		7*
chronic	dog	oral	death, weight loss	60	22.5		8*
reproduction	rat	diet	RBC ChE and brain ChE	37	7.3		9*
reproduction	rat	diet	dec. pup wt. gain	186	37		9*
develop.(1 day)	rat	oral	cholinergic signs	9	3		10*
develop.(1 day)	rabbit	oral	maternal death, ChE signs	30	10		11*
develop.	rabbit	oral	sternebrae (malformed)	30	10		11*
gene mutation	bacteria	<i>in vitro</i>				-	12*
gene mutation	yeast	<i>in vitro</i>				-	13*
gene mutation	CHO cells	<i>in vitro</i>				-	14*
chromosome	mammal					-	15*
DNA damage	mammal					-	16*
DNA damage	human	<i>in vitro</i>				+	17*
gene mutation	bacteria	metabolites				+/-	18-20*

a/ References- 1. Vandekar *et al.*, 1971; 2. Heimann, 1982b; 3. Crawford and Nelson, 1970; 4. Dreist and Popp, 1994; 5. Hahnemann and Ruehl-Fehlert, 1988; 6. Suberg *et al.*, 1984; 7. Hoffman and Groning, 1984; 8. Loser, 1968; 9. Suter *et al.*, 1990; 10. Becker *et al.*, 1989a; 11. Becker *et al.*, 1989b; 12. Herbold, 1982; 13. Herbold, 1985a; 14. Lehn, 1988; 15. Herbold, 1985b; 16. Putman and Morris, 1988; 17. Cid *et al.*, 1990; 18. Herbold, 1983a,b; 19. Herbold, 1984a,b,c,d; 20. Herbold, 1985 c,d.

* Acceptable to DPR under FIFRA guidelines or TSCA.

B. EXPOSURE ASSESSMENT

As there are no direct food uses for propoxur in the United States, no dietary exposures are expected. The USEPA's Non-Occupational Pesticide Exposure Study (USEPA, 1990b) indicated that propoxur was found in the drinking water of one home in Florida at a concentration of 30 ng/L (USEPA, 1990). However, drinking water does not appear to be a significant route of exposure for the human population.

Occupational Exposure

The studies and data which form the basis for estimating worker exposure are described in Sanborn, 1995. These estimates are based on monitoring data for propoxur, and calculations from monitoring data for surrogate active ingredients with similar application rates and chemical properties. Pest Control Operators (PCOs) in the studies wore denim trousers, cotton/polyester long sleeve shirts, leather boots/shoes or cloth sneakers. In addition (or in place of their normal clothing), the PCOs wore cotton coveralls, baseball caps, and chemical-resistant nitrile gloves. Not all formulations require PCOs to wear protective clothing or gloves. However, it is suggested that in case of prolonged exposure, that PCOs should "wear natural rubber gloves, protective clothing, and goggles."

Dosimetry was determined using patches attached to the clothing. Ethanol hand washes were collected to assess hand exposure, and air levels were monitored with personal pumps. Dermal penetration was assumed to be 0.351%/hr and 16%/day (Feldmann and Maibach, 1974). Patches with non-detectable levels of propoxur were given default values equal to 50% of the minimum detection limit. It was assumed that the PCOs were engaged in spraying operations for 8 hours per day. The monitored activities in one location took 1.8 hours to complete. This is defined as one cycle. The mean exposure values used for the risk assessment are shown in Table 14. The geometric mean absorbed dosages for PCOs per 2-hr cycle ranged from 0.16 to 1.47 $\mu\text{g}/\text{kg}\text{-day}$ (Sanborn, 1995). The 95th percentile of the absorbed cycle dosage [95th percentile = (geometric mean) \times (geometric S.D)^{1.645}] for the respective work tasks were: aerosol (1%) applicator, 2.30 $\mu\text{g}/\text{kg}\text{-cycle}$; bait (2%) applicator, 0.61 $\mu\text{g}/\text{kg}\text{-cycle}$; spray (0.95%) applicator, 0.32 $\mu\text{g}/\text{kg}\text{-cycle}$; and spray (70WP) applicator, 8.0 $\mu\text{g}/\text{kg}\text{-cycle}$. Annual average daily dosages ranged from 4.1 to 14.6 $\mu\text{g}/\text{kg}\text{-day}$, and lifetime average daily dosages ranged from 0.5 to 2.0 $\mu\text{g}/\text{kg}\text{-day}$.

Table 14 - Mean occupational exposures to propoxur (Knarr, 1988a,b; Knarr, 1991a,b,c).

Work Task	Absorbed Cycle ^a Dosage (ug/kg-cycle)	AADD ^b (ug/kg-day)	LADD ^c (ug/kg-day)
Aerosol (1%) Applicator (N = 32)	0.95	14.6	2.0
Bait (2%) Applicator (N = 32)	0.19	5.5	0.7
Spray (0.95%) Applicator (N = 32)	0.16	4.1	0.5
Spray (70WP) Applicator (N = 16)	1.47	9.9	1.4

- a/ Geometric mean of one application- assumes that the body weight is 76 kg; dermal penetration is 0.351%/hr; respiratory uptake is 50%. The monitored activities in one location took 1.8 hours to complete. This is defined as one cycle. Data derived from Table 5 of the exposure assessment (Sanborn, 1995).
- b/ Annual Average Daily Dosage: Assumes that the PCOs work 6 hours per day; body weight is 76 kg; dermal penetration is 16%/day; respiratory uptake is 50% and there are 223 days of exposure each year.
- c/ Lifetime Average Daily Dosage: Assumes 9.6 years of occupational exposure during a 70 year lifetime (Sanborn, 1995).

Non-Occupational Exposure

Residents and office workers may be exposed to pesticides upon entering a treated area. Non-occupational exposures may occur through dermal contact with treated surfaces, and, to a lesser extent via inhalation of pesticide vapors. The potential passive exposures of residents to propoxur after crack-and-crevice treatment of a home were based on studies submitted by the registrant (Knarr, 1988a; Knarr, 1991c). The data were derived from wipe samples in various rooms of the home. Analysis of the samples indicated a log-normal distribution of surface residues throughout the house. Air concentrations in the home were more-or-less constant. It was assumed that infants (6-9 mo.) had a body weight of 7.5 kg with 0.45 m² of surface area- 50% of which could be exposed to pesticides (Sanborn, 1995). Their breathing rate was 0.5 m³/hr with 100% inhalation uptake. For children (12 yr), it was assumed they had a body weight of 40.5 kg with 1.37 m² of body surface area, and a breathing rate of 0.9 m³/hr. For adults, the assumptions were: 76 kg body weight; 2.0 m² surface area; 1 m³/hr breathing rate. The geometric means of passive, non-occupational exposures ranged from 2 hour absorbed dosages of 0.22 to 1.4 ug/kg-day (Table 15). Infants, 6-9 months of age, had the highest potential exposure.

