PERMETHRIN
(PERMANONE TICK REPELLENT)

RISK CHARACTERIZATION DOCUMENT

(REVISED)

Medical Toxicology and Worker Health and Safety Branches

Department of Pesticide Regulation

California Environmental Protection Agency

May 9, 1994

PERMETHRIN

EXECUTIVE SUMMARY

The Risk Assessment Process

The risk assessment process consists of four aspects: hazard identification, dose response assessment, exposure assessment, 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 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 types 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 in laboratory animals 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.

The exposure assessment includes an estimation of the potential exposure through the dermal and inhalation routes on an acute (one time), subchronic (seasonal), and chronic (long-term) basis. Exposure is based on the amount of pesticide residue in the air, on clothing, and on skin. The exposure is adjusted for the number of hours exposed per day, body weight, dermal absorption rate, respiratory retention, and breathing rate.

The risk characterization then integrates the toxic effects observed in the laboratory studies, conducted with high dosages of pesticide, to potential human exposures to low dosages. The potential for possible non-oncogenic (non-carcinogenic) adverse health effects in human populations is generally expressed as the margin of safety, which is the ratio of the dosage which produced no effects in laboratory studies to the estimated human exposure dosage. For oncogenic effects, the probability of risk is calculated as the product of the oncogenic potency of the pesticide and the estimated exposure dosage.

Introduction

Permethrin is the common name for (3-phenoxyphenyl) methyl (±)-*cis, trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate, a synthetic pyrethroid repellent/insecticide. Its repellent and insecticidal properties are due to its interference with the conductance of nerve impulses.

The Fairfield American Corporation initially submitted an application for a special local need registration (section 24(c)) to the Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency for its Permanone Tick Repellent which contains 0.5% permethrin as the active ingredient. Severe irritation was seen with the formulation which was

attributed primarily to the inert ingredients. DPR did not recommend registration for this product based on the dermal irritation and its potential oncogenic risk. Fairfield American Corporation has reformulated this product and is now requesting a full registration (Section 3). Fairfield American Corporation is now part of the Roussel Uclaf Corporation. This Risk Characterization Document reevaluates the potential adverse health effects associated with the proposed use of the reformulated product on human clothing for the prevention of tick-borne diseases, such as Lyme disease.

Toxicology

Permethrin produced various neurological effects in laboratory animals typical of pyrethroids. These signs included tremors, salivation, paresthesias, splayed gait, tail erection, depressed reflexes, and tip toe gait. At higher doses, reversible axonal damage was produced. The No-Observed-Effect Level (NOEL) for acute neurological effects was 50 mg/kg and 1.9 mg/kg by the dermal and inhalation routes, respectively, after adjusting for absorption by the dermal and inhalation routes. Permethrin and the revised formulation were moderate skin irritants with an estimated NOEL of 2 mg/cm^2. Permethrin may also be a skin sensitizer based on a study with the technical grade material; however, a NOEL could not be established for this effect.

The systemic effects observed in laboratory animals with subchronic exposure to permethrin included neurological effects, congenital glaucoma, and microscopic liver changes. Although there is some evidence to suggest that the liver changes may be adaptive, DPR concluded that it may be toxicologically significant given the increase in other liver effects, including tumors. The liver changes were the most sensitive effect with a NOEL of 1.2 mg/kg/day after correcting for oral absorption. Dermal irritation was also observed with subchronic exposure to permethrin by the dermal route. The estimated NOEL was 0.05 mg/cm^2.

With chronic exposure to permethrin, microscopic non-oncogenic changes in the testes, adrenal glands, thyroid, lungs, and liver were observed in laboratory animals. After adjusting for oral absorption, the lowest NOEL was 2.1 mg/kg/day based on microscopic changes in the liver and lungs of mice. Chronic exposure to permethrin was also associated with a dose-related increase in benign and malignant lung tumors in three of four mouse studies and benign liver tumors in one mouse study. After adjustment for oral absorption, the oncogenic potency was estimated to be between 8.1×10^{-3} and 1.1×10^{-2} $(mg/kg/day)^{-1}$ based on the incidence of lung tumors in female mice.

Exposure Analysis

Different exposure scenarios were developed for park and forestry workers and the general public. For park and forestry workers, an extreme-case exposure scenario was used in which a person wore a new change of freshly treated clothing each work day for 5 days in a week. The same 5 sets of laundered clothing were then worn the second week, with a different set worn each work day. This two week treatment cycle was repeated throughout the 6-month tick season. For the general public, the extreme-case exposure scenario was similar to workers except the assumption was made that treated clothes were worn 7 days a week, and there was no adjustment for lifetime exposure. In a more likely exposure scenario for the general public, exposure was assumed to be limited to weekends and a two week camping trip during the six-month tick season.

The highest daily dermal exposure to permethrin was estimated to be 0.75 μg/cm^2. The highest daily absorbed dosage of permethrin was 11 μg/kg/day. For park and forestry workers, the average seasonal exposure was 4.2 μg/kg/day. The average seasonal exposure for the general public was 5.9 and 3.2 μg/kg/day based on the extreme-case and more likely exposure scenarios, respectively. When averaged over a year, exposure for park and forestry workers was estimated to be 2.1 μg/kg/day. For the general public, the average annual exposure was 3.0 and 1.6 μg/kg/day based on the extreme-case and more likely exposure scenarios, respectively. To evaluate oncogenic risk, the exposure for park and forestry workers was averaged over a lifetime (1.2 μg/kg/day) assuming 40 years of working exposure. The average annual exposure was used to evaluate the oncogenic risk for the general public.

Risk Evaluation

The risk for the acute, subchronic (seasonal), and non-oncogenic chronic effects is expressed as the margin of safety (MOS) which is a ratio of the NOEL and exposure dosage. The MOS for the acute neurological effects was over 200. The MOS for acute dermal irritation from permethrin was over 2,000. The MOSs for dermal irritation with seasonal exposure were between 100 and 400 based on the various exposure scenarios. The MOSs for liver hypertrophy with seasonal exposure were between 200 and 400 using the different exposure scenarios. The MOSs for liver hypertrophy and alveolar cell proliferation with chronic exposure were all over 700 for the various exposure scenarios.

The theoretical risk for excess cancer is the product of the estimated oncogenic potency of a chemical and the exposure dosage. For the general public, the theoretical risk was approximately one to three in 100,000 with lifetime use. Assuming exposure was limited to occupational use for park and forestry workers, the theoretical risk was approximately one in 100,000.

Conclusions

The potential risk for adverse health effects from the proposed use of the reformulated Permanone Tick Repellent on human clothing was evaluated. For non-oncogenic effects an MOS greater than 100 is usually considered adequately protective. The MOSs for the acute, subchronic and non-oncogenic chronic effects all exceed 100. Generally, an oncogenic risk level less than one in 1,000,000 is desirable. However, the negligible risk level for oncogenicity may range from one in 100,000 to one in 1,000,000, depending on a number of factors such as the weight of evidence, uncertainty in exposure, etc. Regardless, several of the oncogenic risk estimates are outside the range that is normally considered negligible. Further exposure to permethrin could not be reduced under conditions of current use.

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I SUMMARY

Permethrin is the common name for (3-phenoxyphenyl) methyl ()-*cis, trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate, a synthetic pyrethroid repellent/insecticide. Its repellent and insecticidal properties are due to its interference with the conductance of nerve impulses.

The Fairfield American Corporation initially submitted an application for a special local need registration (section 24(c)) to the Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency for their Permanone Tick Repellent which contains 0.5% permethrin as the active ingredient. Severe irritation was seen with the formulation which was attributed primarily to the inert ingredients. DPR did not recommend registration for this product based on the dermal irritation and its potential oncogenic risk. Fairfield American Corporation has reformulated this product and is now requesting a full registration (Section 3). Fairfield American Corporation is now part of the Roussel Uclaf Corporation. This Risk Characterization Document reevaluates the potential adverse health effects associated with the proposed use of the reformulated product on human clothing for the prevention of tick-borne diseases, such as Lyme disease.

Permethrin produced various acute effects including neurological signs typical of pyrethroids and dermal effects including irritation and sensitization. The neurological signs included tremors, salivation, paresthesias, splayed gait, tail erection, depressed reflexes, and tip toe gait. At higher doses, reversible axonal damaged was produced. After adjusting for dermal and inhalation absorption, the No-Observed-Effect-Level (NOEL) for the acute neurological signs was estimated to be 1.9 mg/kg by the inhalation route and 50 mg/kg by the dermal route.

Moderate dermal irritation was observed with both the technical grade permethrin and the revised formulation. The skin irritation from the formulation still appears to be primarily due to the inert ingredients since the severity of the irritation was not significantly reduced compared to the technical grade permethrin. However, due to the volatility of the inert ingredients and the label instructions to dry freshly treated clothes for at least 2-4 hours before wearing, the Department of Pesticide Regulation (DPR) concluded that the potential for dermal irritation with the proposed use would probably be due to permethrin. The estimated NOEL was 2 µg permethrin/cm^2. The technical grade permethrin was also a moderate dermal sensitizer, but there was no evidence of sensitization with the tick repellent formulation. The design of dermal sensitization studies, in general, are not conducive to establishing a NOEL.

Dermal irritation was also observed with repeated dermal applications of permethrin. The estimated subchronic NOEL for dermal irritation was 0.05 µg/cm^2. The systemic effects observed with subchronic exposure include neurological effects (tremors, convulsions, hyperexcitability, irritability, twitching, narcosis with nystagmus), buphthalmos (persistent pupillary membrane or congenital glaucoma), and liver effects (hypertrophy and eosinophilia). Buphthalmos was observed in weanling rats in a reproductive toxicity study in the absence of maternal toxicity. Although the biochemical and ultrastructural changes associated with the liver hypertrophy appear to be reversible suggesting it is adaptive, DPR concluded that the liver hypertrophy may be toxicologically significant given the increased incidence of liver tumors and other non-neoplastic effects in the liver (eosinophilia and peroxisome proliferation) in mice. Liver hypertrophy was the most sensitive endpoint with a NOEL of 1.2 mg/kg/day after adjusting for oral absorption.

Histological changes were observed in the testes (hypoplasia), thyroid (focal disturbances in the growth pattern of follicular cells), adrenal gland (swelling and vacuolization of cells in the zona reticularis and focal degeneration of the cortex), lung (alveolar cell proliferation), and liver (hypertrophy, eosinophilia, peroxisome proliferation) with chronic exposure to permethrin. Liver hypertrophy was the most common effect. After adjusting for oral absorption, the lowest NOEL was 2.1 mg/kg/day based on the alveolar cell proliferation and liver hypertrophy.

There were dose-related increases in lung tumors (benign and malignant) in three of four mouse oncogenicity studies. In one of these mouse studies, there was also a dose-related increase in liver tumors. Furthermore, the latency period was significantly shorter in one of these studies. Although all the tests for gene mutation were negative, two published *in vivo* cytogenetics tests were positive. Permethrin is nearly identical in structure to cypermethrin which produced a similar tumor response in female mice and was also positive in two tests for chromosomal aberrations. Therefore, DPR assumed permethrin was possibly genotoxic and used a linear, low dose extrapolation model to assess the oncogenic risk to humans. The oncogenic potency factor was estimated to be between 8.1×10^{-3} (maximum likelihood estimate or MLE) and 1.1×10^{-2} (95% upper bound or UB) $(mg/kg/day)^{-1}$ based on the incidence of lung tumors in females after adjustment for oral absorption.

Three different exposure scenarios were developed. One for park and forestry workers and two for the general public. For park and forestry workers, an extreme-case exposure scenario was used in which a person wore a new change of freshly treated clothing for 5 days in a week. The same 5 sets of laundered clothing were then worn the second week. This two week treatment cycle was repeated throughout the 6-month tick season. For the general public, the extreme-case exposure scenario was similar to workers except the assumption was made that treated clothes were worn 7 days a week, and there was no adjustment for lifetime exposure. In a more likely exposure scenario for the general public, exposure was assumed to be limited to weekends and a two week camping trip during the 6-month tick season.

The highest daily dermal exposure to permethrin was estimated to be 0.75 $\mu g/cm^2$. The highest daily absorbed dosage of permethrin was 11 µg/kg/day. The absorbed daily dosage (ADD) represents the average daily exposure over the 6-month tick season. The ADD was 4.2 µg/kg/day for park and forestry workers. For the general public, the ADDs were 5.9 and 3.2 µg/kg/day based on the extreme-case and more likely exposure scenarios, respectively. The annual average daily dosages (AADDs) for the general public were estimated to be 3.0 and 1.6 µg/kg/day based on the extreme-case and more likely exposure scenarios, respectively. The AADD for park and forestry workers was 2.1 µg/kg/day. The lifetime average daily dosage (LADD) for park and forestry workers was 1.2 µg/kg/day assuming 40 years of working exposure.

The margin of safety (MOS) is the ratio of the NOEL and exposure dosage. For the acute neurological signs, the MOS was 262. The MOS for dermal irritation was 2667 with acute exposure and between 112 and 333 with seasonal exposure depending on the exposure scenario. An MOS for dermal sensitization was not calculated; however, repeated exposure to the tick repellent formulation may result in a reaction in a segment of the exposed population. The MOSs for liver hypertrophy with seasonal exposure ranged from 203 to 375 depending on the exposure scenario used. With chronic exposure, the MOSs for liver hypertrophy and alveolar cell proliferation were between 700 and 1,312 based on the various exposure scenarios. Generally, a MOS greater than 100 is desirable.

The theoretical oncogenic risk was between 2.4×10^{-5} (MLE) and 3.3×10^{-5} (95% UB) based on an extreme-case exposure scenario for the general public. Using the more likely exposure scenario, the risk decreased to between 1.3×10^{-5} and 1.8×10^{-5} for the general public. The theoretical oncogenic risk for park and forestry workers was between 1.0×10^{-5} and 1.3×10^{-5} assuming exposure was limited to occupational use. Generally, an oncogenic risk level less than 10^{-6} is desirable. However, the negligible risk level for oncogenicity may range from 10^{-5} to 10^{-6}, depending on a number of factors such as the weight of evidence, uncertainty in exposure, etc. Regardless, several of the oncogenic risk estimates were outside the range that is normally considered negligible and acceptable. Further exposure to permethrin could not be reduced under conditions of current use.

II INTRODUCTION

A. BACKGROUND INFORMATION

The Fairfield American Corporation initially submitted an application for a special local need registration (Section 24(c)) to the Department of Pesticide Regulation (DPR) in the California Environmental Protection Agency for their Permanone Tick Repellent which contains 0.5% permethrin, (3-phenoxyphenyl) methyl (±)-*cis, trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (*cis*:*trans* ratio - 35:65), as the active ingredient. The proposed use of this tick repellent formulation is on human clothing primarily for the prevention of tick-borne diseases, such as Lyme disease. This new use for permethrin would involve indirect exposure to humans over a large surface area of the skin. Severe irritation was observed in a dermal irritation study with the formulation in rabbits. The dermal irritation was attributed primarily to the inert ingredients since the irritation was less severe with the technical grade permethrin. DPR denied the Section 24(c) registration of this product based on its potential dermal irritation and oncogenic risk (Lewis and Formoli, 1992). Fairfield American Corporation has since reformulated the product and submitted a dermal irritation study with the revised formulation. Fairfield American Corporation has also become part of the Roussel Uclaf Corporation and is now requesting a Section 3 registration for this product. The purpose of this risk assessment is to reevaluate any potential adverse effects from this reformulated product.

B. BIOLOGICAL ACTIVITY

Permethrin is a synthetic pyrethroid insecticide. Its mechanism of action is similar to DDT in that it interferes with the conductance of nerve impulses through its effects on the sodium channels (Bradbury and Coats, 1989). Permethrin is considered a Type I pyrethroid which causes repetitive firing of nerves as a result of the prolongation of the sodium current, but does not cause large membrane depolarization leading to impulse conduction block like Type II pyrethroids (e.g., cypermethrin). The selective toxicity of synthetic pyrethroids in insects compared to mammals may be partially explained by their more rapid absorption, slower metabolism, and increased affinity for target receptors in insects. The synthetic pyrethroids are also highly toxic to fish apparently due to their less efficient detoxification. The repellent properties of synthetic pyrethroids are thought to be due to their sublethal behavioral effects in insects including cessation of feeding, wandering, flushing out of hiding, hyperactivity, and restlessness.

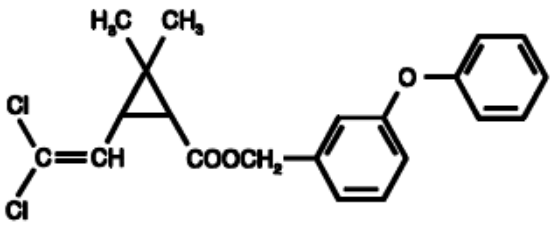
C. PHYSICAL AND CHEMICAL PROPERTIES (ICI Americas Inc., 1983)

1. Common Name:	Permethrin
2. Chemical Name:	(3-phenoxyphenyl) methyl (±)-*cis,trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
3. Trade Names:	Permanone, Ambush, Pounce, Ectiban, FMC 33297, PP 557, BW-21-Z, NRDC 143
4. CAS Registry No.:	52645-53-1

C. PHYSICAL AND CHEMICAL PROPERTIES (continued)

5. Molecular Weight: 391.3

6. Molecular Structure:



7. Empirical Formula: $C_{21}H_{20}Cl_2O_3$

8. Physical State: Clear liquid

9. Odor: Odorless

10. Melting Point: 55.7-56.3°C (*cis*) (Alvarez, 1989)
45.7-46.3°C (*trans*)

11. Boiling Point: 220°C at 0.05 mm Hg

12. Density: 1.0138 at 25°C (Alvarez, 1989)

13. Solubility: Water - 0.07 mg/l at 25°C (Fujie, 1975)
Miscible with most organic solvents

14. Vapor Pressure: 2.15×10^{-8} mm Hg at 25°C (*cis*) (Alvarez, 1989)
0.69×10^{-8} mm Hg at 25°C (*trans*)

15. Henry's Law Constant: 1.0×10^{-7} atm-m^3/mole at 25°C (*cis*) (Alvarez, 1989) 5.1×10^{-8} atm-m^3/mole at 25°C (*trans*)

16. Partition Coefficient (K_{ow}): 3×10^3 (Brandau, 1975)

17. Hydrolysis: Stable under acidic or slightly acidic conditions (pH 3-6) at 25-45°C, but hydrolyzes slowly at pH 9, increasing with temperature ($t_{1/2}$= 3 days at 45°C) (Allsup, 1976). The *cis* isomer is more stable.

18. Photolysis: Degrades slowly in sterile water (pH 5) and soil with exposure to Xenon arc lamp at 25°C (60-86% remained intact after 32-35 days) (Amos and Donelan, 1987; Brown and Leahey, 1987).

III TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Absorption and Excretion

In rats, between 60-85% of permethrin was excreted within 24 hrs after administering a single oral dose to rats (Mills and Mullane, 1976; Gaughan *et al.*, 1977). Approximately 56 and 43% of the applied dose was excreted in the urine and feces, respectively, within 7 days when rats were given a single oral dose of permethrin with a 40:60 *cis:trans* ratio (Mills and Mullane, 1976). However, the pharmacokinetics of permethrin appears to vary between isomers. When the *cis*- and *trans*-isomers were administered separately, 53 and 80% of the applied dose, respectively, were excreted in the urine within 12 days (Gaughan *et al.*, 1977). Fecal excretion represented 43 and 14% of the applied dose for the *cis*- and *trans*-isomers, respectively, of which only 3 and 6% of the applied dose was the unmetabolized parent compound. In another study, the oral bioavailability of permethrin with a 25:75 *cis:trans* ratio was estimated to be approximately 61% by comparing the area under the plasma concentration curve with oral and intravenous administration (Anadon *et al.*, 1991). Although the plasma concentration was only followed for 48 hrs after dosing, this estimate suggests that most of the fecal excretion observed in the other studies is unabsorbed permethrin. Only a small percentage of the applied dose was expired as CO_2 or remained in tissues (Mills and Mullane, 1976; Gaughan *et al.*, 1977). For this risk assessment, the oral absorption rate for the permethrin was estimated to be 70% by multiplying the percentage of each isomer in the technical grade material (*cis*:*trans* ratio ~ 35:65) by their respective urinary excretion rates reported by Gaughan and coworkers (1977) and then adding them together.

The percutaneous absorption of permethrin is generally lower in humans than other mammalian species (Farquhar *et al.*, 1981; Allsup and Hubbell, 1983a&b; Allsup and Hubbell, 1984; Bartelt and Hubbell, 1989; Wang *et al.*, 1981; Shah *et al.*, 1981; Grissom *et al.*, 1987; Sidon *et al.*, 1988; Lythgoe, 1993). In two *in vivo* studies with humans, permethrin was applied to the scalp as a creme rinse, shampoo or aerosol (Farquhar *et al.*, 1981; Allsup and Hubbell, 1983a). In another *in vivo* study, permethrin was applied to the entire body of volunteers as a dermal cream (Allsup and Hubbell, 1984). The absorption rates in all three studies were less than 1%, but the hair, rinses, and cream vehicles may have hindered absorption. Isopropanol was used for the vehicle in a fourth *in vivo* study in which permethrin was applied to the shaved backs of volunteers (Bartelt and Hubbell, 1989). Approximately 0.3 to 2.0 per cent of the applied dose was excreted in 5 days. In an *in vitro* study with human skin, 0.6 percent of the applied dose was absorbed in an 8-hour period (Wang *et al.*, 1981). Although dermal absorption of permethrin was examined in rodents in several studies, they all had deficiencies which made an accurate determination of the dermal absorption rate in rodents difficult (Allsup and Hubbell, 1983b; Shah *et al.*, 1981; Grissom *et al.*, 1987; Lythgoe, 1993). The best estimate was obtained from a study by Sidon *et al.*, (1988) who reported a dermal absorption rate of approximately 45% in rats based on urinary excretion of metabolites for 7 or 14 days after dosing. However, unlike the human studies, this absorption rate was corrected for incomplete excretion by comparing the recovery between dermal and intramuscular administration. The uncorrected dermal absorption rate was 25%. For the purpose of interspecies extrapolation, a dermal absorption rate of 25% was assumed for rats and 2% for humans (Appendix B).

A. PHARMACOKINETICS (continued)

Distribution

After oral administration of permethrin to rats and dogs, the highest residues were found in the fat (Bratt and Slade, 1977; Bratt *et al.*, 1977; Gaughan *et al.*, 1977). The *cis:trans* ratio in the fat was different than in the permethrin administered. Bratt and coworkers (1977) suggested that this was due to the preferential metabolism of the *trans*-isomer. Depending on the time after dosing, residues were detected in the liver and kidney of both rats and dogs. Residues were also detected in the muscle of dogs, but not rats.

Biotransformation

Based on the differences in urinary excretion of the *cis*- and *trans*-isomers, Gaughan and coworkers (1977) suggested that the ester group of the *cis*-isomer is more stable to hydrolysis. Suzuki and Miyamoto (1977) purified an enzyme they identified as pyrethroid carboxyesterase from rat liver microsomes which hydrolyzes the *trans*-isomer 5 to 10 times faster than the *cis*-isomer. This enzyme is inhibited by organophosphates and carbamates and apparently is identical to the carboxyesterase that hydrolyzes malathion and *p*-nitrophenyl acetate.

The major urinary metabolites identified by Gaughan *et al.* (1977) were the *cis*- and *trans*-isomers of the sulfate conjugate of 4'-hydroxy-3-phenoxybenzoic acid, the glucuronide conjugate of dichlorovinyldimethyl cyclopropane-carboxylic acids, and the free and glucuronide conjugates of 3'-phenoxybenzoic acid. The unchanged parent compound was the major product in the feces and fat. Anadon *et al.* (1991) detected *m*-phenoxybenzyl alcohol and acid in the plasma, liver and nervous tissue in rats 48 hours after dosing. The pharmacokinetics and metabolism of permethrin in the dogs, cows, goats, chickens, and swine appears to be similar to rats, involving extensive hydrolysis and oxidation (Mills and Slade, 1977; Sigel *et al.*, 1982).

B. ACUTE TOXICITY

Systemic Effects

The acute toxicity of technical grade permethrin is summarized in Table 1. When technical grade permethrin was administered orally to rats, the clinical signs included (with increasing dose) urinary incontinence, diarrhea, dehydration, changes in abdominal tone, piloerection, facial stains (probably chromodacryorrhea), upward curvature of the spine (possibly opisthotonos), hyperthermia, irregular breathing, tremors, salivation, lacrimation, and increased respiratory rate (Ishmael, 1989). The No-Observed-Effect-Level (NOEL) was 500 mg/kg based on these clinical signs and mortalities. Cantalamessa (1993) found that permethrin was more toxic to 8-21 day old neonatal rats than to adult rats by 3.2 to 4.4 fold. When the neonatal rats and adults were pretreated with an ester inhibitor, the toxicity was increased significantly (~16%) in adults, but not in neonates. Based on this finding, they attributed the greater toxicity to the incomplete development of the esterase enzymes involved the detoxification of permethrin. Since the mortalities and clinical signs were not summarized for each dose level, a NOEL could not be established for either adults or neonates for this study. More neurological effects typical of pyrethroids were observed when rats were exposed to technical grade permethrin by the inhalation route, including paw flicking (probably paresthesias), splayed gait, tail erection, depressed reflexes, and tip toe gait (Brammer, 1989). These may reflect a higher internal dose rather than a route specific effect. Death occurred at air concentrations of 2.28 mg/l (365 mg/kg)

B. ACUTE TOXICITY (continued)

Table 1 - The Acute Toxicity of Technical Grade Permethrin (95.6%)

Test/ Species	Sex	Results	References[a]
Oral LD_{50}			
Rat (adult)	M/F	~800 mg/kg	1
Rat (adult)	M	1500 mg/kg	2
Rat (neonate)	M/F	340-471 mg/kg	
Inhalation LC_{50}			
Rat	M/F	2.30 mg/l (4-hr)	3
Dermal LD_{50}			
Rat	M/F	>2,000 mg/kg	4
Eye Irritation			
Rabbit	F	Mild Irritant	5
Dermal Irritation			
Rabbit	F	Moderate Irritant	6
Dermal Sensitization			
Guinea Pig	F	Moderate Sensitizer[b]	7

a References: 1. Ishmael, 1989; 2. Cantalamessa, 1993; 3. Brammer, 1989; 4. Robinson, 1989a; 5. Leah, 1989a; 6. Robinson, 1989b; 7. Leah, 1989b.
b Maximization Test

and higher. The Lowest-Observed-Effect-Level (LOEL) was 240 µg/l (38 mg/kg[1]). No deaths were observed when technical grade permethrin was applied to the skin of rats at 2 g/kg (the only dose tested), but tip toe gait, upward curvature of the spine, and urinary incontinence were observed in a several animals (Robinson, 1989a).

[1] Assuming a rat breathes 160 l/kg in 4 hours (Zielhuis and van der Kreek, 1979).

B. ACUTE TOXICITY (continued)

The acute toxicity of Permanone Tick Repellent is summarized in Table 2. When the tick repellent formulation was administered orally to rats at 5 g/kg in a "limit test", red nasal discharge, lethargy and moist rales were observed in a few animals (Shapiro, 1989a). Salivation, lethargy, squinting and moist rales were seen in rats exposed to the tick repellent formulation at the

Table 2 - The Acute Toxicity of Permanone Tick Repellent (0.5%)

Test/ Species	Sex	Results	References[a]
Oral LD_{50}			
Rat	M/F	> 5,000 mg/kg	1
Inhalation LC_{50}			
Rat	M/F	>4.84 mg/l (4-hr)	2
Dermal LD_{50}			
Rabbit	M/F	> 2,000 mg/kg	3
Eye Irritation			
Rabbit	M/F	Mild Irritant	4
Dermal Irritation			
Rabbit	M/F	Moderate-Severe Irritant[b]	5-7
Dermal Sensitization			
Guinea Pig	M	Non-sensitizer[c]	8

a References: 1. Shapiro, 1989a; 2. Ben-Dyke *et al.*, 1987; 3. Shapiro, 1989b; 4. Shapiro, 1989c; 5. Shapiro, 1989d; 6. Shapiro, 1989b; 7. Cerven, 1992; 8. Shapiro, 1989d.
b Revised formulation

B. ACUTE TOXICITY (continued)

maximum attainable air concentration of 4.84 mg formulation/l (774 mg formulation/kg) (Ben-Dyke *et al.*, 1987). Hemorrhaging and/or white or pale patches in the lungs were observed in 8/10 treated rats in this study during gross pathological examination. The only systemic signs seen when the tick repellent formulation was applied topically to rabbits at 2 g/kg was weight loss and diarrhea in one animal on days 10 to 14 (Shapiro, 1989b).

Local Effects

Technical grade permethrin produced local effects in several studies including mild eye irritation, moderate skin irritation, and skin sensitization (Table 1). In an eye irritation study, conjunctival erythema, chemosis, and discharge were observed when 0.1 ml of permethrin was instilled in the conjunctival sac of rabbits, but no corneal or iridial effects were seen (Leah, 1989a). In an acute dermal toxicity study, desquamation, edema, thickening, scabs and/or skin eruptions were observed in 9/10 rats which had 2 g/kg applied to a 24 cm^2 area (20 mg/cm^2) (Robinson, 1989a). This was the only dose level tested. These effects persisted in a few animals up to 10 days. Erythema and edema were observed in a dermal irritation study where 0.5 g was applied to 6.25 cm^2 area (Robinson, 1989b). This is equivalent to approximately 80 mg/cm^2. Skin sensitization was observed in a guinea pig maximization test (Leah, 1989b). Technical grade permethrin was applied both intradermally (six 0.05-0.1 ml injections of 10% solution in corn oil with and without Freund's complete adjuvant) on day 0 and topically (undiluted) on day 7 of the induction phase. The animals were challenged on day 21 with both a 30% solution in corn oil and the undiluted test material which were applied topically. Slight to moderate erythema was observed in 6 of 20 animals.

Local effects observed for the tick repellent formulation included mild eye irritation and moderate to severe skin irritation (Table 2). Mild conjunctival erythema, chemosis and discharge were observed in rabbits administered 0.1 ml of the formulation in the conjunctival sac, although no corneal or iridial damage was seen (Shapiro, 1989c). Severe irritation was observed in two studies with the previous formulation of the tick repellent (Shapiro, 1989d&e). In one study, the previous formulation was applied to intact skin for 4 hours (Shapiro, 1989d). Erythema, edema, brown discoloration with dry flaky skin and no hair growth were seen. The erythema, lack of hair growth and dry flaky skin were still present in several rabbits 14 days after exposure. In another study conducted by the same investigator, the previous formulation was applied to intact and abraded skin sites for 24 hours (Shapiro, 1989e). Erythema, edema, yellow/brown discoloration, dry flaky skin, no hair growth and eschar were also observed. Only moderate irritation (erythema and edema) was observed when 0.5 ml of the revised formulation was applied to 10 cm^2 area (50 mg/cm^2) (Cerven, 1992). Both persisted through day 7 in a few animals. By day 14 only erythema was observed in one animal. No dermal effects were reported in the acute dermal toxicity study for the tick repellent formulation, but it is uncertain if the skin was examined for local responses (Shapiro, 1989b). No skin sensitization was observed in guinea pigs using the Buehler patch test in which 0.4 ml of a 12.5% solution in mineral oil was applied topically 3 times per week for 3 weeks during the induction phase (Shapiro, 1989f). The animals were challenged 2 weeks later with the 0.4 ml of a 12.5% solution in mineral oil on a naive site.

A patch test was conducted with 184 volunteers of both sexes that ranged in age from 18 to 80 and represented three races (white, black and asian) (Snodgrass, 1986). The subjects had 0.2 ml of a 40% permethrin solution (technical permethrin, 92.5%, and ethanol, 95%) applied to the upper arm or back 3 times per week for 3 weeks. The patches were left on between applications and kept dry. Two weeks after the induction period, a challenge application was

B. ACUTE TOXICITY (continued)

made on a previously untreated site and removed 72 hours later. The responses were scored at 96 hours. There was no evidence of dermal sensitization, but several subjects noticed a transient burning, stinging or itching.

C. SUBCHRONIC TOXICITY

Inhalation-Rat

U.S. Army Environmental Hygiene Agency, 1980: Twenty Sprague Dawley rats/sex/dose were exposed to aerosolized permethrin (92.7% purity, *cis:trans* ratio 40:60) at 0, 125, 250 or 500 mg/m^3 (0, 30, 60 or 120 mg/kg/day)[2] for 6 hrs/day, 5 days/wk for 13 weeks (Metker, 1980). At the end of the 13-week exposure period, 50% of the rats were submitted for necropsy while the other 50% were allowed to recover for another 90 days before being submitted for necropsy. Oxygen consumption was determined in 5 male rats per dose before, during and after exposure twice a week for 13 weeks. Enzyme induction was evaluated in 10 male rats per dose at the end of the 13 week exposure period by determining hexobarbital induced sleeping time. There was no treatment-related effect on mortalities, body and organ weights, oxygen consumption, and histopathology. Severe tremors and convulsions were observed in the rats exposed to 500 mg/m^3. The induced sleeping time was significantly shortened (43%) at 500 mg/m^3. The NOEL appears to be 250 mg/m^3 (60 mg/kg/day) based on the tremors and convulsions. There were several major deficiencies with this study including no examination of food and water consumption, clinical chemistry, hematology or urinalysis, and only limited individual data for other endpoints.

Inhalation-Guinea Pig

U.S. Army Environmental Hygiene Agency, 1980: Ten Hartley guinea pigs/sex/dose were exposed to aerosolized permethrin (92.7% purity, *cis:trans* ratio 40:60) at 0, 125, 250 or 500 mg/m^3 (0, 14, 28 or 55 mg/kg/day)[3] for 6 hrs/day, 5 days/wk for 13 weeks (Metker, 1980). At the end of the 13-week exposure period, the male guinea pigs were challenged with an intradermal injection 0.05 ml of permethrin to test for sensitization. No treatment-related differences in clinical signs, body and organ weights, sensitization reactions, or histopathological lesions were seen. The NOEL appears to be equal to or greater than 500 mg/m^3 based on the lack of evidence of overt toxicity at the highest dose. This study had several major deficiencies including no examination of food and water consumption, hematology, clinical chemistry or urinalysis, and only limited individual data for other endpoints.

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[2] Assuming a rat breathes 0.24 m^3/kg in 6 hours (Zielhuis and van der Kreek, 1979).

[3] Assuming a guinea pig breathes 0.11 m^3/kg in 6 hours (Zielhuis and van der Kreek, 1979).

C. SUBCHRONIC TOXICITY (continued)

Inhalation-Dog

U.S. Army Environmental Hygiene Agency, 1980: Two Beagle dogs/sex/dose were exposed to aerosolized permethrin (92.7% purity, *cis:trans* ratio 40:60) at 0, 125, 250 or 500 mg/m^3 (0, 12, 25 or 50 mg/kg/day)[4] for 6 hrs/day, 5 days/wk for 13 weeks (Metker, 1980). Pulmonary function (tidal volume, minute volume, transpulmonary pressure, compliance and resistance) was evaluated before and after the 13-week exposure period. There were no treatment-related differences in clinical signs, body and organ weights, clinical chemistry, hematology or histopathology. There was a tendency toward lower compliance and higher resistance in the exposed animals; however, there was no clear dose-related trend and the pneumonia among the treated animals confounds the interpretation of these findings. The NOEL appears to be equal to or greater than 500 mg/m^3 based on the lack of evidence of overt toxicity. There were several other major deficiencies besides the intercurrent disease including inadequate number of animals per group, no examination of food and water consumption or urinalysis, and only limited individual data for other endpoints.