The exposure study used to estimate exposure to a homeowner for flea control on two dogs involved a biomonitoring study of 15 professional dog-groomers who sprayed an average of 20 dogs during an 8-hour workday (Waggoner, 1991). A metabolite of propoxur, 2-iso-propoxyphenol, was measured in urine samples collected from the study's participants, and the 24-hour absorbed dose of propoxur was calculated. The mean absorbed dose, normalized for 2 dogs (Sanborn, 1995), is presented in Table 15. It was assumed that the dogs could be sprayed by a non-professional in a period of 2 hours. The 95th percentile of the absorbed dosage for an adult engaged in spraying 2 dogs per day for ticks was 77.1 $\mu\text{g}/\text{kg}\text{-day}$.

Table 15 - Geometric means of non-occupational exposures to propoxur^a.

Individual	2-Hour Absorbed ^b Dosage ($\mu\text{g}/\text{kg}\text{-day}$)	AADD ^c ($\mu\text{g}/\text{kg}\text{-day}$)	LADD ^d ($\mu\text{g}/\text{kg}\text{-day}$)
Passive Exposure			
Infant (6-9 mo.) ^e	1.46	1.2	*
Adolescent (12 yr) ^e	0.22	0.2	*
Adult ^e	0.37	0.13	0.21
Active Exposure^f			
Dog Groomer, (N=15) (0.25% spray)	10.3	0.75	0.43

a/ From Tables 4, 6, and 7 of the exposure assessment document (Sanborn, 1995).

b/ Average Daily Dosage, assumed to be completed in 2 hours.

c/ Annual Average Daily Dosage; assumes 16 hours awake and 8 hours sleeping each day; assumes exposures take place for 9 days/month, 4 months out of the year.

d/ Lifetime Average Daily Dosage is calculated by adding the AADDs for infants (6-9 months), adolescents (12 yrs) and adults (52 years), and dividing by the 70 year life span.

e/ People living in homes treated with crack and crevice treatments of propoxur for insect control (Sanborn, 1995). These exposures were calculated using default assumptions. It was assumed that infants (6-9 mo) had a body weight of 7.5 kg with 0.45 m² of surface area- 50% of which could be exposed to pesticides. Their breathing rate was 0.5 m³/hr with 100% inhalation uptake. For children (12 yr), it was assumed they had a body weight of 40.5 kg with 1.37 m² of body surface area, and a breathing rate of 0.9 m³/hr. For adults, the assumptions were: 76 kg body weight; 2.0 m² surface area; 1 m³/hr breathing rate.

f/ Pet owner involved in spraying 2 dogs for pesticide control may spray his pets 26 times a year.

* No lifetime exposure to this group.

C. RISK CHARACTERIZATION

Occupational

The margins of safety (MOS) corresponding to various occupational exposure scenarios are presented in Table 16. A margin of safety is defined as the ratio of the dosage of propoxur which produced no effect (NOEL) in a human or laboratory animal study to the dosage of propoxur to which a specific population subgroup is theoretically exposed. In the case of propoxur, a single oral, bolus dose of 360 $\mu\text{g}/\text{kg}$ caused cholinergic signs in a group of humans, while 200 $\mu\text{g}/\text{kg}$ did not. After 30 minutes, another bolus dose of 200 $\mu\text{g}/\text{kg}$ did not cause clinical signs even though the total absorbed dose over the 30 minute period was 400 $\mu\text{g}/\text{kg}$. Up to 1,000 $\mu\text{g}/\text{kg}$ of propoxur was administered over a 2 1/2 hour period without the manifestation of clinical signs. Clearly, then, the duration of exposure is critical. MOSs for mean acute occupational exposures of 1.8 hours duration, based on the 2-hour NOEL of 800 $\mu\text{g}/\text{kg}$ for cholinergic signs in humans, ranged from 544 (applicators handling 70WP) to 5,000 (applicators using 0.95% active ingredient in spray). The MOSs for the 95th percentile of the absorbed cycle dosages ranged from 100 (applicators handling 70WP) to 2,500 for spray applicators using 0.95% formulation. MOSs for potential chronic occupational exposure to propoxur, based on a NOEL of 7 mg/kg-day for hemolytic anemia in dogs, ranged from 479 for aerosol applicators to 1,707 for 0.95% spray applicators. Maximum Likelihood Estimates of excess lifetime risks of cancer ranged from 1 to 6 x 10⁻⁶, based on a Q₁ of 0.003 (mg/kg-day)⁻¹ (Table 16). The upper-bound (95%) excess lifetime risks of cancer for theoretical occupational exposure to propoxur ranged from 2 x 10⁻⁶ to 8 x 10⁻⁶, based on a Q₁* of 0.004 (mg/kg-day)⁻¹.

Table 16 - Margins of Safety and Maximum Likelihood Estimates of excess risk for potential mean occupational exposures to propoxur^a.

<u>Work Task</u>	<u>Acute</u> <u>($\mu\text{g}/\text{kg}\text{-cycle}$)</u>	<u>Acute^b</u> <u>MOS</u>	<u>AADD</u> <u>($\mu\text{g}/\text{kg}\text{-day}$)</u>	<u>Chronic^c</u> <u>MOS</u>	<u>LADD</u> <u>($\mu\text{g}/\text{kg}\text{-day}$)</u>	<u>MLE^d</u> <u>Risk (10⁻⁶)</u>
Aerosol (1%) Applicator	0.95	842	14.6	479	2.0	6
Bait (2%) Applicator	0.19	4,210	5.5	1,272	0.7	2
Spray (0.95%) Applicator	0.16	5,000	4.1	1,707	0.5	1
Spray (70WP) Applicator	1.47	544	9.9	707	1.4	4

a/ Occupational exposures taken from Table 14.

b/ Acute MOSs are based on a 2-hour human NOEL of 800 $\mu\text{g}/\text{kg}$ for cholinergic signs (Vandekar *et al.*, 1971).

c/ MOSs for potential chronic exposure are based on a dog NOEL of 7 mg/kg-day for hemolytic anemia (Hoffmann and Groning, 1984).

d/ Maximum Likelihood Estimate of excess lifetime risk of cancer is based on a Q₁ = 0.003 (mg/kg-day)⁻¹.

Non-Occupational

The margins of safety corresponding to various non-occupational exposure scenarios are presented in Table 17. MOSs for mean acute non-occupational exposures ranged from 97 for pet owner/groomers to 3,636 for adolescents at home after the house had undergone crack and crevice treatment with propoxur. The MOS for the 95th percentile of the absorbed cycle dosage for dog owner/groomers was 13. The MOSs for potential chronic exposure to propoxur, based on the NOEL of 7,000 $\mu\text{g}/\text{kg}$ for hemolytic anemia in dogs, ranged from 5,833 to 53,846, with children (1-5 years) having the lowest MOS. The upper-bound excess lifetime risks of cancer for theoretical non-occupational exposure to propoxur were not greater than 2×10^{-6} , based on a Q_1^* of 0.004 $(\text{mg}/\text{kg}\text{-day})^{-1}$.

Table 17 - Margins of safety for potential non-occupational exposures to propoxur^a.