Diet-Mouse

ICI, 1977: Groups of 20 Swiss-derived mice/sex/dose were fed permethrin (94.7% purity, *cis:trans* ratio) at 0, 80, 200, 400, 1000, 2000 or 4000 ppm (0, 12, 30, 60, 150, 300 or 600 mg/kg/day)[5] for 28 days (Clapp *et al.*, 1977a). The 80 ppm dose level was increased to 10,000 ppm (1,500 mg/kg/day) for the third and fourth week of the study. No mortalities or treatment-related clinical signs were observed; however, a reduction in body weights (6-13%) was observed in the 80/10,000 ppm group. Necropsies were performed on 5 mice/sex/dose from the 0, 2000 and 80/10,000 ppm groups. An increase in liver weights was observed at 2,000 and 10,000 ppm. Eosinophilia of the centrilobular hepatocytes was observed in all mice at 80/10,000 ppm and in two female mice at 2000 ppm. The NOEL appears to be less than 2000 ppm (300 mg/kg/day) at which eosinophilia of the centrilobular hepatocytes was observed. The study had several major deficiencies including no analysis of clinical chemistry, hematology and urinalysis, the lack of histological examination of all of the animals, no individual data, and an inadequate exposure period.

Diet-Rat

Sumitomo Chemical Co., 1975: Permethrin (93.3% purity, 40:60 *cis:trans* ratio) was administered to 16 Sprague-Dawley rats/sex/dose at 0, 375, 750, 1500 or 3000 ppm (0, 25, 49, 101 or 203 mg/kg/day) for 6 months (Kadota, 1975). There were no treatment-related effects on mortalities, body weights, food and water consumption, urinalysis, hematology, clinical chemistry, and gross pathological lesions. Hypersensitivity and tremors were observed up to week 7 at 3000 ppm. A slight increase in liver weights and hypertrophy of the liver parenchymal cells were also observed at 3000 ppm. The NOEL was 1500 ppm (101 mg/kg/day) based on the tremors, hypersensitivity and histopathological changes in the liver. This study had several minor deficiencies including no analysis of the feed to verify compound concentration, no individual data for clinical signs, and incomplete clinical chemistry analysis.

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[4] Assuming a dog breathes 0.10 m^3/kg in 6 hours (Zielhuis and van der Kreek, 1979).

[5] Assuming a 20 g mouse consumes 3 g of feed per day (FDA, 1959).

C. SUBCHRONIC TOXICITY (continued)

Bio/dynamics, 1976: Ten Long-Evans rats were administered permethrin (purity and *cis:trans* ratio not reported) in the diet at 0, 20, 100, 500 or 2500 ppm (0, 1.7, 8.0, 42.8 or 208.8 mg/kg/day) for three months (Killeen and Rapp, 1976a). Tremors were observed at 500 and 2500 ppm during the first week of treatment. Central lobular hepatocyte hypertrophy was observed at 100, 500 and 2500 ppm. Liver weights were also significantly higher at 500 and 2500 ppm. There was no effect on body weights, food consumption, ophthalmology, hematology, clinical chemistry or urinalysis. The NOEL was 20 ppm (1.7 mg/kg/day) based on the liver hypertrophy. There were a few minor deficiencies with this study (no analysis of compound in feed, no individual clinical signs data, and incomplete clinical chemistry analysis).

ICI, 1977: Groups of 8 Wistar-derived rat/sex/dose were fed diets containing permethrin (90.5% purity, *cis:trans* ratio 38:52) at 0, 200, 500, 1000, 2500, 5000 or 10,000 ppm (0, 10, 25, 50, 125, 250 or 500 mg/kg/day)[6] for 28 days (Clapp *et al.*, 1977b). All the animals at 10,000 ppm died in the first 3 days. Several animals at 5000 ppm also died. Prior to death these animals exhibited piloerection, tremors, and hyperactivity. Piloerection, tremors, and hypersensitivity were seen in surviving rats at 5000 ppm and in rats at 2500 ppm. Tremors were also observed at 1000 ppm. Body weights and food consumption were reduced (15-17% and 20-50%, respectively) at 5000 ppm. Blood urea nitrogen was elevated at 500 ppm and higher in females and at 1000 ppm and higher in males. Urinary protein excretion was depressed in males at 5000 ppm. Liver weights were elevated in females at 500 ppm and higher and in males at 2500 ppm and higher. There was no effect on water consumption, hematology or histopathology. The NOEL appears to be 500 ppm (25 mg/kg/day) based on tremors. This study had major deficiencies including an inadequate number animals per group, incomplete clinical chemistry, hematology, and urinalysis, histopathology not performed on all animals, no individual data, and an inadequate exposure period.

U.S. Army Environmental Hygiene Agency, 1987: Sprague-Dawley rats (20, 10, 10, 10 or 20/sex) were administered permethrin (98% purity, *cis:trans* ratio 40:60) in the diet at 0 (untreated), 0 (vehicle=acetone), 100, 200 or 400 mg/kg/day, respectively, for 90 days (Snodgrass and Cantu, 1986). There was a statistically significant reduction (7-9% at termination) in body weights in rats at 400 mg/kg/day. Tremors were observed at 200 and 400 mg/kg/day. Twitching, hyperexcitability, and irritability were also observed at 400 mg/kg/day. All clinical signs disappeared 2 to 3 days after being removed from the treated diet. There were no treatment-related differences in food consumption and histopathological lesions in the central and peripheral nervous system. The NOEL was 100 mg/kg/day based on the tremors. Major deficiencies with this study included no analysis of hematology, clinical chemistry, and urinalysis, incomplete histopathological examination, and no individual data.

[6] Assuming a 400 g rat consumes 20 g of feed per day (FDA, 1959).

C. SUBCHRONIC TOXICITY (continued)

Capsule-Dog

Bio/dynamics, 1976: Groups of 4 Beagle dogs/sex/dose were administered permethrin (purity and *cis:trans* ratio not reported) in gelatin capsules at 0, 5, 50 or 500 mg/kg/day for three months (Killeen and Rapp, 1976b). Tremors were observed in several dogs at 500 mg/kg/day. One of the dogs with tremors also exhibited narcosis with nystagmus on one occasion. Increased relative and absolute liver weights without accompanied histological changes were at 50 and 500 mg/kg/day. There was no effect on body weights, food consumption or histopathological lesions. The NOEL was 50 mg/kg/day based on the tremors. There were a few minor deficiencies with this study (no individual clinical signs data, and incomplete clinical chemistry analyses).

Inveresk Research International, 1976: Four Beagle dogs/sex/dose were administered permethrin (89.4-98.8% purity; *cis:trans* ratio not reported) at 0, 10, 100 or 2000 mg/kg/day for 3 months (Edwards *et al.*, 1976). There were no treatment-related effects on mortality, food and water consumption, ophthalmology, hematology, urinalysis, and gross and histopathological lesions. Tremors were observed a few hours after dosing in dogs at 2000 mg/kg/day. After 13 weeks, the female bodyweights at 2000 mg/kg/day were lower (14%) than the controls, but the difference was not statistically significant. The relative liver weights were significantly higher in dogs at 2000 mg/kg/day. The NOEL was 100 mg/kg/day based on the tremors and increased liver weights. This study had minor deficiencies including no individual clinical signs and incomplete clinical chemistry analyses.

Dermal-Rat

ICI, 1989: Permethrin (95.6% purity, *cis:trans* ratio 39:61) was applied topically to 5 Alpk:APfSD rats/sex/dose at 0, 50, 150 and 500 mg/kg/day (0, 0.5, 1.6, 4.9 mg/cm^2/day)[7] for 6 hrs/day for 21 consecutive days (Milbourn, 1989). No treatment-related systemic effects or gross pathological lesions were observed. Dermal irritation was observed at all dose levels and included erythema, edema, desquamation, and scabbing. The NOEL for systemic effects was 500 mg/kg/day, the highest dose tested. The NOEL for local effects was less than 50 mg/kg/day (0.5 mg/cm^2/day) based on desquamation, edema, and scabbing. DPR found this study acceptable based on Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) guidelines.

D. CHRONIC TOXICITY/ONCOGENICITY

Dietary-Mouse

Four mouse oncogenicity studies were submitted to DPR (Hogan and Rinehart, 1977; Ishmael and Litchfield, 1988; Tierney and Rinehart, 1979; James, 1980). All four were unacceptable to DPR based on significant deviations from the FIFRA guidelines.

[7] The dose was estimated based on an application site of 6 cm x 4 cm and the average body weight for each group and sex during the exposure period.

D. CHRONIC TOXICITY/ONCOGENICITY (continued)

Bio/dynamics Mouse I, 1977: Groups of 75 CD-1 mice/sex/group were fed permethrin (purity unknown, *cis*:*trans* ratio 40:60) at 0, 20, 500 or 4000 ppm (0, 3, 75 or 600 mg/kg/day)[5] for 2 years in the first Bio/dynamics mouse oncogenicity study (Hogan and Rinehart, 1977). The highest dose level was changed from 100 to 4000 ppm (15 to 600 mg/kg/day) at week 21. There was no evidence of an oncogenic effect, but this study had major deficiencies (inadequate analysis of diet, dose selection, changes in dose levels). DPR determined the NOEL was 500 ppm (75 mg/kg/day) based on mortality observed at 4000 ppm (600 mg/kg/day), the LOEL. The U.S. Environmental Protection Agency (U.S. EPA) considered this study negative for oncogenic effects and gave it a CORE grade[8] of "supplementary" with a NOEL of 20 ppm (3 mg/kg/day). No basis for the NOEL was stated.

ICI, 1977: In a 98 week study conducted by ICI, 70 Alderley Park (Swiss-derived) mice/sex/group were administered permethrin (purity 94.0-98.9%, *cis*:*trans* ratio 40:60) in the diet at 0, 250, 1000 or 2500 ppm (0, 37.5, 150, or 375 mg/kg/day)[5] (Ishmael, 1988). The incidence of benign lung tumors in male mice exhibited a dose-related trend (Table 3). The incidence in malignant lung tumors in female mice was also significant by trend analysis. However, the incidence was not significantly greater than the controls in either sex by pair-wise comparison. When compared to concurrent controls, the latency period for lung tumors was reduced (7.2%) in the high-dose males; however, it increased slightly (5.8%) in the high-dose females. The differences in either case were not significant. Although equivocal, DPR initially concluded there was no oncogenic effect since the incidence was within the normal historical range (10-50%) for this strain.

Other non-oncogenic effects were observed histopathologically in the liver (proliferation of the smooth endoplasmic reticulum (SER), increased microbodies (peroxisomes) in centrilobular hepatocytes, and eosinophilia of hepatocytes at 1000 and 2500 ppm (150 and 375 mg/kg/day, respectively) and kidney (decreased vacuolization of the proximal tubular epithelium in males at all dose levels). Significantly higher liver weights in high-dose females and significantly lower kidney weights in high-dose males were reported. The toxicological significance of these liver and kidney effects were uncertain.

DPR identified numerous deficiencies with this study including the lack of overt toxicity, the inadequate analysis of the diet, a misdosing incident during weeks 24-28, and the lack of pathology for non-neoplastic lesions. The initial reviewer of this study did not think there was sufficient information to establish a NOEL. The U.S. EPA also considered this study negative for an oncogenic effect, but they did not give it a CORE grade. The U.S. EPA determined the NOEL was 250 ppm (37.5 mg/kg/day) based on the liver effects.

Bio/dynamics Mouse II, 1979: In the Bio/dynamics Mouse II study, permethrin (purity 94.5-96.7%, *cis*:*trans* ratio 40:60) was administered in the feed to 75 CD-1 mice/sex/group at 0,

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[8] In evaluating studies, the U.S. EPA assigns a CORE grade of guideline, minimum, supplementary or invalid. Guideline means it is scientifically valid and meets FIFRA guidelines. Minimum means it has minor deficiencies, but is scientifically valid. Supplementary means it is has major deficiencies, but has some useful data. Invalid means it has major deficiencies and is not valid scientifically.

Table 3. Incidence of Pulmonary Tumors in ICI Mouse Oncogenicity Study after Administering Permethrin in the Diet for 98 Weeks[a]

	Dose Level (ppm)			
	0	250	1000	2500
	MALES			
Adenoma	10/36[++] (28%)	6/41 (15%)	13/40 (32%)	16/37 (43%)
	FEMALES			
Adenoma	11/48 (23%)	8/50 (16%)	11/48 (23%)	14/46 (30%)
Adenocarcinoma	0/43[+] (0%)	0/45 (0%)	0/43 (0%)	1/36 (3%)
Combined	11/48[+] (23%)	8/50 (16%)	11/48 (23%)	15/46 (33%)

a The incidence was expressed as the number of tumor bearing animals per animals at risk. The number in parentheses represents the incidence in percentage.
[+] Significant trend at $p < 0.05$ based on a dose-weighted chi-square trend test (Peto *et al.*, 1980).
[++] Significant trend at $p < 0.01$ based on a dose-weighted chi-square trend test.

20, 2500 or 5000 ppm (0, 3, 375 or 750 mg/kg/day)[5] for females and 0, 20, 500 or 2000 ppm (0, 3, 75 or 300 mg/kg/day)[5] for males for 104 weeks (Tierney and Rinehart, 1979). The evidence of an oncogenic effect was strongest in this study. There was a highly significant increase in the incidence of alveolar cell adenomas in females at all dose levels with a dose-related trend (Table 4). The incidence of alveolar cell carcinomas was also significantly increased at the high-dose level in females and exhibited a dose-related trend. In addition, a significant increase in hepatocellular adenomas was observed in females at the mid- and high-dose levels with a dose-related trend. In males, the incidence of hepatocellular adenomas was significantly higher at all dose levels and had a dose-related trend (Table 5). However, the combined incidence of liver tumors in males was only significant at the mid-dose level and did not exhibit a dose-related trend. The lack of a significant trend for the combined incidence of liver tumors in males may be related to the poor survival rate at the high-dose level. Although not statistically significant, the latency period for liver and lung tumors in the high-dose males was shortened by 6.7 and 3.7%, respectively, when compared to the concurrent controls. In contrast, the latency period was only slightly reduced for liver tumors (0.5%) and increased for lung tumors (8.6%) in females, but these differences were also not significant.

D. CHRONIC TOXICITY/ONCOGENICITY (continued)

Table 4. Incidence of Lung and Liver Tumors in Females in the Bio/dynamics Mouse II Oncogenicity Study after Administering Permethrin in the Diet for 24 Months[a]

	Dose Level (ppm)			
	0	20	2500	5000
Alveolar cell adenoma	9/71^{+++} (13%)	17/65* (26%)	24/68** (35%)	29/69*** (42%)
Alveolar cell carcinoma	6/66^{++} (9%)	7/61 (11%)	11/59 (19%)	15/62* (24%)
Lung Tumors - Combined	15/71^{+++} (21%)	24/65* (37%)	35/68*** (51%)	44/69*** (64%)
Hepatocellular adenoma	2/64^{+++} (3%)	4/60 (7%)	22/61*** (36%)	28/65*** (43%)
Hepatocellular carcinoma	4/49 (8%)	3/54 (6%)	3/47 (6%)	2/50 (4%)
Liver Tumors - Combined	6/64^{+++} (9%)	7/60 (12%)	25/61*** (41%)	30/65*** (46%)

a The incidence was expressed as the number of tumor bearing animals per animals at risk. The number in parentheses represents the incidence in percentage.
$^{++}$ Significant trend at $p < 0.01$ based on a dose-weighted chi-square trend test.
$^{+++}$ Significant trend at $p < 0.001$ based on a dose-weighted chi-square trend test.
* Significantly different from the control group ($p < 0.05$) based on the Fisher's exact test.
** Significantly different from the control group ($p < 0.01$) based on the Fisher's exact test.
*** Significantly different from the control group ($p < 0.001$) based on the Fisher's exact test.

The incidences in Tables 4 and 5 are based on a second reading of the slides by an independent pathologist contracted by the U.S. EPA (Ackerman, 1981). Although the dose-related trends were generally the same between the two readings, there were a few significant differences in the incidence. One major difference was in the incidence of hepatocellular adenomas and carcinomas in males. In the initial reading, the incidence of hepatocellular adenomas (16/63, 21/62, 18/62 and 17/56) was not significant by pairwise comparison with concurrent controls or trend analysis. The incidence of hepatocellular carcinomas (4/66, 6/63, 13/63 and 5/60) and the combined incidence of liver tumors (20/66, 27/63, 31/63, 22/60) were significantly increased at the mid-dose level, but did not exhibit a dose-related trend. The other

D. CHRONIC TOXICITY/ONCOGENICITY (continued)

Table 5. Incidence of Lung and Liver Tumors in Males in the Bio/dynamics Mouse II Oncogenicity Study after Administering Permethrin in the Diet for 24 Months[a]

	Dose Level (ppm)			
	0	20	500	2000
Alveolar cell adenoma	16/72 (22%)	15/69 (22%)	15/67 (22%)	17/68 (25%)
Alveolar cell carcinoma	7/48 (15%)	5/53 (9%)	13/54 (24%)	4/31 (13%)
Lung Tumors - Combined	23/72 (32%)	20/69 (29%)	28/67 (42%)	21/68 (31%)
Hepatocellular adenoma	6/64[+] (9%)	17/63** (27%)	15/63* (24%)	17/56** (30%)
Hepatocellular carcinoma	16/67 (24%)	12/64 (19%)	19/64 (30%)	8/59 (14%)
Liver Tumors - Combined	22/67 (33%)	29/64 (45%)	34/64* (53%)	25/59 (42%)

a The incidence was expressed as the number of tumor bearing animals per animals at risk. The number in parentheses represents the incidence in percentage.

[++] Significant trend at $p < 0.01$ based on a dose-weighted chi-square trend test.

* Significantly different from the control group ($p < 0.05$) based on the Fisher's exact test.