	Acute ($\mu\text{g}/\text{kg}\text{-cycle}$)	Acute ^b MOS	AADD ($\mu\text{g}/\text{kg}\text{-day}$)	Chronic ^c MOS	LADD ($\mu\text{g}/\text{kg}\text{-day}$)	MLE ^d Risk (10^{-6})
Passive Exposure						
Child (1-5 yr) ^e	1.46	548	1.2	5,833	-	-
Adolescent (12 yr) ^e	0.22	3,636	0.2	35,000	-	-
Adult ^e	0.40	2,000	0.13	53,846	0.21	0.6
Active Exposure^f						
Dog Groomer (0.25% spray)	10.30	97 ^g	1.0	7,000	0.59	1

a/ Exposures taken from Table 13.

b/ Acute MOSs are based on a 2-hour human NOEL of 800 $\mu\text{g}/\text{kg}$ for cholinergic signs (Vandekar *et al.*, 1971).

c/ MOSs for potential chronic exposure are based on a dog NOEL of 7 $\text{mg}/\text{kg}\text{-day}$ for hemolytic anemia (Hoffmann and Groning, 1984).

d/ Maximum likelihood estimate of the excess lifetime risk of cancer is based on a $Q_1 = 0.003$ $(\text{mg}/\text{kg}\text{-day})^{-1}$.

e/ People living in homes treated with crack and crevice treatments of propoxur for insect control.

f/ Pet owner involved in spraying 2 dogs with pesticide control sprays 26 times a year, for 70 years.

g/ Because of the different period of exposure, the acute MOS was based on a 2 1/2-hour human NOEL of 1,000 $\mu\text{g}/\text{kg}$ for cholinergic signs (Vandekar *et al.*, 1971).

V. RISK APPRAISAL

Risk assessment is a process used to evaluate the potential for exposure and the likelihood that the toxic effects of a substance may 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. This, in turn, results in uncertainty in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, risk assessment for all chemicals has similar types of uncertainty. However, the degree or magnitude of the uncertainty varies depending on the availability of the data and the exposure scenarios being assessed. Risk, the probability of a compound causing an adverse health effect, is a product of the potential exposure and the toxicity of a compound. Estimation of both of these aspects involves varying degrees of uncertainty, which can affect the accuracy of the risk characterization. Overestimates of potential exposure or toxicity will lead to excessive projections of risk, while under valuation of these aspects would result in underestimates of risk.

In the absence of scientific evidence to the contrary, effects reported in laboratory studies are expected to occur in humans at similar dosages. When the NOEL is from a laboratory animal study, a MOS of 100 is generally be considered adequate for protection against potential chronic toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for inter-species variability. This latter uncertainty factor assumes that humans are 10 times more sensitive to the chronic effects of a toxin than are laboratory animals (Davidson *et al.*, 1986; Dourson and Stara, 1983,1985; USEPA, 1986b). If the NOEL is from a human study, a benchmark of 10 is used, incorporating a single uncertainty factor for intraspecies variability. Specific areas of uncertainty associated with this risk assessment for propoxur are delineated in the following discussion.

Acute Toxicity. The acute NOEL for propoxur was based on human oral exposure leading to cholinergic signs (Vandekar *et al.*, 1971). Even though a single, bolus dose of 0.36 mg/kg produced short-lasting stomach discomfort, blurred vision, moderate facial redness and sweating, five oral doses of 0.2 mg/kg at 30 minute intervals, up to 2 1/2 hours, did not cause cholinergic signs. This indicates that carbamylation of cholinesterase, caused by bolus oral doses of propoxur, is rapidly reversed in the human body (Ellenhorn and Barceloux, 1988). However, the preponderance of occupational or non-occupational acute exposure to propoxur was through the dermal route (approximately 99% in most instances). As absorption via the dermal route (Feldman and Maibach, 1974) is generally slower than absorption from the gut, decarbamylation, body metabolism, and clearance probably limit the effects of acute dermal exposure to propoxur. Consequently, the margins of safety under actual exposure conditions are probably greater than indicated in this document.

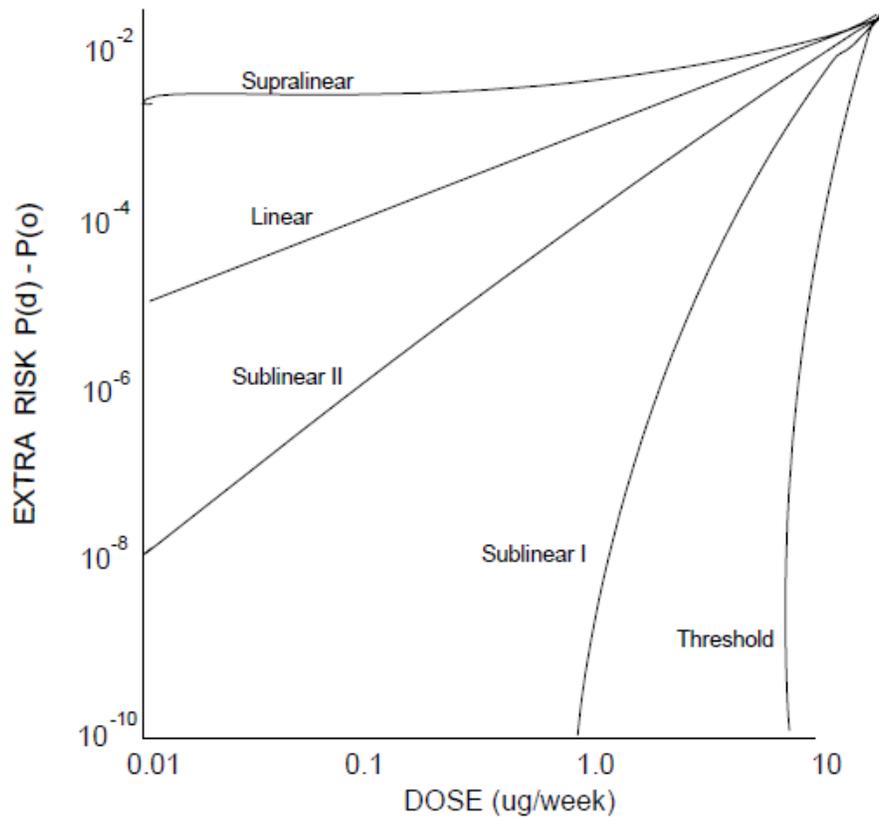
Chronic Toxicity

The 1-year NOEL for hemolytic anemia in the dog, 7 mg/kg-day (Hoffmann and Groning, 1984), used to evaluate the health risks from potential annual exposures to propoxur was greater than the acute NOEL of 0.2 mg/kg for clinical signs. Two factors probably account for this seeming discrepancy in the dose required for toxicity. Propoxur was administered via the diet in the repetitive dosing studies, and was therefor absorbed over an extended period of time each day. Thus, as stated above, there was time available for decarbamylation of the acetylcholinesterase (Ellenhorn and Barceloux, 1988). Secondly, adaptation occurs in response to repetitive dosing with cholinesterase inhibitors (WHO, 1986), so the animals can tolerate higher doses of propoxur without exhibiting clinical signs.

Oncogenicity

It was possible to extrapolate to the possible oncogenic effects of low doses of propoxur potentially experienced by humans by fitting a mathematical model to the dose-response data in the laboratory animal studies. However, the true shape of the dose-response curve at dosages several orders of magnitude below the range of measurable values cannot be determined experimentally (NAS, 1983). Figure 4 presents an example of curves generated by five different mathematical models which fit experimental data in the measurable range equally well. In the low dose range, where the effects cannot be determined experimentally, the predicted effects are very different. These mathematical models are not equally plausible from a biological standpoint. Most scientists agree that the supralinear model can be discarded because a biological mechanism that would give rise to that type of low dose response is hard to imagine. The threshold model is based on the assumption that below a particular dose there is no adverse effect. Because the data on the genotoxicity of propoxur are equivocal, there is a possibility that a threshold for the oncogenicity of propoxur exists. The linearized multistage model, which was used to estimate the oncogenic risks, represents a theoretical upper bound on the risk of bladder cancer caused by potential exposures to propoxur (Figure 4).

Figure 4. Results of alternative extrapolation models for the same experimental data. The dose response functions were developed for data from a benzopyrene carcinogenesis experiment with mice (NAS, 1983).



Exposure Estimates

All measurements of occupational and non-occupational exposure were conducted during a period of two or three days. Extrapolation from short-term exposure measurements to estimates of potential chronic exposure may result in inaccuracies (USEPA, 1992b). In some of the occupational exposure studies, nearly 80% of the sample body patches had no detectable levels of propoxur residue. As a default value, these samples were assumed to have propoxur residues at 50% of the Minimum Detection Limit (Sanborn, 1995). Such an assumption leads to an overestimate of the actual exposure, as the amount of propoxur on the 25 cm² patch is assumed to be representative of the amount per unit area on the entire body surface (e.g. chest area = 3290 cm²).

In the absence of biological monitoring data, theoretical acute and chronic non-occupational exposures of homeowners were estimated from measured air concentrations and surface residue levels. The extrapolation from these values to an absorbed dosage entails making a number of untested default assumptions, including time spent in various rooms, breathing rates, activity patterns, and clothing worn (Sanborn, 1995). Also, it was assumed that a private home would be treated, professionally, for insect pests three times a year, every year, for 70 years. This assumption may lead to an overestimate of exposure to a homeowner, as the average stay at a given residence in California was calculated to be 7 years (Liu *et al.*, 1993).

The other non-occupational exposure scenario involved a resident who sprayed pet dogs to control fleas and ticks. The absorbed dosage of propoxur had to be estimated from a study which used measured urinary metabolite levels to estimate the absorbed daily dose (Waggoner, 1991). It was assumed that the amount of exposure was linearly related to the number of dogs treated, but unrelated to the duration or mode of exposure (Sanborn, 1995). Yet, the toxicology (see above) indicated the duration and route of exposure are critical factors. Consequently, the acute exposure is probably much less than estimated. This is underscored by the fact that none of the 15 dog handlers in the Waggoner study exhibited clinical signs, even though they received 10 times the exposure attributed to a pet owner.

Potential lifetime exposure depends upon the assumption that an individual would maintain ownership of two dogs (not the same two dogs) for 70 years, and would spray the same product to control ticks and fleas a few minutes a day every two weeks during that period of time. The use of an LADD to approximate lifetime exposure from intermittent doses of a chemical may underestimate risk 2 to 5 fold, but is more likely to overestimate it by several orders of magnitude (Murdoch *et al.*, 1992; Murdoch and Krewski, 1988; Kodell *et al.*, 1987; Morrison, 1987).

VI. CONCLUSIONS

Using current toxicity data and exposure data, the calculated margins of safety (MOSs) for potential acute occupational exposure of PCOs to propoxur were greater than 10, the value conventionally recommended to protect people from the toxic effects of a chemical determined in a human study. All MOSs for potential chronic occupational exposures to propoxur were greater than 100, the value conventionally recommended to protect people from the toxic effects of a chemical determined in a laboratory animal study. MOSs for potential acute or chronic passive non-occupational exposures to propoxur were greater than the values conventionally recommended to protect people from the toxic effects of a chemical. Maximum Likelihood Estimates (MLE) of excess lifetime risks of cancer from occupational exposure to propoxur ranged from 1×10^{-6} to 6×10^{-6} . The upper-bound (95%) excess lifetime risks of cancer for theoretical occupational exposure to propoxur ranged from 2×10^{-6} to 9×10^{-6} . None of the MLE for excess lifetime risks of cancer from non-occupational exposures to propoxur exceeded 1×10^{-6} . The upper-bound excess lifetime risks of cancer for theoretical non-occupational exposure to propoxur were not greater than 2×10^{-6} .

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APPENDICES

APPENDIX A

Exposure Estimation

Human Exposure Assessment for Propoxur

by

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HS-1655

January 16, 1990

Revised September 10, 1996

California Environmental Protection Agency
Department of Pesticide Regulation
Worker Health and Safety Branch
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ABSTRACT

The issues that have driven the need for a human exposure assessment for propoxur are those related to its acute toxicity and oncogenic potential. The metabolism of propoxur in animals and man results in extensive ring and ring-substituent hydroxylation. Applicator exposure to propoxur depends on the type of product handled and the number of applications. Applicators have absorbed daily dosage (ADD) values that range from 6.7-23.9 $\mu\text{g}/\text{kg}/\text{day}$. After residential crack-and-crevice treatment, the occupant ADD values for infants, 12-yr old children and adults were estimated to be 12.5, 2.0 and 1.2 $\mu\text{g}/\text{kg}/\text{day}$, respectively. The adult who experiences exposure to propoxur during their entire life will have an estimated Lifetime Average Daily Dosage (LADD) of 0.19 $\mu\text{g}/\text{kg}/\text{day}$. For an individual who sprays two dogs with an aerosol containing 0.25% propoxur, the ADD is 10.5 $\mu\text{g}/\text{kg}/\text{day}$. After a fogger application, infants are estimated to have an ADD of 45.8 $\mu\text{g}/\text{kg}/\text{day}$. This human exposure assessment has been written to support the Department's risk assessment for propoxur.

APPENDIX B

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY DEPARTMENT OF PESTICIDE REGULATION WORKER HEALTH AND SAFETY BRANCH

PROPOXUR

January 16, 1990
Revised September 10, 1996

INTRODUCTION

The issues that have driven the need for a human exposure assessment for propoxur are those related to its acute toxicity and oncogenic potential. Propoxur, 2-(1-methylethoxy) phenyl *N*-methylcarbamate, is a colorless, crystalline solid (molecular formula C₁₁H₁₅NO₃) that is used as a home insecticide, in pet collars and as an aerosol spray for control of insects and mites that affect pets. Some physical properties of propoxur are listed below:

Melting point (°C)	84-87
Water solubility (ppm)	1750
Octanol/water partition coefficient	36
Vapor pressure (mm Hg, 25 °C)	0.000021

EPA/CALIFORNIA STATUS

A Reregistration Standard for propoxur has not been issued by the United States Environmental Protection Agency. There was no federal requirement for the development of exposure studies involving mixer/loader/applicators or home occupants exposed to this insecticide during or after application.