** Significantly different from the control group ($p < 0.01$) based on the Fisher's exact test.

major difference between the two readings was in the incidence of the lung tumors in females. In the initial reading, the incidence of pulmonary adenomas (12/70, 14/68, 28/68 and 26/69) and the combined incidence of lung tumors (14/70, 15/68, 30/68 and 29/69) in females was not significantly higher at the low-dose level and there was not a significant increase in pulmonary carcinomas (2/49, 1/55, 2/47 and 3/47) by pair-wise comparison to concurrent controls or trend analysis.

D. CHRONIC TOXICITY/ONCOGENICITY (continued)

Historical control data for CD-1 mice were not submitted to DPR by Bio/dynamics, but the U.S. EPA received historical control data from Bio/dynamics which indicates that the normal range for lung adenomas in female mice is 0-8% (Rinde, 1989). The incidence of lung carcinomas in female mice were slightly lower (0-4.9%). The normal range for lung adenomas in male mice was similar to females; however, the incidence of lung carcinomas in males was slightly higher (4-14%). The normal ranges for hepatocellular adenomas and carcinomas in female mice were only 0-8% and 0-5%, respectively. The incidence of these tumors in male CD-1 mice is higher (0-12% and 0-12%, respectively). Based on this historical control data, the incidence of the lung and liver tumors in both sexes is clearly outside the normal range.

Other non-neoplastic lesions were identified. In the initial pathology report, a decrease in testes weight associated with testicular hypoplasia (histologically) was observed at 2000 ppm (300 mg/kg). In the second pathology report, there was a statistically significant increase in the incidence of multifocal alveolar cell proliferation in females and hepatocytomegaly (liver hypertrophy) in both sexes at the mid- and high-dose levels. An increase in hepatocytomegaly was also observed at 20 ppm, but the increase was not statistically significant. There was also a significant increase in the mortality rate in the males at 2000 ppm. DPR determined the NOEL was 20 ppm (3 mg/kg/day) based on the hepatocytomegaly in both sexes and the alveolar cell proliferation in females. The U.S. EPA also set the NOEL at 20 ppm based on lung and liver weight increases in females and decreased testes weight and deaths in males. Both the U.S. EPA and DPR considered the Bio/dynamics Mouse II study positive for an oncogenic effect. The one major deficiency that DPR identified for this study was inadequate husbandry. The U.S. EPA did not give this study a CORE grade.

Wellcome, 1980: Wellcome conducted a study in which 75 CFLP mice/sex/dose were fed permethrin (purity unknown, *cis*:*trans* ratio 25:75) in the diet at 0, 10, 50, 250 mg/kg/day for 91 weeks (James, 1980). There was also equivocal evidence of an oncogenic effect in this study. The incidence of benign lung tumors in female mice was significant by both trend analysis and pair-wise comparison with the controls at the high-dose level, 250 mg/kg/day (Table 6). The incidence of malignant lung tumors in females was also significant by trend analysis. When the incidence of benign and malignant lung tumors were combined for this study, it was highly significant by trend analysis and when compared to controls at the high-dose level. Furthermore, the latency period for lung tumors in the high-dose females was significantly reduced (7.1%) by the Student's t-test ($p < 0.05$). However, the incidence of lung tumors, even at the high-dose level, was within the normal range (10-30%) for this strain based on the historical control data submitted by the registrant. The incidence in the controls was unusually low. Initially, DPR did not believe this study demonstrated a possible oncogenic effect by itself. However, when the mouse studies were later reviewed collectively, DPR concluded the findings from this study supported an oncogenic effect. The U.S. EPA considered it positive for lung tumors.

Non-oncogenic effects observed in the high-dose animals (increased liver weights in males, increased kidney weights in females and cuboidal/columnar metaplasia in alveolar

D. CHRONIC TOXICITY/ONCOGENICITY (continued)

Table 6. Incidence of Lung Tumors in Wellcome Mouse Oncogenicity Study after Administering Permethrin in the Diet for 91 Weeks[a]

	Dose Level (ppm)			
	0	10	50	250
	MALES			
Adenoma	23/93 (25%)	13/68 (19%)	15/69 (22%)	15/73 (21%)
Adenocarcinoma	3/95 (3%)	1/70 (1%)	2/69 (3%)	1/73 (1%)
Combined	26/95 (27%)	14/70 (20%)	17/69 (25%)	16/73 (22%)
	FEMALES			
Adenoma	3/84^{+++} (4%)	5/62 (8%)	6/66 (9%)	13/68** (19%)
Adenocarcinoma	0/61^{+} (0%)	0/49 (0%)	1/58 (2%)	2/57 (4%)
Combined	3/84^{+++} (4%)	5/62 (8%)	7/66 (11%)	15/68*** (22%)

a The incidence was expressed as the number of tumor bearing animals per animals at risk. The number in parentheses represents the incidence in percentage.
$^{+}$ Significant trend at $p < 0.05$ based on a dose-weighted chi-square trend test.
$^{+++}$ Significant trend at $p < 0.001$ based on a dose-weighted chi-square trend test.
** Significantly different from the control group at $p < 0.01$ based on the Fisher's exact test.
*** Significantly different from the control group at $p < 0.001$ based on the Fisher's exact test.

epithelium in both sexes) were of uncertain toxicological significance. Both the U.S. EPA and DPR determined the NOEL for chronic toxicity was 250 mg/kg/day, the highest dose tested. DPR found that this study did not conform to FIFRA guidelines due to the lack of dose level justification and information regarding the purity of the test material. The U.S. EPA did not give this study a CORE grade.

D. CHRONIC TOXICITY/ONCOGENICITY (continued)

Historical control data for CD-1 mice were not submitted to DPR by Bio/dynamics, but the U.S. EPA received historical control data from Bio/dynamics which indicates that the normal range for lung adenomas in female mice is 0-8% (Rinde, 1989). The incidence of lung carcinomas in female mice were slightly lower (0-4.9%). The normal range for lung adenomas in male mice was similar to females; however, the incidence of lung carcinomas in males was slightly higher (4-14%). The normal ranges for hepatocellular adenomas and carcinomas in female mice were only 0-8% and 0-5%, respectively. The incidence of these tumors in male CD-1 mice is higher (0-12% and 0-12%, respectively). Based on this historical control data, the incidence of the lung and liver tumors in both sexes is clearly outside the normal range.

Other non-neoplastic lesions were identified. In the initial pathology report, a decrease in testes weight associated with testicular hypoplasia (histologically) was observed at 2000 ppm (300 mg/kg). In the second pathology report, there was a statistically significant increase in the incidence of multifocal alveolar cell proliferation in females and hepatocytomegaly (liver hypertrophy) in both sexes at the mid- and high-dose levels. An increase in hepatocytomegaly was also observed at 20 ppm, but the increase was not statistically significant. There was also a significant increase in the mortality rate in the males at 2000 ppm. DPR determined the NOEL was 20 ppm (3 mg/kg/day) based on the hepatocytomegaly in both sexes and the alveolar cell proliferation in females. The U.S. EPA also set the NOEL at 20 ppm based on lung and liver weight increases in females and decreased testes weight and deaths in males. Both the U.S. EPA and DPR considered the Bio/dynamics Mouse II study positive for an oncogenic effect. The one major deficiency that DPR identified for this study was inadequate husbandry. The U.S. EPA did not give this study a CORE grade.

Wellcome, 1980: Wellcome conducted a study in which 75 CFLP mice/sex/dose were fed permethrin (purity unknown, *cis*:*trans* ratio 25:75) in the diet at 0, 10, 50, 250 mg/kg/day for 91 weeks (James, 1980). There was also equivocal evidence of an oncogenic effect in this study. The incidence of benign lung tumors in female mice was significant by both trend analysis and pair-wise comparison with the controls at the high-dose level, 250 mg/kg/day (Table 6). The incidence of malignant lung tumors in females was also significant by trend analysis. When the incidence of benign and malignant lung tumors were combined for this study, it was highly significant by trend analysis and when compared to controls at the high-dose level. Furthermore, the latency period for lung tumors in the high-dose females was significantly reduced (7.1%) by the Student's t-test ($p < 0.05$). However, the incidence of lung tumors, even at the high-dose level, was within the normal range (10-30%) for this strain based on the historical control data submitted by the registrant. The incidence in the controls was unusually low. Initially, DPR did not believe this study demonstrated a possible oncogenic effect by itself. However, when the mouse studies were later reviewed collectively, DPR concluded the findings from this study supported an oncogenic effect. The U.S. EPA considered it positive for lung tumors.

Non-oncogenic effects observed in the high-dose animals (increased liver weights in males, increased kidney weights in females and cuboidal/columnar metaplasia in alveolar

Table 7. Incidence of Pulmonary Tumors in Bio/dynamics Rat Chronic Toxicity/ Oncogenicity Study after Administering Permethrin in the Diet for 24 Months[a]

	Dose Level (ppm)			
	0	20	100	500
	MALES			
Adenoma	1/59 (2%)	3/55 (5%)	4/57 (7%)	5/56 (9%)
Adenocarcinoma	0/59 (0%)	0/55 (0%)	2/57 (3%)	0/56 (0%)
Combined	1/59 (2%)	0/55 (5%)	6/57 (11%)	5/56 (9%)
	FEMALES			
Adenoma	1/56 (2%)	0/58 (0%)	2/58 (3%)	2/57 (4%)

a The incidence was expressed as the number of tumor bearing animals per animals at risk. The number in parentheses represents the incidence in percentage.

increase in the incidence of focal disturbances in the growth pattern of follicular cells in the thyroid in high-dose males that died during weeks 53 to 103. The NOEL and LOEL were 10 and 50 mg/kg/day, respectively, based on liver hypertrophy. The major deficiencies identified by DPR were the lack of information regarding the diet analysis and purity of the test article. Despite these deficiencies, the U.S. EPA gave this study a CORE grade of "guideline" with the same NOEL.

Capsule-Dog

In a one-year chronic dog study conducted by ICI, 6 beagle dogs/sex/group were given permethrin (purity 92.5%, *cis*:*trans* ratio 32:60) in capsules with corn oil as the vehicle at 0, 5, 100 or 1000 mg/kg/day (Kalinowski *et al.*, 1982). The NOEL and LOEL were 5 and 100 mg/kg/day, respectively, based on liver hypertrophy, adrenal alterations (swelling and vacuolation of cells in the zona reticularis and focal degeneration of the cortex), and decreased weight gain. DPR found no deficiencies with this study. The U.S. EPA gave this study a CORE grade of "guideline" with the same NOEL.

D. GENOTOXICITY

Gene Mutation

Three reverse mutation assays have been conducted with *Salmonella typhimurium* strains, TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation (Longstaff, 1976; Simmon, 1976; Callander, 1989). All were negative, but only the study conducted by ICI (Callander, 1989) meets the FIFRA guidelines according to DPR. A mouse lymphoma L5178Y/TK+/- assay was also conducted for permethrin, with and without metabolic activation (Clive, 1977). There was no evidence of mutagenicity in this study and DPR found no deficiencies in the study conduct. Published reports on the mutagenicity of permethrin were also negative (Miyamoto, 1976; Moriya *et al.*, 1983; Pluijmen *et al.*, 1984; Garrett *et al.*, 1986; Pednekar *et al.*, 1987; Gupta *et al.*, 1990; Sebastian and Korte, 1990; Johnson, 1991). These include several Ames assays, two *Escherichia coli* reverse mutation assays, an assay with V79 Chinese hamster cells, an assay with marine bioluminescent bacteria, *Photobacterium phosphoreum*, and a *Drosophila* sex-linked recessive lethal (SLRL) assay. The validity of the SLRL assay is questionable because very low doses were used in this assay due to the high toxicity of permethrin in insects.

Structural Chromosomal Aberrations

Two negative *in vivo* micronucleus assays were submitted to DPR by registrants. In a study conducted ICI Americas Inc., male rats (12 controls and 8/treatment group) were injected i.p. with permethrin (94% purity, *cis*:*trans* ratio 40:60) once or in 5 daily doses at 0, 600, 3000 or 6000 mg/kg (Anderson and Richardson, 1976). Rats were sacrificed 24 hours after the single injection and 6 hours after the last dose with multiple injections. DPR found this study acceptable. In a second study conducted by Zeneca Inc. (formerly ICI Americas Inc.), 5 CD-1 mice/sex/dose/time were administered permethrin (93.1% purity; *cis:trans* ratio not reported) by oral gavage in corn oil at 200 (males) or 320 (females) mg/kg (Fox and Mackay, 1993). The mice were sacrificed at either 24 or 48 hours after dosing. However, this study was unacceptable to DPR since there was no analysis of the dosing material to confirm concentration and stability.

Two dominant lethal studies submitted by registrants were also negative. In a study conducted by Inveresk Research International, 15 male CD-1 mice/group were given permethrin (purity 95.3%, *cis*:*trans* ratio 40:60) orally on 5 consecutive days at 0, 15, 48 or 150 mg/kg/day (McGregor and Wickramaratne, 1976a). In a Wellcome study, 10 male CD-1 mice/group were administered permethrin (purity unknown, *cis*:*trans* 25:75) orally at 0 or 452 mg/kg/day, for 5 days (Chesher *et al.*, 1975). DPR found major deficiencies in both studies. The Inveresk study had no explanation for the deaths of 5% of its females and an insufficient number of pregnant females per interval. The Wellcome study had only one dose level, an inadequate number of pregnant females, variable fertility and number of dead implants making interpretation of results difficult. The U.S. EPA only reviewed the Wellcome study and did not give it a CORE grade, but determined it was not mutagenic at 452 mg/kg.

The results from published reports on the clastogenic effects of permethrin were inconsistent. Woodruff et al. (1983) reported negative results from a test for partial or complete chromosome loss in *Drosophila melanogaster*. In this test, males were administered permethrin in a feeding solution at 5 ppm for 3 days prior to mating with untreated *mus*-302 repair defective females. The F1 male progeny were screened for chromosome loss. The sensitivity of this assay is not known since this is not a commonly used assay for chromosomal aberrations. The findings

from this study are also questionable because only low doses were tested due to the high toxicity of permethrin to insects.

Hoellinger et al. (1984) also reported negative results from an *in vivo* micronucleus test at the 13th Annual Meeting of the European Environmental Mutagen Society. However, the abstract lacked sufficient information (number, sex and species/strain of animals, purity and *cis*:*trans* ratio of permethrin, dose levels, route of administration) to make interpretation of their findings possible. In a subsequent study, Hoellinger et al. (1987) reported a slight, but significant ($p < 0.01$) increase in micronuclei (0.71% vs. 0.25% in control) when permethrin was administered in olive oil by gavage at 139 mg/kg to female rats 30 and 6 hrs before removing the bone marrow. Paldy (1981) also reported a slight, but significant increase ($p < 0.05$) in chromosomal aberrations (5% vs. 2%) in bone marrow from mice. In this study, 10 male CFLP mice/group were administered permethrin (purity and *cis*:*trans* ratio unknown) orally once at 150 mg/kg or in 5 daily doses at 45.2 mg/kg. The animals were sacrificed 24 hours after the last dose and the bone marrow was examined microscopically for chromatid gaps, isogaps, breaks, and chromosome type deletions with acentric fragments and translocations. A dose-related increase in micronuclei was observed in an *in vitro* assay using human lymphocytes without metabolic activation (Herrera *et al.*, 1992). This increase was not observed with metabolic activation; however, due to the difference in the incubation time with metabolic activation, it is unclear if the metabolic activation suppressed this genotoxic effect or there was insufficient time to produce this effect. Barrueco *et al.* (1992) also reported a dose-related increase in chromosomal aberrations without metabolic activation. The incubation time was shorter with metabolic activation which may explain the lack of response with the metabolic activation.

Other Genotoxic Effects

The induction of unscheduled DNA synthesis (UDS) by permethrin was examined in primary rat hepatocytes in an ICI study (Trueman, 1988). There was no evidence of induced DNA repair in this study. DPR did not find any deficiencies with this study. Garrett et al. (1986) reported negative findings for permethrin using the *E. coli* polA assay, the *Bacillus subtilis* rec assay, the *Saccharomyces cerevisiae* D3 mitotic recombination assay, and the UDS assay in human lung fibroblasts. Miyamoto (1976) also reported negative findings with the *E. coli* w3623 polA, uvrA, and recA strains, *B. subtilis* M45 recA strain, and the *S. typhimurium* TA1538 uvrB strain. Herrera *et al.* (1992) reported a slight increase in sister chromatid exchanges in an *in vitro* assay with human lymphocytes without metabolic activation. There were differences in the response (one negative, one positive) between the two donors when metabolic activation was added. Hasegawa and Ito (1992) found no increase in altered foci (glutathione *S*-transferase positive foci) in the livers of rats exposed to permethrin in the diet at 4,000 ppm for 6 weeks after an initial dose of diethylnitrosamine (200 mg/kg) 2 weeks earlier. One week after permethrin exposure began, the rats were subjected to a two-thirds partial hepatectomy.

E. REPRODUCTIVE TOXICITY

Bio/dynamics, 1977: Twelve male and 24 female Long-Evans rats were fed permethrin (purity unknown, *cis*:*trans* ratio 40:60) at 0, 20 or 100 ppm (0, 1 or 5 mg/kg/day)[6] for 3 generations with 2 liters per generation (Schroeder and Rinehart, 1977). No treatment-related adverse reproductive effects were found, but the study had several major deficiencies that were identified by DPR. These included the lack of a MTD and the absence of histopathology on the parental animals. The NOEL was greater than the highest dose tested, 100 ppm (50 mg/kg/day).