On May 17, 1985, the Office of Environmental Health Hazard Assessment (OEHHA) submitted a study entitled "An Assessment of the Hazard From Pesticide Absorption From Surfaces." This assessment was aimed at home-use pesticides that pose a hazard of possible acute adverse effects due to inhalation, dermal absorption, or ingestion exposure. At the request of OEHHA, products containing propoxur for general home use were placed into reevaluation on June 27, 1985. On February 9, 1987, DPR requested indoor exposure information. The basic manufacturer of propoxur has submitted indoor exposure data to support use of the product as a crack and crevice spray.

There are currently 117 products containing propoxur registered for use in California.

USAGE

Formulations of propoxur are utilized to control pestiferous insects in home and garden situations as well as to control ticks and fleas on pets. The amount of propoxur sold in

California in 1993 was approximately 22,483 lbs (ISB, 1995). The quantity used and required to be reported in 1993 was 2,535 lbs (DPR, 1995). The approximately 9-fold difference between these data reflect the use of products containing propoxur in situations *i.e.*, flea and tick products, that are not required to be reported.

LABEL PRECAUTIONS

The signal word on all formulations of propoxur is “WARNING” or “CAUTION”, depending upon the amount of active ingredient and the type of formulation.

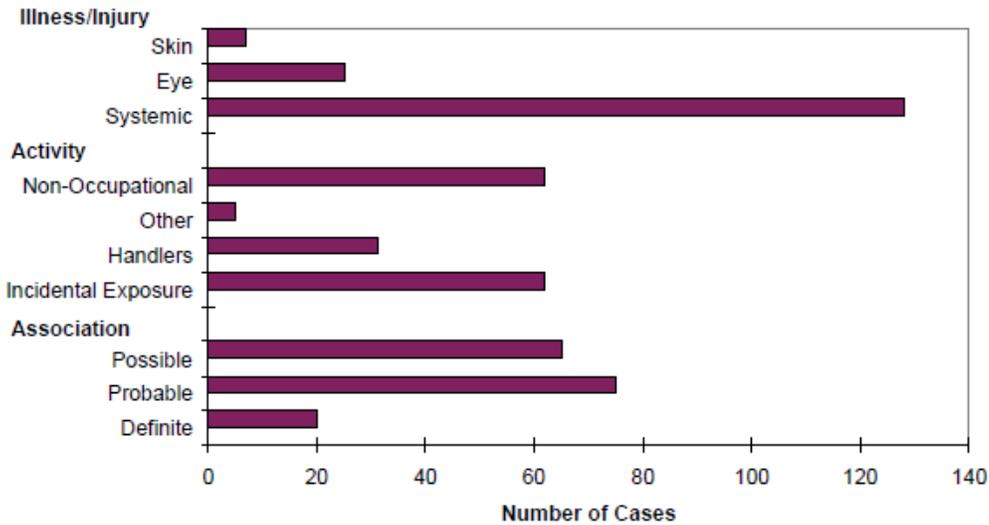
Statements like the following are on the labels:

May be fatal if swallowed, inhaled, or absorbed through the skin. Do not get in eyes, on skin or on clothing. In case of prolonged exposure, wear natural rubber gloves, protective clothing, and goggles. Do not contaminate food. Wash hands, arms and face thoroughly with soap and water before eating smoking. Wash all contaminated clothing with soap and hot water before reuse.

REPORTED ILLNESS/INJURY

The figure below summarizes the data on 160 illnesses associated with exposure to propoxur when used alone for the years 1982-1993. These are described with respect to type of illness or injury, strength of association of illness and exposure and circumstances (activity) where the exposure occurred. With respect to the type of symptoms reported, there were 128 illnesses that were systemic in nature, 25 associated with eye injuries and 7 cases related to skin problems. Of the 160 incidents, 62 occurred away from the occupational environment, the remainder occurred while the person was at work. Sixty-two occupational exposures occurred incidental to their work activity (in situations such as restaurants, office buildings or other places where individuals not involved in the pesticide application become ill during or after the treatment), 31 were exposed while applying propoxur and five occurred in other situations. With respect to the causal categorization of the illnesses, 20 cases were designated as definitely related to propoxur exposure, 75 cases assessed as probably related to exposure and the remainder (65) as possibly related to exposure to this insecticide.

Illnesses Associated with Propoxur, 1982-1993



PLANT RESIDUES

Since there are not any registrations in California for application of this insecticide on crops, dermal contact with plant residues as a route of worker exposure is not relevant for this document.

DERMAL TOXICITY

The dermal LD₅₀ of propoxur is 800-1000 mg/kg in rats (Anon., 1986). This low level of dermal toxicity is 8-10-fold greater than the oral dose required to elicit an LD₅₀. The significantly lower toxicity by the dermal route suggests that the skin provides protection for absorption of a lethal dose. Propoxur is not a skin irritant or sensitizer (Sheets, 1990).

ANIMAL METABOLISM

The metabolism of propoxur has been examined in several animal species including man. The human studies were the result of an individual who attempted to commit suicide by a *per os* administration of an unknown amount of propoxur (Eben *et al.*, 1985a). The urine of this patient was collected 16 hours after admission to the clinic for treatment of the poisoning. The metabolites isolated from the urine of this individual were identified by mass spectrometry, infrared and nuclear magnetic resonance spectrometry. The major pathways of metabolism, like that of the rat, involved *O*-deisopropylation, hydrolysis, and *N*-demethylation at the five position of the aromatic ring (Eben *et al.*, 1985b). The absence of hydroxylation at the three position of the aromatic ring in humans is in contrast to the rat where metabolism studies demonstrated ring hydroxylation at this position. The major metabolite in the human was 2-isopropoxy 5-hydroxyphenyl *N*-methyl carbamate. Two unexpected metabolites isolated from the human urine were 2-isopropoxy 4-nitrophenol and 1,5-dihydroxy-2-(1-methylethylbenzylurea). The metabolic pathways to these last two metabolites lack literature precedent.

Registrant data cited in the dog flea-treatment exposure study indicated that humans treated with propoxur excreted in the first 16 hours approximately 85% of the metabolite, 2-*iso*-propoxyphenol (Waggoner, 1991). The registrant data regarding the uptake and metabolism of propoxur after oral and dermal administration have been reconfirmed in published work by Meuling *et al.*, 1991.