ICI, 1977: A possible adverse developmental effect was identified in another reproductive toxicity study conducted by Hodge *et al.* (1977) in which 12 male and 24 female Wistar-derived rats were administered permethrin (purity 94.0-98.9%, *cis*:*trans* ratio 40:60) in the feed at 0, 500, 1000 or 2500 ppm (0, 25, 50 or 125 mg/kg/day)[6] for 3 generations with 2 litters per generation. Buphthalmos, described clinically as a large red eye and histopathologically as a persistent pupillary membrane, was observed in both generations of weanlings at all treatment levels tested (Table 8). While the incidence of buphthalmos was low, < 2% of the high-dose pups were affected, there was a highly

Table 8. Incidence of Buphthalmos and Liver Hypertrophy Among Neonates in an ICI Three-Generation Rat Reproductive Toxicity Study[a]

	Dose Level (ppm)			
	0	500	1000	2500
Buphthalmos				
Pups Affected	0/1252^{+++} (0%)	2/1241 (0.2%)	18/1383*** (1.3%)	19/1408*** (1.3%)
Litters Affected	0/121^{+++} (0%)	1/120 (0.8%)	14/130*** (10.8%)	15/131*** (11.4%)
Liver Hypertrophy				
F3b Pups Affected	1/20^{+++} (5%)	6/20* (30%)	11/20*** (55%)	18/20*** (90%)

[a] The number in parentheses represents the incidence in percentage.
$^{+++}$ Significant trend at $p < 0.001$ based on a dose-weighted chi-square trend test.
* Significantly different from the control group ($p < 0.05$) based on the Fisher's exact test.
*** Significantly different from the control group ($p < 0.001$) based on the Fisher's exact test.

E. REPRODUCTIVE TOXICITY (continued)

significant dose-related trend. The finding that genetic factors may be involved in the etiology of this defect (Nishimura and Okamoto, 1976) has raised the possibility that the method of parental selection, and not the test compound, resulted in the skewed distribution of affected litters. Pedigree data from the breeding colony suggests a multifactorial mode of inheritance (additive effect of several liability genes and environmental exposure) for buphthalmos. Evidence supporting this mode of inheritance include: absence of identified carrier males in the pedigrees of 4 of the 30 litters affected; lack of an association between consanguinity and number of affected pups per litter, and the presence of a dose response. The observation of whole body tremors in the dams around the time of parturition has also been suggested as a possible cause of the eye defect. The lack of an association between convulsions and birth defects in mice (Finnell and Chernoff, 1982), along with the absence of an association between maternal tremors and buphthalmos in the present study, rules out this possibility as a cause of the eye defect. Based on this rationale, DPR concluded the incidence of buphthalmos, even at the low-dose level, was toxicologically significant with a developmental NOEL less than 500 ppm (25 mg/kg/day).

Centrilobular hypertrophy, evaluated histologically only in F3b weanlings, was observed at all dose levels (Table 8). This effect was not considered an adverse reproductive or developmental effect, but rather a systemic effect similar to that observed in adult rats in the combined chronic toxicity/oncogenicity studies at higher dose levels. The parental NOEL was 500 ppm (25 mg/kg/day) based on tremors. DPR found no major deficiencies with this study. The U.S. EPA gave it a CORE grade of "guideline" with a NOEL less than 500 ppm for offspring.

F. DEVELOPMENTAL TOXICITY

Gavage-Mouse

Wellcome, 1974: No treatment-related developmental effects were seen in a mouse teratology study in which 20-23 female CD-1 mice were given permethrin (purity and *cis*:*trans* ratio unknown) in corn oil by oral gavage at 0 or 400 mg/kg/day from days 6-15 of gestation (James, 1974a). However, DPR identified several major deficiencies with this study including the lack of maternal toxicity, one dose level was tested, no purity of test material was reported and there was no analysis of the dosing solutions. The maternal and developmental NOELs were greater than 400 mg/kg, the highest dose tested. The U.S. EPA gave this study a CORE grade of "minimum" with no teratogenic, fetotoxic or maternal effects at 400 mg/kg.

Gavage-Rat

Wellcome, 1974: Twenty to 23 female Wistar rats were given permethrin (purity and *cis*:*trans* ratio unknown) in corn oil by oral gavage at 0 or 200 mg/kg/day on days 6-16 of gestation in the Wellcome study (James, 1974b). There was no evidence of a teratogenic or developmental effect. However, an MTD may not have been reached since there was no clear evidence of maternal toxicity at 200 mg/kg/day. The maternal and developmental NOELs were greater than or equal to 200 mg/kg/day. DPR found this study unacceptable.

F. DEVELOPMENTAL TOXICITY (continued)

Inveresk Research International, 1976: Groups of 20 female CD Sprague-Dawley rats received permethrin (purity 95.3%, *cis*:*trans* ratio 40:60) in corn oil by oral gavage at 0, 22.5, 71 or 225 mg/kg/day on days 6-16 of gestation. There was also no evidence of a teratogenic or developmental effect in this study. However, an MTD may not have been reached based on the lack of any evidence of maternal toxicity at 225 mg/kg/day, the highest dose tested. The maternal and developmental NOELs were greater than or equal to 225 mg/kg/day. This study was unacceptable to DPR.

ICI, 1988: Maternal and fetal toxicity was observed in a teratology study in which 24 pregnant Alpk:APfSD rats/group were administered permethrin (purity 93.9%, *cis*:*trans* ratio 38:62) in corn oil by oral gavage at 0, 15, 50 or 150 mg/kg/day on gestation days 7-16 (Hodge, 1988). The maternal toxicity included decreased food consumption and weight gain, tremors, and head flicks in dams at 150 mg/kg/day. The maternal effects were observed within the first few days of dosing. Decreased body weights and delayed ossification were also observed in fetuses at this dose level. Consequently, the maternal and developmental NOEL for this study was 50 mg/kg/day. DPR found this study acceptable.

Gavage-Rabbit

Wellcome, 1974: In the study conducted by James (1974c), 6-7 female Dutch belted rabbits received permethrin (purity unknown, *cis*:*trans* ratio 25:75) in corn oil by oral gavage at 0 or 400 mg/kg/day on gestation days 6-18. DPR identified numerous deficiencies in this study including inadequate number of pregnant females; only a single dose level was tested; no purity of test material was stated; there was no analysis of the dosing material; and no historical control data were provided. The maternal and developmental NOEL was greater than 400 mg/kg/day, the highest dose tested.

ICI, 1980: DPR found no major deficiencies in a teratology study in which 18 Dutch rabbits were given permethrin (purity 92.5%, *cis*:*trans* ratio 32:60) in a 0.5% Tween 80 aqueous vehicle by oral gavage at 0, 600, 1200 or 1800 mg/kg/day on days 6-18 of gestation (Richards *et al.*, 1980). Decreased weight gain and excessive fur in the stomach were observed at 1200 and 1800 mg/kg/day in the dams. Tremors were also observed at 1800 mg/kg/day. Embryotoxicity (increased post-implantation loss) occurred at 1200 and 1800 mg/kg/day. Mean fetal weights were lower at 1800 mg/kg/day. The maternal and developmental NOEL for this study was 600 mg/kg based on the decreased maternal weight gain and embryotoxicity, respectively.

G. NEUROTOXICITY

The California Birth Defects Prevention Act of 1984 (SB 950) requires registrants of organophosphate pesticides to submit a study for acute delayed neurotoxicity to DPR. Hens are the preferred species for this test since they are more sensitive to organophosphate-induced delayed neuropathy (OPIDN) than rodents. Although not required for synthetic pyrethroids, an acute delayed neurotoxicity test in hens was submitted to DPR and was negative. Peripheral nerve damage has been observed in rodents after administration of near lethal doses of several synthetic pyrethroids including permethrin (Vijverberg and van den Bercken, 1990). The pyrethroid-induced axonopathy differs from OPIDN in that the peripheral nerve damage is reversible and rodents are more sensitive than hens and dogs. Dose-related increases in beta-glucuronidase and beta-galactosidase activity were found in rats receiving 400 to 1200 mg/kg/day

by oral gavage for 7 days (Rose and Dewar, 1983). These enzymes are associated with repair processes indicating some peripheral nerve damage had occurred. There was evidence of peripheral nerve damage in several supplemental studies submitted to DPR (Glaister *et al.*, 1977; Okuno, 1976; James *et al.*, 1977).

Gavage-Hen

Huntingdon Research Centre, 1977: Groups of 15, 5, and 10 hens were given permethrin (12 g/kg, purity 94.9%, *cis*:*trans* ratio 36:59), TOCP (500 mg/kg) and water, respectively, by oral gavage, then observed for 21 days (Ross *et al.*, 1977). On Day 21, the test and negative control birds received a second dose and were observed another 21 days. Prior to redosing, the test birds were protected with atropine and 2-PAM. There was no evidence of peripheral nerve damage. DPR found no deficiencies with this study.

Diet-Rat

ICI, 1977: In a study conducted by Glaister *et al.* (1977), 10 Wistar-derived male rats/group were administered permethrin (purity 90.4%, *cis*:*trans* ratio 40:60) in the diet at 0, 2500, 3000, 3750, 4500, 5000 or 7500 ppm (0, 125, 150, 187.5, 225, 250 or 375 mg/kg/day)[6] for 14 days. Mortalities were observed at 5000 and 7500 ppm (8/10 and 10/10, respectively). Minor histological and ultrastructural changes were observed in the sciatic nerves of rats receiving 5000 ppm (250 mg/kg/day) including swelling and increased vesiculation of unmyelinated nerves, hypertrophy of Schwann cells, contraction of axoplasm and formation of myelin whorls in residual spaces and fragmentation of myelinated axons. The nerves from rats receiving 7500 ppm (375 mg/kg/day) were not examined because morphological changes were not expected to have developed in the time before the rats died (< 24 hours).

Sumitomo Chemical Co., 1976: Okuno (1976) observed swelling, nodal demyelination and disintegration of the sciatic nerves in SD-SLC rats (8 controls and 16 treated/sex) fed permethrin (93.3%) in the diet at 0 or 6000 ppm (0 or 300 mg/kg/day)[6] for 8 days. Three males and two females in the treatment group died.

Wellcome, 1976: In a study conducted by James *et al.* (1977), 10 female Wistar rats/group were fed permethrin (purity unknown) with different *cis*:*trans* ratios (90:10, 40:60, and 25:75) at 0 or 6000 ppm (0 or 300 mg/kg/day)[6] for 16 days. Vacuolation of myelinated fibers was the only neuropathological found. Interpretation of this finding is difficult because the incidence was not related to clinical signs, the lesion was seen in controls to some extent and complete histological examination of control animals were not performed.

H. IMMUNOTOXICITY

There is some evidence that permethrin causes immunosuppression. Permethrin inhibited the mitogenic response of murine lymphocytes *in vitro* at very low concentrations (~10^{-5} to 10^{-6} M) (Stelzer and Gordon, 1984). Immunosuppression was also observed in an *in vivo* study where chickens were fed diets containing permethrin at 0.01, 0.1 or 1.00 ppm for six weeks starting from the day of hatching (McCorkle *et al.*, 1980). After 6 weeks, the antibody response to *Brucella abortus*, a T-cell independent antigen, were depressed.

IV RISK ASSESSMENT

A. HAZARD IDENTIFICATION

Acute Toxicity

The effects observed with acute exposure are summarized in Table 9. In addition to the effects observed in the LD_{50}/LC_{50} studies, some effects observed in the developmental toxicity studies were also included as acute effects. These include maternal effects observed within the first 7 days of exposure and all fetal effects. Permethrin caused various neurological effects typical of pyrethroids. These signs (tremors, salivation, paresthesias, splayed gait, tail erection, depressed reflexes, and tip toe gait) were most apparent when administered by the inhalation route. At higher doses, rodents developed reversible axonal damage when exposed from 1 to 16 days (Rose and Dewar, 1983; Vijverberg and van den Bercken, 1990; Glaister *et al.*, 1977; Okuno, 1976; James *et al.*, 1977). Rodents appear to be more sensitive to this pyrethroid-induced axonopathy than dogs or hens. The lowest LOEL for the acute neurological signs was in rats with a single 4-hour inhalation exposure (240 µg/l or 38 mg/kg[1]) (Brammer, 1989). The NOEL was estimated to be 24 µg/l (3.8 mg/kg) by dividing the LOEL by an uncertainty factor of 10. Assuming a 50% respiratory uptake, the adjusted NOEL was estimated to be 1.9 mg/kg. With oral exposure, the lowest LOEL was 150 mg/kg which came from a developmental toxicity study (Hodge, 1988). The NOEL for this study was 50 mg/kg. Assuming the oral absorption rate is 70%, the adjusted NOEL was 35 mg/kg. With dermal exposure, the LOEL was 2000 mg/kg with a single, 24-hour exposure. The NOEL was estimated to be 200 mg/kg by dividing the LOEL by an uncertainty factor of 10. Assuming the dermal absorption in rats is 25%, the adjusted NOEL was 50 mg/kg. The adjusted NOEL from the developmental toxicity study appears to be lower than the adjusted NOEL from the dermal toxicity study (35 vs. 50 mg/kg). However, the oral NOEL was not used because the dosing was repeated over several days rather than on a single day, and the dose was administered in a bolus rather than more gradually as would occur with dermal or inhalation exposure. Although the acute neurological toxicity for permethrin appears to be greater by the inhalation route, the dermal route is the main route of exposure from the proposed use of this product. Therefore, both the inhalation and dermal NOELs were used in evaluating potential exposure.

Permethrin caused several adverse dermal effects when applied to the skin of laboratory animals including irritation and sensitization. Severe dermal irritation (desquamation, edema, thickening, scabbing and skin eruptions) was observed in an acute dermal toxicity study with the technical grade permethrin when applied at 20 mg/cm^2 and held in contact with the skin for 24 hrs with occlusive dressings (Robinson, 1989a). Moderate dermal irritation was observed with both the technical grade permethrin and the revised tick repellent formulation when applied at 50-80 mg/cm^2 and held in contact with the skin for 4 hours with semi-occlusive or occlusive dressings (Robinson, 1989b; Cerven, 1992). While the dermal irritation caused by the revised formulation appears to be less severe than that caused by the original formulation, it still appears to be primarily due to the inert ingredients since there was not a significant reduction in the response from the technical grade permethrin to the revised formulation. However, there is a strong possibility that under actual use conditions most of the inert ingredients will evaporate before reaching the skin. The label on the formulation states to spray the clothes outdoors while not being worn and then allow them to dry for at least 2-4 hours depending on the humidity.

Table 9. Acute Adverse Effects for Permethrin and Respective NOELs and LOELs[a]

Species	Exposure	Route/Effect	NOEL (mg/kg)	LOEL (mg/kg)	Ref.[b]
		Inhalation[c]			
Rat	Single, 4-hr	Piloerection, paw flicking, splayed gait, tremors, tip toe gait, tail erection	(3.8)[d]	38	1*
		Oral			
Rat	Single, gavage	Diarrhea, dehydration, urinary incontinence, piloerection, upward curvature of the spine	500	750	2*
Mouse	9 Days, gavage	None	400 (HDT)[e]	---	3
Rat	10 Days, gavage	None	200 (HDT)	---	4
Rat	10 Days, gavage	None	225 (HDT)	---	5
Rat	9 Days, gavage	Maternal: Reduced weight gain & food consumption, tremors, head flicks	50 50	150 150	6*
		Fetal: Reduced fetal weights, delayed ossification			
Rabbit	12 Days, gavage	None	400 (HDT)	---	7
Rabbit	12 Days, gavage	Maternal: Tremors	1200	1800	8*
		Fetal: Increased post-implantation loss	600	1200	
		Dermal			
Rat	Single, 24-hr	Systemic: Tip toe gait, urinary incontinence, upward curvature of the spine	(200)[d] (2)[d,f]	2000 20[f]	9*
		Local: Desquamation, edema, thickening, scabs, skin eruptions			

a NOELs = No-Observed-Effect Levels; LOELs = Lowest-Observed-Effect Levels
b References: 1. Brammer, 1989; 2. Ishmael, 1989; 3. James, 1974a; 4. James, 1974b; 5. McGregor and Wickramaratne, 1976b; 6. Hodge, 1988; 7. James, 1974c; 8. Richards *et al.*, 1980; 9. Robinson, 1989a.
c Inhalation dosages were converted to mg/kg by assuming that a rat breaths 160 l/kg in 4 hours (Zielhuis and van der Kreek, 1979).
d NOEL estimated by dividing the LOEL by an uncertainty factor of 10.
e HDT = Highest Dose Tested
f Estimated based on an exposure area of 6 cm x 4 cm and the average body weight from the rats in the study. Units are mg/cm^2.
* Acceptable based on FIFRA guidelines

Therefore, the risk for dermal irritation was evaluated based on exposure to the technical grade permethrin rather than the formulation. The dermal toxicity study for permethrin was selected for estimating a NOEL for dermal irritation because of the longer exposure period and more severe skin reactions. The NOEL was estimated to be 2 mg/cm^2 by dividing the LOEL by an uncertainty factor of 10.

Despite the fact that moderate sensitization was observed with the technical grade permethrin in a guinea pig maximization test, there was no evidence of dermal sensitization in patch tests when the tick repellent formulation was applied topically to guinea pigs and when a 40% permethrin solution was applied topically to human volunteers (Leah, 1989b; Shapiro, 1989d; Snodgrass, 1986). However, the patch test is not as sensitive a test for dermal sensitization as the maximization test in guinea pigs and possibly humans. A NOEL was not established for dermal sensitization since the design of these studies, in general, are not conducive to establishing a NOEL.

Subchronic Toxicity

The adverse effects associated with subchronic exposure to permethrin are summarized in Table 10. Included in this summary are some maternal effects observed in developmental toxicity studies after 7 days of exposure and all effects observed in reproductive toxicity studies. Neurological effects including tremors, convulsions, hyperexcitability (hypersensitivity), irritability and narcosis with nystagmus were also seen in the subchronic studies primarily at the higher doses. Liver effects (liver hypertrophy and eosinophilia) were also common. Liver hypertrophy appeared to be the most sensitive endpoint. The liver hypertrophy in rats was associated with induction of cytochrome P-450, aminopyrine-N-demethylase, and proliferation of the smooth endoplasmic reticulum (SER) (Hart *et al.*, 1977). These biochemical and ultrastructural changes were readily reversible after treatment was terminated (Bradbrook *et al.*, 1977). Some investigators considered the liver hypertrophy to be adaptive and not toxicologically significant (Ishmael and Litchfield, 1977; Kalinowski *et al.*, 1982; Hart *et al.*, 1977; Bradbrook *et al.*, 1977). However, DPR has concluded that the liver hypertrophy may be toxicologically significant given the increased incidence of liver tumors and other non-neoplastic effects in the liver (eosinophilia and increased peroxisomes in hepatocytes) in mice in the chronic exposure studies. The lowest LOEL for liver hypertrophy was 8 mg/kg/day which was observed in a 3 month feeding subchronic study in rats (Killeen and Rapp, 1976a). The NOEL in this study was 1.7 mg/kg/day. After correcting for oral absorption, the adjusted NOEL was 1.2 mg/kg/day. Although a higher NOEL was established in an acceptable 21-day dermal toxicity study which is a more significant route of exposure, this study was not used due to its shorter duration.

A possible developmental effect, buphthalmos, was observed in weanling rats in a reproductive toxicity study in the absence of maternal toxicity (Hodge *et al.*, 1977). It should be noted that buphthalmos was not reported in any of the teratology studies with permethrin. This absence may be attributed to differences in the methods used for fetal versus weanling examination. In fetal examinations, the eyes of the fetuses are closed at the time of examination, thereby making a diagnosis of buphthalmos extremely difficult, if not impossible. Fetal soft tissue examination of the optic region relies on the gross observation of Wilson freehand razor sections. This method does not allow for the detection of persistent pupillary membrane as did the

Table 10. Subchronic Adverse Effects for Permethrin and Respective NOELs and LOELs[a]

Species	Exposure	Route/Effect	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Ref.[b]
		Inhalation[c]			
Rat	6 hrs/day, 5 days/wk, 13 wks	Tremors, convulsions	60	120	1
Guinea pig	6 hrs/day, 5 days/wk, 13 wks	None	55 (HDT)[d]	---	
Dog	6 hrs/day, 5 days/wk, 13 wks	None	50 (HDT)	---	
		Oral			
Mouse	28 Days, diet	Eosinophilia of centrilobular hepatocytes	---	300	2
Rat	28 Days, diet	Tremors	100	200	3
Rat	3 Months, diet	Liver hypertrophy	1.7	8.0	4
		Tremors	8.0	42.8	
Rat	90 Days, diet	Tremors	100	200	5
Rat	6 Months, diet	Tremors, hypersensitivity, liver hypertrophy	101	203	6
Rat	3-gen., 2-litter, diet	None	5 (HDT)	---	7
Rat	3-gen., 2-litter, diet	Parental: Tremors	25	50	8*
		Neonatal: Buphthalmos, liver hypertrophy	(2.5)[e]	25	
Rabbit	12 days, gavage	Decreased weight gain, excessive fur in stomach	600	1200	9*
Dog	3 Months, capsule	Tremors	50	500	10
Dog	3 Months, capsule	Tremors, increased liver weight	100	2000	11
		Dermal			
Rat	6 hrs/day, 21 days	Systemic: None	500	---	12*
		Local: Desquamation, edema, scabs	(0.05)[e,f]	0.5[f]	

a NOELs = No-Observed-Effect Levels; LOELs = Lowest-Observed-Effect Levels

b References: 1. Metker, 1980; 2. Clapp *et al.*, 1977a; 3. Clapp *et al.*, 1977b; 4. Killeen and Rapp, 1976a; 5. Snodgrass and Cantu, 1986; 6. Kadota, 1975; 7. Schroeder and Rinehart, 1977; 8. Hodge *et al.*, 1977; 9. Richards *et al.*, 1980; 10. Killeen and Rapp, 1976b; 11. Edwards *et al.*, 1976; 12. Milbourn, 1989.

c Dosages were converted to mg/kg by assuming in the inhalation studies that a rat, guinea pig, and dog breathes 0.24, 0.11, and 0.10 m^3/kg, respectively, in 6 hours (Zielhuis and van der Kreek, 1979). In the oral studies, ppm were converted to mg/kg/day by assuming a mouse, rat, and dog consumes 0.15, 0.05, and 0.025 kg food per kg body weight per day, respectively (FDA, 1959).

d HDT = Highest Dose Tested

e NOEL estimated by dividing the LOEL by an uncertainty factor of 10.

f Estimated based on an exposure area of 6 cm x 4 cm and the average body weight from the rats in the study. Units are mg/cm^2.

* Acceptable based on FIFRA guidelines.

hhistological evaluation carried out on weanling rats in the reproductive toxicity study. Considering these differences, it is not surprising that concordance for buphthalmos was not achieved between the two study types. Since the estimated NOEL for buphthalmos (2.5 mg/kg/day) is higher than the lowest NOEL for liver hypertrophy (1.7 mg/kg/day), no further reduction in the NOEL used to evaluate subchronic exposure was needed to protect for this effect.

Dermal irritation (desquamation, edema, and scabs) were also observed in the 21-day dermal toxicity study. The LOEL for this endpoint was 50 mg/kg/day. Using the average body weight from the study and the area of the application site, the LOEL was converted to 0.5 mg/cm^2. The NOEL was estimated to be 0.05 mg/cm^2 by dividing the LOEL by an uncertainty factor of 10.

Chronic Toxicity

The adverse effects observed with chronic exposure to permethrin are summarized in Table 11. Liver hypertrophy was the most common non-oncogenic effect observed in chronic studies including two rat chronic studies (Ishmael and Litchfield, 1977; McSheehy *et al.*, 1980), two mouse oncogenicity studies (Ishmael and Litchfield, 1977; Tierney and Rinehart, 1979), and one dog chronic study (Kalinowski *et al.*, 1982). The lowest LOEL for liver hypertrophy with chronic exposure was 50 mg/kg/day which was observed in two different mouse oncogenicity studies (Ishmael and Litchfield, 1988; McSheehy *et al.*, 1980). Other effects on the liver were seen including peroxisome proliferation and eosinophilia which were seen in mice at 150 mg/kg/day (Ishmael and Litchfield, 1988). In addition to the liver effects, several other effects were observed with chronic exposure to permethrin including testicular hypoplasia in male mice at 300 mg/kg/day (Tierney and Rinehart, 1979), alveolar cell proliferation in female mice at 375 mg/kg/day (Tierney and Rinehart, 1979), focal disturbances in the growth pattern of follicular cells of the thyroid gland of male rats at 250 mg/kg/day (McSheehy *et al.*, 1980), and adrenal lesions (swelling and vacuolization of cells in the zona reticularis and focal degeneration of the cortex) and decreased body weight gain in dogs at 100 mg/kg/day (Kalinowski *et al.*, 1982). The lowest NOEL for the various chronic effects was 3 mg/kg/day based on the alveolar cell proliferation (females) and liver hypertrophy (both sexes) (Tierney and Rinehart, 1979). After correcting for oral absorption, the adjusted NOEL was 2.1 mg/kg/day.

Weight of Evidence for Oncogenicity

There is evidence of an oncogenic effect from permethrin in three out of the four mouse oncogenicity studies. In an ICI study, there was a positive trend in the incidence of benign lung tumors in males and in malignant lung tumors in females (Ishmael and Litchfield, 1988). The incidence of benign lung tumors in females in a Wellcome study was significant by both trend analysis and pair-wise comparison with controls at the high-dose level, 250 mg/kg/day (James, 1980). The female mice in this study also had a increase in malignant lung tumors which exhibited a dose-related trend. However, the most persuasive evidence of an oncogenic effect was from the Bio/dynamics Mouse II study in which the incidence of benign lung and liver tumors in females was highly significant by both trend analysis and pair-wise comparison with the

Table 11. Non-Oncogenic Chronic Adverse Effects for Permethrin and Respective NOELs and LOELs[a]

Species	Exposure	Effect	NOEL[b] (mg/kg/day)	LOEL (mg/kg/day)	Ref.[c]
Mouse	2 years	Mortality (M)	75	600	1
Mouse	98 weeks	Liver: SER[d] proliferation, eosinophilia, increased peroxisomes in hepatocytes	---	150	2
Mouse	2 years	Alveolar cell proliferation (F), liver hypertrophy (M&F)	3	75(M) 375(F)	3
Mouse	91 weeks	None	250 (HDT)[e]	---	4
Rat	2 years	Enzyme induction, liver hypertrophy, histological changes in liver cells	25	50	2*
Rat	2 years	None	25 (HDT)	---	5
Rat	2 years	Liver hypertrophy	10	50	6
Dog	1 year	Liver hypertrophy, adrenal alterations, decreased weight gain	5	100	7*

a NOEL = No-Observed-Effect Level; LOEL = Lowest-Observed-Effect Level
b Dosages in ppm were converted to mg/kg/day by assuming a mouse, rat, and dog consumes 0.15, 0.05, and 0.025 kg food per kg body weight per day, respectively (FDA, 1959).
c References: 1. Hogan and Rinehart, 1977; 2. Ishmael and Litchfield, 1988; 3. Tierney and Rinehart, 1979; 4. James, 1980; 5. Braun and Rinehart, 1977; 6. McSheehy *et al.*, 1980; 7. Kawlinowski *et al.*, 1982.
d SER = Smooth Endoplasmic Reticulum
e HDT = Highest Dose Tested
* Acceptable study based on FIFRA guidelines

controls at the mid- and high-dose levels (375 and 750 mg/kg/day) (Tierney and Rinehart, 1979). There was also an increase in benign liver tumors in males in this study that was significant at all dose levels and had a dose-related trend. There was additional evidence of an oncogenic effect from these three studies in that the latency period for lung tumors was shortened at the high-dose level, although the difference was only statistically significant in the Wellcome study.

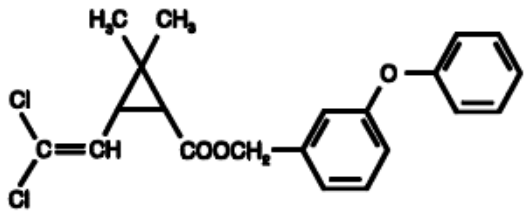
The evidence for oncogenicity from the rodent bioassays, however, is limited for the following reasons. First, the incidence of lung tumors in the ICI and Wellcome mouse studies were within the normal range based on historical control data for the Swiss-derived strains used in these studies (Alderley Park SPF Swiss-derived and CFLP). Lung tumors are relatively common

(10-50%) in Swiss mice 16 months or older (Percy and Jonas, 1971; Sher, 1974). Second, the tumor response was primarily an increase in benign tumors. Third, the increased incidence in tumors was not significant until dose levels approached the MTD (≥ 250 mg/kg/day). The MTD appears to be around 300-600 mg/kg/day based on an increase in mortalities in males at the high-dose level in two studies (Bio/dynamics Mouse I and II) and SER proliferation in another study (ICI). Finally, there was no statistically significant increase in tumors in the three rat oncogenicity studies (Ishmael and Litchfield, 1988; Braun and Rinehart, 1977; McSheehy *et al.*, 1980).

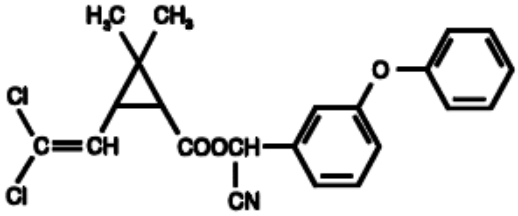
Interpretation of the mouse oncogenicity studies is confounded by problems in the conduct of these studies. DPR did not find any of the mouse oncogenicity studies acceptable based on the FIFRA guidelines. The lack of dose level justification was a problem in all except the Bio/dynamics Mouse II study. In two studies (Bio/dynamics Mouse I and ICI) there was inadequate analysis of the diet for permethrin concentration. These two studies had other problems including changes in dose levels (Bio/dynamics Mouse I), misdosing (ICI), and lack of pathology for non-neoplastic lesions (ICI). The Wellcome study lacked test article characterization, and the Bio/dynamics Mouse II study had inadequate husbandry.

The genetic toxicology data for permethrin are equivocal. Many of the studies were negative including tests for gene mutation (several Ames tests, two *E. coli* WP2 uvrA assay, an assay with V79 Chinese hamster cells, a *Drosophila* SLRL test, an assay with *Photobacterium phosphoreum*, and a mouse lymphoma assay), structural chromosomal aberrations (three *in vivo* micronucleus assays, two dominant lethal tests, and an assay for partial or complete chromosome loss in *Drosophila*) and other genotoxic effects (two UDS assays, an *E. coli* polA assay, a *B. subtilis* rec assay, a *S. cerevisiae* D3 mitotic recombination assay, and an *in vivo* assay for altered liver foci in rats) (Longstaff, 1976; Simmon, 1976; Callander, 1989; Clive, 1977; Moriya *et al.*, 1983; Pluijmen *et al.*, 1984; Garrett *et al.*, 1986; Pednekar *et al.*, 1987; Gupta *et al.*, 1990; Sebastian and Korte, 1990; Johnson, 1992; Anderson and Richardson, 1976; Fox and Mackay, 1993; McGregor and Wickramaratne, 1976a; Chesher *et al.*, 1975; Woodruff *et al.*, 1983; Hoellinger *et al.*, 1984; Trueman, 1988; Hasegawa and Ito, 1992). However, there are two published *in vivo* cytogenetic tests that were positive, a micronucleus assay in female rats, and a chromosomal aberration assay in mice (sex not identified) (Hoellinger *et al.*, 1987; Paldy, 1981). In both studies, the responses were slight, but statistically significant. An increase in micronuclei, chromosomal aberrations, and sister chromatid exchanges were also observed in *vitro* assays with human lymphocytes without metabolic activation (Herrera *et al.*, 1992; Barrueco *et al.*, 1992). Interpretation of the results from the various positive studies is difficult since they were all in published reports which lack sufficient information to evaluate the quality of these studies. However, without adequate justification to dismiss the positive studies, DPR assumed they were conducted properly and the clastogenic effects were treatment-related.

Permethrin is structurally similar to another synthetic pyrethroid, cypermethrin, which also produced lung tumors in female Swiss mice at 1600 mg/kg/day (WHO, 1989). The structures of the two pyrethroids are identical except cypermethrin has a cyano group attached to the phenoxybenzyl moiety.



Permethrin



Cypermethrin

The genetic toxicology studies for cypermethrin were negative except for two tests for chromosomal aberrations. One of these tests was an *in vivo* sister chromatid exchange assay in mouse bone marrow cells. Cypermethrin also induced a significant increase in micronuclei in mouse bone marrow cells when administered in the diet at 900 mg/kg for 7 or 14 consecutive days or when applied topically 4 times at 360 mg/kg. When cypermethrin was administered intraperitoneally (a single injection at 60 or 180 mg/kg or 2 to 3 injections at 60 mg/kg), no significant increase in micronuclei was observed.

DPR has concluded that the possible oncogenic effect of permethrin in mice cannot be ignored despite the deficiencies in these studies. The evidence from at least two of the mouse studies (Wellcome and Bio/dynamics Mouse II) is fairly compelling. In our opinion, the deficiencies in these studies could result in a false negative study, but not in a false positive study. The oncogenic effect does not appear to be limited to benign tumors, one tumor site, or one sex. Furthermore, the latency period was significantly shorter in one of these studies. Although all the gene mutation tests for permethrin were negative, several cytogenetic tests were positive. Permethrin is nearly identical in structure to cypermethrin which produced a similar tumor response in female Swiss mice and was positive in two tests for chromosomal aberrations. Therefore, DPR has decided that the prudent approach is to assume that permethrin is possibly genotoxic and to use a linear, low dose extrapolation model to assess the oncogenic risk to humans.

Quantitative Assessment of Toxicological Effects

The strongest evidence of an oncogenic effect was found in the Bio/dynamics Mouse II study. Therefore, the tumor incidence from this study was used to calculate the oncogenic potency for permethrin. Oncogenic potency estimates (Table 12) for females were calculated using the linearized multistage model, GLOBAL86. Dosages were converted to human equivalent dosages using a scaling factor of body weight to the 3/4 power. A maximum likelihood estimate (MLE) and 95% upper bound (UB) (i.e., theoretically highest possible estimate) for oncogenic potency were calculated for each tumor site in which there was a significant trend. Oncogenic potency estimates were also calculated for the liver tumors in the males of the Bio/dynamics Mouse II study using the multistage-Weibull time-to-tumor model, MULTI-WEIB, since poor survival may have affected the incidence of these tumors.

The highest oncogenic estimates were for combined liver tumors in the males from the Bio/dynamics Mouse II study; however, these values were not used for the risk calculations because it is uncertain what effect the poor survival had on the incidence and liver tumors are

Table 12. Maximum Likelihood Estimates (MLE) and 95% Upper Bound (UB) Estimates of Oncogenic Potency from the Bio/dynamics Mouse II Study (Tierney and Rinehart, 1979)

Tumor Type	Sex	MLE	95% UB
		$(mg/kg/day)^{-1}$	
Alveolar cell adenomas	F	2.9×10^{-3}	4.4×10^{-3}
Alveolar cell carcinomas	F	1.4×10^{-3}	2.5×10^{-3}
Lung Tumors Combined[a]	F	5.7×10^{-3}	7.8×10^{-3}
Hepatocellular adenomas	F	4.9×10^{-3}	6.3×10^{-3}
Liver Tumors Combined[a]	F	4.8×10^{-3}	6.4×10^{-3}
Hepatocellular adenomas, Multistage-Weibull[b]	M	1.0×10^{-3}	2.0×10^{-3}
Liver Tumors Combined, Multistage-Weibull[a,b,c]	M	1.2×10^{-2}	2.4×10^{-2}

a The incidences of alveolar cell adenomas and carcinomas were combined for estimating the oncogenic potency in the lung. The incidences of hepatocellular adenomas and carcinomas were combined for estimating the oncogenic potency in the liver.
b The MLE and 95% UB were calculated with the multistage-Weibull time-to-tumor model, MULTI-WEIB, assuming that tumors were fatal in animals that died. Included all animals examined, except those with autolysis where no liver tumor was found.
c Convergence failed, therefore, the values may not be accurate.

common in male mice. Furthermore, an increase in liver tumors were only observed in this one study, whereas an increase in lung tumors were seen in three of the four mouse oncogenicity studies. Therefore, the oncogenic potency estimates based on the lung tumors in females were used for the risk calculations. The MLE and 95% UB were 5.7×10^{-3} and 7.8×10^{-3} $(mg/kg/day)^{-1}$, respectively, for oncogenic potency.