DERMAL ABSORPTION

There are several reports on the dermal penetration of propoxur in different animal species and humans. A recent study evaluated the dermal penetration of ¹⁴C-propoxur in male rats at four nominal doses (0.65, 6.91, 69.5 and 692 ug/cm²) using 0.25 ml/rat of a 1:1 ethanol:water solution as the dosing vehicle (Eigenberg, *et al.*, 1988). The shaved, treated area (15 cm²) on the dorsum was covered with gauze glued to a rubber ring. There were 24 animal per dose and sacrifice times were 0.5, 1, 2, 4, 8, and 24 hours post-treatment with four animals per dose terminated at each time point. Material balance was satisfactory as the recoveries for the doses ranged from 83-110%. Samples analyzed in this study were urine (excreted as well as urine in the bladder at the time of sacrifice) feces, blood, carcass, skin at the application site (digested), skin rinse of the application site [25 mL aqueous (5%) Contrad solution] and wash of the rubber ring and gauze. The equation below characterizes the method to calculate the percent absorption:

$$\text{Absorption} = \frac{\sum (\text{urine, feces, blood, skin site*}, \text{carcass})}{(\text{Amount applied})} \times 100$$

*Bound-skin residue

Table I summarizes the data for absorption of propoxur in rats at 8 and 24 hours post-treatment:

Table 1. Dermal absorption (%) of propoxur in rats: Effect of dose and time

Dose (ug/cm ²)	<u>0.65</u>	<u>6.91</u>	<u>69.2</u>	<u>692</u>
<u>Sacrifice Time (hr)</u>				
8	48.9	56.9	43.3	17.9
24	44.3	55.4	43.3	46.2

Sanborn WH&S, 1996 after Eigenberg, 1988

Another dermal penetration study involved the application of ¹⁴C-propoxur in acetone at a dose rate of 4 ug/cm² to the forearms of six humans (Feldmann and Maibach, 1974). The treated area ranged from 2.8-28 cm² and the experiment had a 120-hr duration. Urinary radioactivity was monitored and the amount absorbed was corrected for incomplete recovery by the use of data derived from an intravenous administration. The data in Table 2 at 8 and 24 hours can be compared to the rat dermal penetration data in Table 1 for the same time periods.

When similar doses are compared, the data in Tables 1 and 2 suggest that rat skin, when compared to human skin, is about 3.5-fold more permeable to propoxur at 24 hours. Since the

dosing vehicles were different (acetone for the human and 1:1 water/ ethanol for the rat) a direct comparison is not possible.

Table 2. Dermal absorption of propoxur in man at 8 and 24 hours

<u>Time (hrs)</u>	<u>Absorption (%)</u>
8	4.2
24	16

Sanborn WH&S, 1996, after Feldmann and Maibach, 1974

HOME OCCUPANT AND WORKER EXPOSURE

Home occupant (infant, child and adult)

The initial focus of concern for this insecticide was the estimated exposure infants might experience after propoxur application for flea control in carpets. A study by Hackathorn and Eberhart (1983) was used to estimate infant exposure. Berteau *et al.* (1989) reviewed this and other data to develop a hazard assessment. These exposure estimates, developed without biological monitoring, were high because default values were used for respiratory uptake, dermal absorption, and 100% of the residue on the treated areas was considered transferable to the infant. The assumed transfer rates from carpet and carpet contact area were used without the benefit of experimental data derived from gauze wipes and hand residue data.

The second human indoor exposure estimate for propoxur was related to the previous studies of Hackathorn and Eberhart (1983) and Berteau *et al.* (1989) in that the same exposure modeling scheme (variable time on different treated areas) was utilized. The studies differed in the application method. Knarr (1988) used 0.49-1.3 oz a.i./house (N = 5) applied as a crack-and-crevice treatment. Air samples were collected at 0, 6, 12, 24 and 48 hours post-application. Carpet, linoleum, dishes, silverware and upholstery were monitored by the use of coupons (pieces of carpet, upholstery, foil, etc. that were placed as surrogates to collect residues and to simulate the actual item). Coupons were collected at the same time intervals as air samples. Damp gauze pads were utilized to wipe the residues from the various matrices. In addition to the wipe sampling, the coupons also were extracted with ethanol to determine the "total residue". In this study, in contrast to the previous study, hands were first wiped across the treated matrices and then they were washed with ethanol for comparison to the gauze wipe samples. This type of comparison attempts to estimate the rate of transfer from a treated matrix to human skin.

With the exception of the air levels, the data for the individual matrices were extraordinarily variable and demonstrated little propensity for decay over the monitoring period. Additional evidence for the extreme variability of the data is the observation that the standard deviations of the geometric means were often two- to four-fold higher than the mean values. In contrast, the relatively constant air values for each sampling ranged over the course of the 48-hour sampling period from a high of 11.1 ug/m³ in the basement to a low of 2.1 ug/m³ in the bedroom. The limited air exchange in the basement probably accounts for the higher levels in this area. Table 3 summarizes the residue data and illustrated the variability of the data.

Table 3. Indoor environmental data variability after a crack-and-crevice treatment with propoxur^{a/}

<u>Room</u>	<u>Matrix</u>	<u>Surface Residue (ug/ft²)</u> [GM ^{b/} (GMSD)] ^{c/}	<u>Air (ug/m³)</u> [GM (GMSD)]
Kitchen Floor	Vinyl	21 (22)	4.0 (2.1)
Living Room Floor	Carpet	0.99 (3.6)	2.3 (2.2)
Bedroom Floor	Carpet	1.1 (4.7)	1.5 (2.2)
Basement Floor	Carpet	5.1 (5.0)	7.2 (3.2)
Bathroom Floor	Vinyl	1.6 (38)	3.1 (2.4)
Kitchen Counter	Vinyl	2.4 (16)	
Living Room	Fabric	0.4 (2.8)	
Bedroom Room	Fabric	0.4 (3.2)	

a/ DPR Reg. Doc. 50021:226

b/ Geometric mean

c/ Geometric standard deviation

Sanborn WH&S, 1996, after Dean, 1992

Six exposure scenarios were developed for an infant crawling on several floor coverings that had various amounts of propoxur. For the purposes of the exposure assessment, the registrant initially used the **highest** residue found at any sampling period on any matrix. In addition, it was assumed that infants spent all of their waking hours at the highest residue. The kinetic model for dermal absorption and elimination used in the initial carpet study, based on the dermal absorption study of Feldmann and Maibach, 1974 was used in this exposure assessment.

The crack-and-crevice study contained some useful information with respect to estimation of exposure to humans after this type of treatment with propoxur. The extreme variability in the residue data on the various matrices is not unexpected as this spot spraying treatment method precludes uniform residue distribution. In contrast to surface matrix residues of propoxur, the air levels were relatively constant in each room which is expected as they reach equilibrium with the residues on the treated surfaces.