B. EXPOSURE ASSESSMENT

The label for the permethrin tick repellent recommends spraying the front and back of a complete outfit (shirt, trousers and cap) for approximately 60 seconds each during which approximately half the contents of the container (85 g) is dispensed. The label states not to

retreat clothing within two weeks of the previous treatment. For park and forestry workers, an extreme-case exposure scenario was assumed in which a person wore a new change of clothing each work day for 5 days in a week, each of which was freshly treated. The same 5 sets of laundered clothing were then worn the second week, with a different set worn each work day. This two week treatment cycle was repeated throughout a 6-month period during which the ticks that carry Lyme disease were active.

Laundering does not remove all the permethrin residues from treated clothes (Snodgrass, 1988). Approximately 20-33% is removed with the first washing and 6% with the second washing. Consequently, the greatest exposure occurs towards the end of the tick season on the days the clothes are treated. The highest estimated dermal exposure to permethrin on these days was 0.75 µg/cm^2, assuming that 90% of the spray (76.5 g) reached the clothing with a surface area of approximately 18,000 cm^2, and a migration rate of the formulation from the fabric to the skin of 0.9% per day during the first week and 0.56% during the second week, a laundry removal rate of 20% with the first washing and 6% with the second washing (Appendix B). The absorbed dermal dosage of permethrin towards the end of the tick season was estimated to be as high as 3.9 µg/kg/day for a 70 kg person, assuming the dermal absorption rate was 2% during a 24 hr period. However, most of the permethrin exposure on these days occurred by the inhalation route. The estimated absorbed inhalation dosage was 7.1 µg/kg/day, assuming the application period was 120 seconds, 10% of the spray remained in the applicator's breathing zone with a volume of 2.5 m^3, the breathing rate was 29 liters per minute, and the respiratory uptake was 50%. The combined absorbed dermal and inhalation dosage on these days was 11.0 µg/kg/day.

During the six-month tick season, the average daily dermal exposure to permethrin for park and forestry workers was estimated to be 0.32 µg/cm^2. The absorbed daily dosage (ADD) represents the average daily dosage from both inhalation and dermal exposure during the tick season. For park and forestry workers, the ADD was estimated to be 4.2 µg/kg/day. Assuming a 6-month exposure period, the annual average daily dose (AADD) was 2.1 µg/kg/day. The lifetime average daily dosage (LADD) for park and forestry workers was 1.2 µg/kg/day assuming an exposure over 40 years of a 70 year lifespan.

Two exposure scenarios were developed for the general public. An extreme-case exposure scenario was similar to workers except the assumption was made that treated clothes were worn 7 days a week. All other assumptions were the same as workers, except there was no adjustment for lifetime exposure. Based on this scenario, the average daily dermal exposure for the general public during the tick season was estimated to be 0.44 µg/cm^2. The ADD was 5.9 µg/kg/day and the AADD was 3.0 µg/kg/day. A more likely exposure scenario for the general public assumed daily use on the weekends and a two week camping trip during the 6-month tick season. During the first week of the camping trip, 7 changes of freshly treated clothing were worn, then laundered and worn again the second week. Using this exposure scenario for the general public, the average daily dermal exposure during the tick season was only 0.15 µg/cm^2. The ADD and AADD were reduced to 3.2 and 1.6 µg/kg/day, respectively.

C. RISK CHARACTERIZATION

Acute Toxicity

The risk for acute effects is expressed as a margin of safety (MOS). The MOS is the ratio of the NOEL to the exposure dosage.

$$Margin\ of\ Safety = \frac{NOEL}{Exposure\ Dosage} \qquad \text{(Eq. 1)}$$

The hazard index is simply the inverse of the MOS.

$$Hazard\ Index = \frac{Exposure\ Dosage}{NOEL} \qquad \text{(Eq. 2)}$$

When NOELs are available for different routes of exposure and exposure occurs by more than one route, a combined MOS can be calculated. A combined MOS is the inverse of the sum of the hazard indices for each route.

$$Margin\ of\ Safety\ (Combined) = \frac{1}{Hazard\ Index_{route\ 1} + Hazard\ Index_{route\ 2}} \qquad \text{(Eq. 3)}$$

For acute effects, the highest single daily exposure dosage (11.0 µg/kg/day) was used to calculate the margin of safety. The adjusted NOELs for acute neurological effects by the dermal and inhalation routes were 50 and 1.9 mg/kg, respectively. The combined MOS for the neurological effects was 262. Approximately 98% of the combined hazard index was due to inhalation exposure.

The estimated MOS for acute dermal irritation from permethrin was 2667 based on the estimated NOEL of 0.2 mg/cm^2 and the highest daily dermal exposure (0.75 µg/cm^2). An MOS for dermal sensitization was not estimated since a NOEL was not established for this effect.

Subchronic Toxicity

A subchronic dermal toxicity study with the revised formulation was not available, so the MOS for dermal irritation had to be calculated using an estimated NOEL from a 21-day dermal toxicity study with the technical grade permethrin (0.05 mg/cm^2). The MOS for dermal irritation with repeated exposure to permethrin during the tick season was 156 for park and forestry workers based an average daily dermal exposure of 0.32 µg/cm^2. For the general public, the MOSs for dermal irritation were 112 using the extreme-case exposure scenario (average daily dermal exposure - 0.44 µg/cm^2) and 333 using the more likely exposure scenario (average daily dermal exposure - 0.15 µg/cm^2).

Although NOELs from subchronic inhalation and dermal studies were available, they were not used due to deficiencies with the studies. Therefore, a combined MOS was not calculated. The lowest adjusted NOEL for systemic effects with subchronic exposure was 1.2 mg/kg/day based on liver hypertrophy in a 3-month feeding study. The MOSs were calculated using this NOEL and the ADDs for different exposure scenarios. For park and forestry workers, the subchronic MOS was 286 based on an ADD of 4.2 µg/kg/day. For the general public, the subchronic MOSs were 203 for the extreme-case exposure scenario (ADD - 5.9 µg/kg/day) and 375 for the more likely exposure scenarios (ADD - 3.2 µg/kg/day).

C. RISK CHARACTERIZATION (continued)

Chronic Toxicity

Non-oncogenic Effects

A combined MOS could also not be calculated for chronic exposure since permethrin was only administered by the oral route in the chronic studies. The MOSs were calculated using the adjusted NOEL for chronic effects (2.1 mg/kg/day) and the AADDs for the different exposure scenarios. For park and forestry workers, the chronic MOS was 1,000 using an AADD of 2.1 µg/kg/day. For the general public, the chronic MOSs were 700 based on the extreme-case exposure scenario (AADD - 3.0 µg/kg/day) and 1,312 based on the more likely exposure scenario (AADD -1.6 µg/kg/day).

Oncogenic Effects

The estimated risk for oncogenic effects was calculated by multiplying the oncogenic potency factor (Table 12) by the exposure dosage.

Oncogenic Risk = *Oncogenic Potency Factor x Exposure Dosage* (Eq. 4)

Since the oncogenic potency factors were calculated using the external dosages, they were also adjusted by dividing them by the oral absorption rate, 70%. The resultant oncogenic potency factors for female lung tumors were 8.1×10^{-3} (MLE) and 1.1×10^{-2} (95% UB) $(mg/kg/day)^{-1}$. Using the extreme-case exposure scenario (AADD - 3.0 µg/kg/day) and the adjusted oncogenic potency factors for lung tumors in females, the estimated risk to the general public was between 2.4×10^{-5} (MLE) and 3.3×10^{-5} (95% UB). Using the more likely exposure scenario for the general public, the estimated risk decreased to between 1.3×10^{-5} and 1.8×10^{-5} for the general public (AADD - 1.6 µg/kg/day). Assuming exposure was limited to occupational use with park and forestry workers (LADD - 1.2 µg/kg/day), the estimated risk was between 1.0×10^{-5} and 1.3×10^{-5}.

D. RISK APPRAISAL

Exposure Assessment

The high lipophilicity of permethrin and its ability to bind to fibers, particularly cotton fibers, contribute to its persistence on clothing (Snodgrass, 1988; Braun *et al.*, 1990). It is unknown what effect, if any, the binding of permethrin to the fibers may have on its ability to migrate to the skin. Permethrin may bind so tightly to the fibers that it does not easily migrate. The effect of bleaching, ironing and other washing related activities on the persistence of permethrin on clothing is also unknown.

The highest dermal absorption rate in a human study was obtained with an isopropanol vehicle. The inert ingredients in the tick repellent formulation may result in a significantly lower or higher absorption rate. Dermal absorption could have also been underestimated since urinary excretion was followed for only 5 days and no pharmacokinetic data after intravenous injection in humans was available.

D. RISK APPRAISAL (continued)

DPR is concerned about the potential for misuse of this product since it will be available to the general public. Exposure was assumed to be one application per day, 2-7 days/week. The average person may not use this product as frequently, so the exposure dosage could be less. However, if the product is applied more frequently than directed or applied directly to the skin, the oncogenic risk increases significantly. Washing permethrin treated clothes with other untreated clothes may result in contamination of the untreated clothes, leading to higher exposure dosages (Braun *et al.*, 1990). The proposed label lacks specific laundering instructions to avoid contamination of untreated clothes.

Acute Toxicity

Generally, an MOS of at least 100 is considered adequate allowing for an uncertainty factor of 10 for interspecies variation and another uncertainty factor of 10 for intraspecies variation. The MOSs for the acute neurological effects were greater than 100. Although neonatal animals appear to be more sensitive to the acute neurotoxicity of permethrin, the difference in oral LD_{50} values between adults and neonates was less than 5 fold (Cantalamessa, 1993). This difference is well below the default uncertainty factor of 10 used to account for differences in sensitivity within the human population. Therefore, the intraspecies uncertainty factor was considered adequate to protect infants and children.

For local effects, an MOS greater than 10 if often considered adequate; however, due to the severity of the skin reactions at the LOEL and the uncertainty regarding the contribution of the inert ingredients to the dermal irritation under actual use conditions, an MOS greater than 100 would be preferable for adequate protection. The MOS for acute dermal irritation was greater than 100. The MOS may have been overestimated due to the uncertainty regarding the evaporation of the inert ingredients. However, it may have been underestimated since it is unknown to what extent the inert ingredients might accumulate on the fabric or migrate across the fabric to the skin.

Although an MOS could not be estimated for dermal sensitization, some cases of sensitization are expected in humans based on the moderate sensitization observed with the technical grade permethrin in a guinea pig maximization test. Furthermore, the calculation of an MOS for dermal sensitization may not be appropriate because it is uncertain if a threshold can be demonstrated for this effect.

Subchronic Toxicity

The MOSs for liver hypertrophy and dermal irritation with subchronic exposure to permethrin were above 100 for all three exposure scenarios. The same uncertainties regarding the contribution of the inert ingredients to the dermal irritation apply to the subchronic exposure as well. If the liver hypertrophy is only an adaptive response as some have proposed and is unrelated to the eosinophilia and liver tumors, the MOS for systemic effects with subchronic exposure may have been higher. However, the MOS would not increase dramatically because the next most sensitive endpoint with subchronic exposure was buphthalmos in neonates which had an estimated NOEL of 2.5 mg/kg/day (1.7 mg/kg/day after adjusting for oral absorption).

D. RISK APPRAISAL (continued)

Chronic Toxicity

Non-oncogenic Effects

The MOSs for alveolar cell proliferation and liver hypertrophy with chronic exposure to permethrin were greater than 100 for all three exposure scenarios. The uncertainties regarding the liver hypertrophy and oral absorption rate apply to chronic exposure as well. The MOSs for liver hypertrophy with chronic exposure may have been slightly overestimated since liver hypertrophy was also observed at the lowest dose in the Bio/dynamics Mouse II study on which the chronic NOEL was based (Tierney and Rinehart, 1979). However, the incidence at the lowest dose level was not statistically significant. Given the uncertainty regarding the toxicological significance of this endpoint, a further reduction of the NOEL by an additional uncertainty factor was not warranted.

Oncogenic Effects

Generally, an oncogenic risk level less than 10^{-6} is desirable. However, the negligible risk level for oncogenicity may range from 10^{-5} to 10^{-6}, depending on a number of factors such as the weight of evidence, uncertainty in exposure, etc. For permethrin, the genetic toxicology data is equivocal. Although two published *in vivo* cytogenetics tests were positive, all the other genetic toxicology studies were negative, including all the gene mutation tests and an acceptable *in vivo* cytogenetics test submitted by the registrant. Also, there is some evidence that permethrin causes immunosuppression in two published reports, suggesting a threshold mechanism may be involved. Permethrin inhibited mitogenic response in murine lymphocytes *in vitro* and depressed the antibody response to a T-cell independent antigen in chickens *in vivo*. Regardless, several of the oncogenic risk estimates for this permethrin tick repellent formulation were outside the range that is normally considered negligible and acceptable.

In 1981 the FIFRA Scientific Advisory Panel (SAP) reviewed all the rodent oncogenicity studies and concluded that none of the mouse studies were adequate for doing a quantitative risk assessment. They had serious concerns regarding the Bio/dynamics Mouse II study, in particular the pathological examination which was conducted by an independent laboratory. The SAP decided there was no clear indication of tissue examination by the pathologist during necropsy and were concerned about the selection of tissue for histological examination. The SAP also did not consider it appropriate to compare the tumor incidence from this study with historical control data because the study conduct compromised the findings.

More recently, the peer review committee for the Health Effects Division (HED) in the Office of Pesticide Programs at the U.S. EPA classified permethrin as a possible human carcinogen (EPA category C carcinogen) based on the evidence of oncogenicity in one species (mouse) and recommended a quantitative risk assessment approach for permethrin based on (a) two tumor types (liver and lung) in one species of which one (lung) was malignant, (b) the dose-related response in the mouse, (c) suggestive evidence in the Long-Evans rat and (d) supportive structure-activity relationship information (Ackerman, 1981). The U.S. EPA asked the FIFRA SAP for a second review of the permethrin oncogenicity data. The SAP agreed that permethrin was a category C carcinogen, but still did not recommend a quantitative risk assessment (Jaeger, 1989). Although the SAP did not support this approach, the HED's final decision was to do a quantitative risk assessment. The oncogenic potency factor calculated by the U.S. EPA for permethrin was 1.8×10^{-2} $(mg/kg/day)^{-1}$ based on the lung tumors in females from the Bio/dynamics Mouse II study (Gardner, 1990). The U.S. EPA has approved the use of permethrin on military combat

uniforms; however, exposure was assumed to be limited to 16 hours/day for 6 years over a 75 year lifespan (Gardner, 1990). FDA has also approved a permethrin lotion for head lice in humans which would involve direct exposure, but for a shorter time period.

V RISK MITIGATION

The Worker Health and Safety Branch determined that the exposure for Permanone Tick Repellent could not be further mitigated under the conditions of current use (Appendix D).

VI CONCLUSIONS

The risks for effects associated with the use of the revised Permanone Tick Repellent on human clothing were evaluated. Generally, a margin of safety of at least 100 is desirable when the NOEL is based on animal data to allow for interspecies and intraspecies variation. The margins of safety for acute, subchronic and chronic effects were all greater than 100 for both the general public and park and forestry workers.

The negligible risk level for oncogenicity may range from 10^{-5} to 10^{-6}, depending on a number of factors, such as, the weight of evidence, uncertainty in exposure, etc. The overall goal is a risk level no greater than 10^{-6}. Several of the oncogenic risk estimates were greater than the range that is normally considered negligible. Additional exposure to permethrin cannot be mitigated under the conditions of current use.

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VIII APPENDICES

APPENDIX A SB 950 Summary of Toxicology Data

APPENDIX B Human Exposure Assessment

APPENDIX C Oncogenicity Computer Model Printout

APPENDIX D Exposure Mitigation

APPENDIX A

SUMMARY OF TOXICOLOGY DATA

PERMETHRIN

SB 950 #231

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PERMETHRIN

Chemical Code # 2008, Tolerance # 378
SB 950 # 231

PERMETHRIN

January 9, 1987
Revised 12/9/87, 9/19/88, 12/8/89, 4/16/90, 5/30/90, 9/10/90, 5/9/91, 10/4/91, 6/25/93

I. DATA GAP STATUS

Combined rat:	No data gap, no adverse effect
Chronic dog:	No data gap, possible adverse effect
Onco mouse:	No data gap, possible adverse effect
Repro rat:	No data gap, possible adverse effect
Terato rat:	No data gap, no adverse effect
Terato rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotox:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 121635 and 989591 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T930625
Revised by Stanton Morris, 6/25/93

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

299 to 305 048981 to 048987, "21Z: Potential Toxicity and Oncogenicity in Dietary Administration to Rats for a Period of 104 Weeks", (Wellcome Foundation, and Life Science Research, LSR: 80/WRL003/283, 7/2/80). Permethrin, no purity stated; fed to Wistar rats, 60 + 15 (for hematology) per sex per group at 0, 10, 50 or 250 mg/kg/day; NOEL = 10 mg/kg (liver hypertrophy); 80% mortality in high dose males with earlier deaths starting at 4 months; unacceptable but possibly upgradeable (diet analysis and purity of test article.) Gee, 1/2/87.
EPA 1-liner: Guideline; NOEL = 10 mg/kg/day (increased liver weight, disturbance in thyroid growth at 250 mg/kg/day, body tremors.) Oncogenic potential negative. Note: One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.