Table 4. Estimated absorbed daily dosages (ADD) for three age groups after a propoxur crack-and-crevice treatment using highest residue on each matrix

<u>Age</u>	<u>ADD (ug/kg/day)</u>
Infant (6-9 mo) ^{a/}	14.2-3,192 ^{d/}
Child (12 yrs) ^{b/}	336
Adult ^{c/}	188

a/ Infant Parameters: 7.5 kg weight; 0.45 m² surface area; 0.5 m³/hr breathing rate; 100% inhalation uptake; 50% surface area exposure; 16 hrs awake, 8 hours sleeping.

b/ Child Parameters: 40.5 kg weight; 1.37 m² surface area; 0.9 m³/hr breathing rate; 100% inhalation uptake; 50% surface area exposure; 16 hrs awake, 8 hours sleeping.

c/ Adult Parameters: 76 kg weight; 2.0 m² surface area; 1.0 m³/hr breathing rate; 100% inhalation uptake; 50% surface area exposure; 16 hrs awake, 8 hours sleeping.

d/ Range related to multiple exposure scenarios, *i.e.*, kitchen, bedroom, etc.

Sanborn WH&S, 1996 after Knarr, 1988a

The novel technique, developed by the registrant, involving damp gauze pad wipes of surfaces with known amounts of propoxur that are then compared to hands rubbed across the same treated surfaces, may be useful for studies of pesticide dermal exposure assessment. However, whole-body dosimetry and/or urinary monitoring for 2-*iso*-propoxyphenol would provide a more representative estimate of exposure.

In view of the previously discussed surface residue data variability, a subsequent re-analysis of these exposure data by the registrant used geometric means for all propoxur residues rather than the highest value on the sampling coupons (which tended to overestimate the contribution of exposure from the bathroom) (Knarr, 1991; Dean, 1992). The exposures for the three age groups using geometric means of the residue data are summarized in Table 5 below.

A LADD value was only calculated for the adult. Addition and amortization of the infant (1-5 years) and the 12-year-old child (6-18 years) dosages to the dosages experienced by the adult (19-70 years) provided the adult LADD. The adult LADD value is larger than the adult AADD value because of the contribution from exposures before they became adults.

Table 5. Estimated exposure of three age groups to propoxur using geometric mean residue data of matrices after a crack-and-crevice treatment

<u>Age group</u>	<u>2-hr AD^{a/}</u> (<u>µg/kg</u>)	<u>ADD^{b/}</u> (<u>µg/kg/day</u>)	<u>AADD^{c/}</u> (<u>µg/kg/day</u>)	<u>LADD^{d/}</u> (<u>µg/kg/day</u>)
Infant	1.46	12.5 ^{e/}	1.23	
12-yr old	0.22	2.0	0.20	
Adult	0.37	1.2	0.12	0.19

a/ 2-Hr. Absorbed Dosage (AD) - This calculation is required for comparison to the human acute toxicology endpoint estimated by Vanderkar *et al.*, 1971

b/ Absorbed Daily Dosage (ADD) - See Table 3 for physiological parameters

c/ Annual Average Daily Dosage (AADD) - 9 days/month, 4 months/year

d/ Lifetime Average Daily Dosage (LADD) =

ADD [Infant(1-5 yrs)+12 year old (6-18 yrs)+ Adult (19-70 yrs)]/70 years.

e/ This is the highest of six scenarios described for the infant

Sanborn WH&S 1996, after Knarr 1991c & Dean 1992

Commercial Applicator (aerosol and pump spray, bait, wettable powder)

There are four contemporary exposure studies involving applicators of various formulations of propoxur. The applicators in all four studies wore denim trousers, cotton/polyester long-sleeved shirts, leather boots/shoes or cloth sneakers. In addition to or in place of their normal clothing, cotton coveralls, baseball caps and chemical resistant nitrile gloves were worn by the applicators. Dermal monitoring was conducted according to the methods of Durham and Wolfe (1962). Patches were attached under the clothing. Hand exposure was measured by washing with absolute ethanol. Air levels were monitored with a personal pump run at 1 L/min drawing air through a quartz microfiber air filter. Each of the studies, had 16 or 32 “replicates” and 3-4 applicators for each formulation. In order to obtain the number of replicates listed in the table below, each applicator applied the formulation several times.

None of these studies involved biological monitoring. ADD values were calculated from the residues on the patches inside the clothing along with a dermal penetration value of 16% taken

from the work of Feldmann and Maibach, 1974. For the calculation of the Cycle Absorbed Dosage (CAD), a dermal penetration of 0.351%/hour was used along with the average a time worked for each spray task. This calculation is necessary as these values can be directly compared with the work of Vanderkar et al., 1971 who found that humans could tolerate 5 doses of propoxur (one-half hour apart) at 0.2 mg/kg without the observation of overt cholinergic signs. With respect to the analysis of the patches, 80-100% were below the limit of detection for the first three entries in Table 6. For the patches with residue values below the limit of detection, one-half the limit of detection was used in the development of the exposure assessment. The values of N in the first column are the number of replicates that were used to calculate the central tendency estimates.

Two out of the four ADD estimates above (2% bait, 0.95% spray) are less than the exposure in Table 5 estimated for infants (12.5 ug/kg/day) after a crack-and-crevice treatment. For the applicator spraying a 70 WP, the exposure (ADD) is about 1.4-fold greater than the exposure of the infant and 14-fold greater that the adult after a crack-and-crevice application. With respect to formulations commonly applied for nuisance and public health insect control in California, only the WP and aerosol formulations are routinely used (Munro, 1992).

Table 6 Exposure of humans during application of four formulations of propoxur
Geometric Mean, Geometric Standard Deviation (GSD) and, [95th percentile]

Product	mg/person			CAD ^{a/}	(ug/kg/day)		LADD ^{e/}
	Dermal	Inhalation	Total		ADD ^{b/}	AADD ^{d/}	
Aerosol (1%) ^{f/} (N = 32)	0.85 (2.6)	0.03 (1.7)	0.90 (2.5)	0.95 (1.71) [2.30]	23.9 ^{c/}	14.6	2.0
Bait (2%) ^{g/} (N = 32)	0.35 (1.7)	0.002 (1.8)	0.35 (1.7)	0.19 (2.04) [0.61]	9.0 ^{c/}	5.5	0.7
Spray (0.95%) ^{h/} (N = 32)	0.26 (1.8)	0.002 (1.8)	0.27 (1.8)	0.16 (1.40) [0.32]	6.7 ^{c/}	4.1	0.5
Spray (70WP) ^{i/} (N = 16)	1.20 (2.3)	0.18 (3.1)	1.5 (2.3)	1.47 (2.80) [8.0] ^k	16.4 ^{j/}	9.9	1.4

a/ Cycle Absorbed Dose: Dermal penetration 0.351%/hr; body weight 76 kg; respiratory uptake 50% (Raabe, 1988), normalized to 2 hours.

b/ ADD (Absorbed Daily Dosage): Body weight 76 kg; dermal penetration 16%/24 hr; respiratory uptake 50% (Raabe, 1988).

c/ 12 cycles/day, one cycle = one application

d/ AADD (Annual Average Daily Dosage): 223 days of exposure (Munro, 1992)

e/ LADD (Lifetime Average Daily Dosage): 9.6 years of exposure (Munro, 1992), 70-year life

f/ Combined: DPR Reg. Docs. 50021: 182 Table 1 and 50021: 203, Table 1

g/ Combined: DPR Reg. Docs. 50021: 181 Table 1 and 50021: 206, Table 1

h/ DPR Reg. Doc. 50021: 181, Table 1

i/ DPR Reg. Doc. 50021: 182, Table 1

j/ Each cycle = 1.8 hr per footnote i, therefore 4.4 cycles/8-hr day

k/ 95th percentile = Geometric mean x GSD^{1.645}

Sanborn WH&S 1996 after Knarr 1988b, 1988c, 1991a, 1991b & Dean 1988a, 1988b

Flea control on dogs (spray)

A study evaluated the exposure of individuals spraying dogs with a product containing 0.25% propoxur (Waggoner, 1991). This product is intended for homeowners rather than a professional grooming salon service. The products used by the latter are generally used in the form of a pet dip and may contain products other than propoxur. The time for each application ranged from 1-2 minutes/dog. There were 15 applicators who sprayed propoxur on 20 dogs. Urine samples were collected for 24 hours post-application. Registrant studies in humans with propoxur determined that approximately 85% of the metabolite, 2-iso-propoxyphenol, was excreted in the first 16 hours. The registrant data regarding the uptake and metabolism of propoxur after oral and dermal administration have been reconfirmed by some recently published studies by Meuling *et al.*, 1991. The urinary output was corrected for the difference in molecular weight between propoxur and 2-iso-propoxyphenol. The average urine volume in the twenty-four hour collection was 1685 ± 1094 ml (range 296-3790 ml). These data have been used to estimate ADD, AADD and LADD values for a homeowner who owns 2 dogs and sprays them 26 times during the year. These estimates are in Table 7.

Table 7: Exposure of applicators to propoxur (0.25%) during spraying of Sergeant's Flea and Tick Spray for Dogs

<u>ADD^{a/}</u>	ug/kg <u>AADD^{b/}</u>	<u>LADD^{c/}</u>
10.3		
3.4 ^{d/}		
77.1 ^{e/}	0.75	0.43

a/ ADD: Absorbed daily dosage for dog owner with two dogs

b/ AADD: Average annual daily dosage for 26 two-dog applications

c/ LADD: Lifetime average daily dosage

d/ Geometric mean (GM) standard deviation (GSD)

e/ 95th percentile = GM x (GSD)^{1.645}

Sanborn, 1996 after Waggoner, 1991

Area-wide treatment from indoor fogger application (infants)

The use of area-wide applications of propoxur is no longer allowed in California, but was common at the time the re-evaluation was initiated. The exposure of an infant after application of a fogger was estimated from environmental data following a propoxur fogger release (Maddy *et al.*, 1984, 1987) and the exposure model developed for a chlorpyrifos area spray by Vaccaro *et al.*, 1991. The study by Vaccaro *et al.*, 1991, measured hand washes of individuals who mimicked the ambulatory behavior of infants. To provide an estimate of absorbed dosage, urine samples were analyzed for metabolites of chlorpyrifos.

The estimated exposure data from a fogger application were compared to the propoxur exposure after an area-wide spray in Table 7 using the data (Hackathorn and Eberhart, 1983) and the exposure model of Vaccaro *et al.*, 1991. The assumptions used for the different routes of exposure are as follows:

Hand/Oral:

The residues on the adult hands as measured by Vaccaro *et al.*, 1991 were extrapolated down to the surface area of the infant and were adjusted up (area spray) or down (fogger) in relation to the application rate of propoxur as compared to chlorpyrifos. The default value of 100% for absorption after insertion of the hand into the mouth was the same assumption employed in the exposure modeling of Vaccaro *et al.*, 1991.

Dermal:

The estimated dermal exposure of Vaccaro *et al.*, 1991 of 4.1 ug/kg was adjusted for the application rates (fogger or area spray) and for the increased dermal absorption of propoxur (16%) as compared to chlorpyrifos (3%).

Inhalation:

The average air level 4-24 hours post-application was taken from the studies of Maddy *et al.*, (1984) and Hackathorn and Eberhart (1983). For estimates of exposure via this route, 100% respiratory uptake and a respiratory rate of 0.5 ug/m³ for infants were used to make these exposure assessments consistent with previously discussed exposure assessments of this age group.

Table 8: ADD values for infants exposed to propoxur after fogger or area spray based on environmental concentrations

<u>Application Type</u>	<u>Environmental Concentrations</u>		<u>Infant ADD (ug/kg/day)</u>
	<u>Residue (ug/cm²)</u>	<u>Air Level (ug/m³)</u>	
Fogger	11.8	14.1	45.8
Area Spray	40.0	16.1	116.9
Crack-and-Crevices a/ Table 4			12.5 ^{a/}

Sanborn WH&S, 1996

The estimated infant exposure to propoxur after either a fogger or area spray were prepared without biological monitoring. The exposure to residue after a fogger application approximates the exposure of an individual spraying ~1.5 kg of propoxur as a wettable powder during a crack-and-crevice treatment and is almost 4-fold greater than the infant exposure after a crack-and-crevice treatment. Estimated exposure to the infant after an area spray, is almost 10-fold greater than the crack-and-crevice treatment and 10-fold greater than a person treating two dogs with propoxur. These are likely overestimates as there was no biological monitoring which would provide, as in the dog flea applications, a more representative estimate of the absorbed dose.

Finally, if studies similar to those conducted by Vaccaro *et al.*, 1991 with chlorpyrifos, which incorporated biological monitoring, were conducted with propoxur, it is likely that both of these exposure estimates would be significantly reduced.

EXPOSURE APPRAISAL

The assessment of human exposure for this active ingredient is based primarily on information involving studies with propoxur and not surrogates. The only surrogate data used was for a broadcast application which is no longer allowed in California. There are applicator exposure studies involving examples of the multiple formulations that are currently registered. There is an exposure study involving pet groomers treating dogs in which biological monitoring was used. There is also a dermal absorption study in humans, eliminating the need to use laboratory animal data that may be not representative of humans.

However, there are several underlying factors that are very conservative in nature and tend to make these exposure estimates conservative (tend to overestimate exposure). The exposures estimated for the applicators may be high because, with the exception of the applicators treating with the 70WP, the dosimeter residue values were below the limit of detection. To estimate exposure in this case the calculations use residues at one-half the limit of detection. Exposure to home occupants following propoxur treatment was based on residues transferred to hands. These residues were measured empirically and then incorporated in to a model that took into account the dermal absorption and urinary elimination. Neither total dermal exposure nor biological monitoring were conducted. For infants, biological monitoring was never considered because of ethical considerations associated with human subjects review and informed consent. The exposure scenario with the best estimate of exposure involved treatment of dogs with propoxur. In this study, biological monitoring was used to estimate the absorbed dose. It is thought that biological monitoring more accurately estimates absorbed dose, provided that the pharmacokinetics are understood.

In summary, the human exposure assessment for propoxur is based primarily on information developed from studies using this active ingredient. For this reason the estimates of exposure to propoxur for the various scenarios are much less subject to assumptions than if they were based primarily on exposure information from surrogate chemicals.

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APPENDIX B

Calculation of Cancer Potency