**051, 052 989518, 989510, "PP557: Two Year Feeding Study in Rats", (ICI, 12/19/77, CTL/P/357). Permethrin, 10 batches ranging from 93.1% to 98.9%, cis: trans 36/62 to 44/55; fed in the diet to SPF Wistar-derived rats, 60/sex/group, at 0, 500, 1000 or 2500 ppm, 2 years; NOEL = 500 ppm (nominal); acceptable with minor variances (inadequate pathology tables - actual number of tissues examined not given, DOT and terminal sacrifices were not combined for non-neoplastic findings, 7/32 analyses of diet showed > 15% from nominal content of AI.) Christopher, 6/20/85 and Gee, 1/2/87.
EPA 1-liner: Minimum; Sys NOEL < 500 ppm (effects on liver - pharmacological). Oncogenic potential negative. Note: One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.

389 072756, "Chronic Toxicity and Carcinogenic Evaluation of Permethrin in Rats and Mice", Fundamental and Applied Toxicology, 11:308-322, 1988, (ICI Chemical Industries, 5/19/87). Permethrin technical (93.9% pure--nominal cis-trans ratio of 40:60) was fed in diet for 104 weeks to Alpk:AP (Wistar derived) rats at 0 (vehicle = diet), 500, 1000 or 2500 ppm (12/sex/group). An additional 12/sex/group were designated for an interim kill at 52 weeks. Swiss-derived mice were fed 0, 250, 1000 or 2500 ppm permethrin (100 mice-50/sex) for 98 weeks and 20/sex were designated for interim kill at 26 and 52 weeks. **No adverse effect.** RATS: Mortality $\leq$ 50%. NOEL = 500 ppm (tremors and hypersensitivity to noise during the first 2 weeks of the study at 2500 ppm; liver hypertrophy at $\geq$ 1000 ppm; vacuolated hepatocytes at 2500 ppm). No oncogenic effects were produced by permethrin. MICE: NOEL = 1000 ppm (slight elevation in benign lung tumor incidence in males; decrease in body weight gain). Benign lung tumors were not considered to represent a carcinogenic effect, however other studies (cited in the literature) have demonstrated lung tumors in mice at $\geq$ 2500 ppm permethrin. According to this study: "The conclusion of the USEPA (Federal Register 1982) and its SAP (Gray, 1981) was that permethrin has a low oncogenic potential in mice but none in the rat and that the oncogenic potential for humans was nonexistent or extremely low." The Joint Meeting on Pesticide Residues in 1982 concluded that based upon long-term rodent studies, permethrin was not oncogenic to humans (FAO, 1983). M. Silva, 11/16/89.

CHRONIC TOXICITY, RAT

087 989506, Draft of a study by Burroughs-Wellcome, Life Science Research, no date. Christopher, 6/26/85. See 48981-87.

010, 011, 022, 024 013347, 013348, 989535 and 989579, "A Twenty-four Month Oral Toxicity/Carcinogenicity Study of FMC 33297 in Rats", (Bio/dynamics, 11/30/77, Project no. 74R-1022). Permethrin, no purity stated - ratio given as cis:trans, 40:60 in memos of FMC; fed in the diet at 0, 20, 100 or 500 ppm to 60/sex/group, Long Evans rats, 2 years; unacceptable (dose selection with inadequate high dose - no significant signs of toxicity, no purity of test article, inadequate samplings and analyses of diet.) Christopher, 6/24/85. EPA 1-liner: Minimum; Sys NOEL = 20 ppm (liver changes - pharmacologic). Oncogenic potential negative. Note: One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.

009 013936 "A Pathologic and Morphometric Study of the Nervous System of Rats Fed FMC 33297." (P. J. Dyck et al., Mayo Clinic, 12/8/77) Long-Evans rats from the 2-year study and the two-generation study at Bio/dynamics were shipped to the Mayo Clinic for evaluation. See appropriate one-liners for further details. The highest dose was 500 ppm in the two-year study. Animals were perfused and peripheral nerves (sural and tibial), brain stem and spinal cord with ganglia were taken for histological examination by light microscopy. No treatment-related findings were reported. All groups, including controls, had some abnormalities. No worksheet. Gee, 5/9/91.

009 013928, One-year histopathology for 013347.

023 989515, Revised histopathology report for 013347.

278 050808, Summary of ophthalmological findings for 013347.

CHRONIC TOXICITY, DOG

****297 004866**, "Permethrin: One Year Oral Dosing in Dogs", (ICI, Alderly Park, UK, 2/24/82, Report No. CTL/P/647, Study No. PD0350). Permethrin, 92.5%, 32.3/60.2, cis/trans; given in gelatin capsules prepared with corn oil for 52 weeks at 0, 5, 100 or 1000 (reduced from 2000 after 2 days) mg/kg/day to 6/sex/group; high dose dogs received 2 or 3 capsules daily, others received one capsule - seven capsules prepared for each animal after weekly weighing; absorption measured by analysis of urine; neurological exams at pre-test and at 13, 26, 39 weeks and at term; NOEL = 5 mg/kg/day (liver hypertrophy, adrenal alterations and decreased weight gain in both sexes); no treatment-related neoplasms were reported. **Adverse effect** on adrenal glands at mid and high doses. Acceptable. Gee and Martz, 1/9/87.
EPA 1-liner: Guideline; NOEL = 5 mg/kg/day (increased alkaline phosphatase, increased liver weights and hepatocellular swelling.) At 1000 mg/kg/day - tremors, convulsions, in-co-ordination, excessive salivation, vomiting early in study; increase platelet count; decreased protein, albumin, and Ca^{++} levels; and increases in adrenal lesions; body weight loss.

ONCOGENICITY, RAT

See under combined rat.

ONCOGENICITY, MOUSE

087 989520, Draft of study by Burroughs-Wellcome, no date. Christopher, 6/26/85. See 048988 to 048997.

306 to 315 048988 to 048997, "Carcinogenicity Study in Mice with Permethrin (21Z73)", (Wellcome, 1980, HEFG-80-29). Permethrin, lot C8165-106, 25:75, cis:trans, no purity stated; fed to CFLP mice, 100/sex in controls, 75/sex/group in test groups, at 0, 10, 50 or 250 mg/kg/day for 91 weeks; NOEL = 250 mg/kg/day (HDT). Unacceptable (dose selection needs justification and purity of test article). Diets were prepared weekly and adjusted for body weight and food consumption. The incidence of lung tumors in high dose females was statistically significant in relation to the concurrent controls. Volume 315, Tab 47, presents historical control data as discussed with EPA showing the value for the females falls within the range and close to the mean while the concurrent control for the study is inordinately low. The conclusion, therefore, is the lung tumors are not of biological significance. In addition, two other oncogenicity studies in mice did not report this finding. Gee, 1/2/87.
EPA 1-liner: No CORE grade - 1/30/85; NOEL = 250 mg/kg/day (HDT). Study is considered positive for lung tumors. One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.
[Note: The setting of the NOEL at 250 mg/kg/day and the finding of the study as positive for lung tumors by EPA appears to be in conflict. Gee, 5/30/90]

012 013349, "A Twenty-four Month Oral Carcinogenicity Study of FMC 33297 in Mice", (Bio/dynamics, 11/30/77, Project no. 74-1100). Permethrin, no purity stated, 40:60, cis:trans ratio; fed in the diet at 0, 20, 500 or 4000 ppm to CD-1 mice, 75/sex/group over 2 years; doses were increased from 20, 100 and 500 ppm at week 21; apparent NOEL = 500 ppm (mortality); unacceptable (dose selection and changes, no purity of test article, inadequate samplings of diet for analysis - twice only in first year with none before dose change, time to tumor analysis needed.) Christopher, 6/27/85.
EPA 1-liner: Supplementary; Sys NOEL = 20 ppm. Not considered oncogenically positive.

279 050812, Histopathology report for 13349. Study remains unacceptable.

025 989529, Histopathology for 13349.

053, 054 989517, 989509, "PP557: Whole Life Feeding Study in Mice", (ICI, 12/28/77, CTL/P/359). Permethrin, 8 batches ranging from 94.0 to 98.9%, cis:trans ratio for each batch is included; fed in the diet at 0, 250, 1000 or 2500 ppm for 98 weeks, 70/sex/group. Unacceptable (inadequate analysis of diet over the study, mis-dosing incident with high and low diets being switched weeks 24 - 28 for 10 mice/group, questionable if adequate high dose). Christopher, 6/26/85. UNACCEPTABLE, supplemental information (065823) did not upgrade this study. (Gee, 9/16/88).
EPA 1-liner: No CORE grade; Sys NOEL = 250 ppm (liver effects - pharmacologic). Not oncogenic. Note: One of five studies considered in setting non-oncogenic NOEL of 5 mg/kg/day used for ADI determination.

053 989507, Interim report for 989517.

177 014918, "A Twenty-four Month Oral Carcinogenicity Study of FMC 33297 in Mice" (Biodynamics, 1976, 76-1695). Summary only. See #57754 for full report.

342 057754 "A Twenty-four Month Oral Carcinogenicity Study of FMC 33297 in Mice (Mouse II)." (Bio/Dynamics, Inc., 10/9/79, Project 76-1695)

Permethrin, technical, batches MRR 176 and MRR 807 were 94.5% and 96.7%, respectively; fed in the diet at 0, 20, 500 or 2000 ppm for males and 0, 20, 2500 or 5000 ppm for females - doses were lowered from 100, 2500, and 5000 ppm at month three at the sponsor's request - no rationale given; 75/sex/group Charles River CD-1, COBS mice; NOEL = 20 ppm (increased incidence of bronchioalveolar adenomas and hepatomas in females at mid- and high-doses, decreased testes weight and increased mortality in the high-dose males, increased hepatocellular carcinomas in mid-dose males, increase in hepatocytomegally). **Possible adverse neoplastic effect.** Initially reviewed as unacceptable (J. Gee, 12/1/87). Sponsor submitted data on test article purity and diet analysis (see 367 066541). EPA requested a second histopathological evaluation by an independent pathologist (see 415 088951). The study remains UNACCEPTABLE and not upgradeable (inadequate husbandry). (Gee, 5/9/91).
EPA 1-liner: No CORE grade; Sys NOEL = 20 ppm; Sys LEL = 2500 ppm in females liver and lung weight increases; 500 ppm in males (testis weight depression, deaths) Study is considered as positive for lung and liver tumors.

415 088951 Second evaluation of histopathology by Experimental Pathology Laboratories requested by EPA for 057754.

177 014919, "Advisory Opinion on the Oncogenic Potential of Permethrin, Scientific Advisory Panel, FIFRA. March 20, 1981", Panel report discusses both rat and mouse studies. The rat studies failed to show carcinogenic effects. "The mouse studies are clouded." Panel states the ICI and Burroughs-Wellcome studies "...appear well controlled and properly carried out." The Wellcome study suggested a potential for pulmonary neoplasms. The two attributed to FMC had problems with execution. "The Panel expressed a marked lack of confidence in the pathological findings of the FMC Mouse II Study." The FMC studies "...suggest but do not show a potential for the production of pulmonary and hepatic proliferative lesions, an unease, not a definitive demonstration." The panel concluded that the rat and mouse studies coupled together suggest a very weak oncogenic potential. Gee, 1/2/87.

389 072756, "Chronic Toxicity and Carcinogenic Evaluation of Permethrin in Rats and Mice", Fundamental and Applied Toxicology, 11:308-322, 1988, (ICI Chemical Industries, 5/19/87). Permethrin technical (93.9% pure--nominal cis-trans ratio of 40:60) was fed in the diet for 104 weeks to Alpk:AP (Wistar derived) rats at 0 (vehicle = diet), 500, 1000 or 2500 ppm (12/sex/group). An additional 12/sex/group were designated for an interim kill at 52 weeks. Swiss-derived mice were fed 0, 250, 1000 or 2500 ppm permethrin (100 mice-50/sex) for 98 weeks and 20/sex were designated for interim kill at 26 and 52 weeks. **No adverse effect.** RATS: Mortality $\leq$ 50%. NOEL = 500 ppm (tremors and hypersensitivity to noise during the first 2 weeks of the study at 2500 ppm; liver hypertrophy at $\geq$ 1000 ppm; vacuolated hepatocytes at 2500 ppm). No oncogenic effects were produced by permethrin. MICE: NOEL = 1000 ppm (slight elevation in benign lung tumor incidence in males; decrease in body weight gain). Benign lung tumors were not considered to represent a carcinogenic effect, however other studies (cited in the literature) have demonstrated lung tumors in mice at $\geq$ 2500 ppm permethrin. According to this study: "The conclusion of the USEPA (Federal Register 1982) and its SAP (Gray, 1981) was that permethrin has a low oncogenic potential in mice but none in the rat and that the oncogenic potential for humans was nonexistent or extremely low." The Joint Meeting on Pesticide Residues in 1982 concluded that based upon long-term rodent studies, permethrin was not oncogenic to humans (FAO, 1983). M. Silva, 11/16/89.

SUMMARY: Although no single study meets all of the requirements for an adequate study, taken as a whole and considering the number of tests conducted, the data gap is considered filled with a possible adverse

neoplastic effect (see Record No. 057754, reviewed 9/16/88). (Gee, 9/16/88). In the process of developing a risk assessment document, the total data base for female mouse oncogenicity was re-examined in light of the possible adverse effects identified in the second study conducted at Bio/dynamics (057754). An earlier review (1/2/87) of a study in mice conducted by Wellcome (CDFA Record Nos. 048988 to 048997) had dismissed the statistically significant finding of lung tumors in females as being well within the limits of historical control data for the same strain of mice and, therefore, of doubtful biological significance. Re-review of the Wellcome study (Gee and Aldous, 5/90), on its own, resulted in no change for the individual study. However, considered with the Bio/dynamics (057754), the findings at 250 mg/kg/day in 048988, etc., support the effects seen at 2500 and 5000 ppm in lungs of female mice. Noted also are two other studies on file which were negative for oncogenic effects in mice at similar doses - an earlier Bio/dynamics study and an ICI study. CDFA will take a conservative approach at this time in characterizing the risk of permethrin, keeping in mind that the data are not consistent. A definitive replacement mouse oncogenicity study is strongly recommended. This would address the shortcomings of those studies on file and either confirm or refute the oncogenicity. If further testing in the mouse is conducted and submitted, the total data base will be re-evaluated. (Gee, 5/30/90)

REPRODUCTION, RAT

013 014906, "A Three Generation Reproduction Study of FMC 33297 in Rats", (Bio/dynamics, 12/15/77, no. 74-1101). Permethrin, no purity stated, cis:trans ratio was 40:60; fed to 12 males/24 females per group at 0, 20 or 100 ppm, 3 generation-2 litters per generation; dosed for 61 days before mating; NOEL > 100 ppm (HDT) - nominal; unacceptable (inadequate high dose, no histopathology on breeders.) No adverse reproductive effect reported. Christopher, 6/20/85.
EPA 1-liner: Minimum. NOEL > 100 ppm.

****052, 053 031817, 038830, 038831**, "PP557: 3 Generation Reproduction Study in Rats", (ICI, no. CTL/P/361, 12/20/77). Permethrin, 7 batches with purity ranging from 94.0 to 98.9% (cis:trans ratios of 36:61 to 44:55), was fed in the diet to groups of 12 male and 24 female Wistar derived rats at dose levels of 0 (diet control), 500, 1000 or 2500 ppm for 3 generations, 2 litters per generation. Tremors were observed in parental animals at 2500 ppm, and occasionally at 1000 ppm. Centrilobular hypertrophy of the liver, and buphthalmos (defined pathologically as persistent pupillary membranes), were observed at all treatment levels. The nominal parental NOEL = 500 ppm (tremors); nominal developmental NOEL < 500 ppm (abnormal liver and ocular histopathology). The study was initially reviewed as acceptable by J. Christopher (6/20/85), and a possible adverse health effect of centrilobular hypertrophy noted. Upon re-evaluation and consideration of the data provided in record numbers 087189 and 091347, the study remains **ACCEPTABLE**, and the **POSSIBLE DEVELOPMENTAL ADVERSE HEALTH EFFECT** of buphthalmos is noted. The centrilobular hypertrophy is considered a transient physiological response to the treatment, and as such, does not constitute a possible adverse developmental or reproductive health effect (G. Chernoff, 7/18/90).
EPA 1-liner: Guideline. NOEL < 500 ppm, offspring show centrilobular hepatocyte hypertrophy and cytoplasmic eosinophilia and buphthalmos with persistent pupillary membranes. Body tremors in parents at 1000 ppm and 2500 ppm and in offspring at 2500 ppm.

413 087189, "Permethrin Three-Generation Reproduction Study in Rats, Additional Information on the Incidence of Buphthalmos", (Hodge, M.C.E. and G.J.A. Oliver, ICI Central Toxicology Laboratory, 10/22/87). The results of a one week study monitoring the incidence of buphthalmos in the Animal

Breeding Unit providing animals for the rat reproduction study (CDFA Record Nos. 031817, 038830-31). The worksheet is filed as W031817.S01 (G. Chernoff, 9/10/90).

414 091347, "Additional Information on the Incidence of Buphthalmos: Family Trees of Individual Pups Affected and Family Trees of Probable 'Carrier' Parents", (Hodge, M.C.E., ICI Central Toxicology Laboratory, 8/23/90). Pedigree data supplemental to the rat reproduction study (CDFA Record Nos. 031817, 038830-31). The worksheet is filed as W031817.S01 (G. Chernoff, 9/10/90).

TERATOGENICITY, RAT

052 031816, "PP557: 3 Generation Reproduction Study in Rats." (ICI, 12/20/77, no. CTL/P/361). Permethrin, breeders are F2b of reproduction study; 11-12 litters examined; breeders exposed in utero as well to 0, 500, 1000 or 2500 ppm; nominal developmental NOEL $\geq$ 2500 ppm; unacceptable (protocol - both sexes treated, other differences.) Christopher, 6/20/85.

036 989570, "Teratogenicity Study in Rats of ICI-PP 557," (Inveresk Res. International, 2/76, IRI no. 404898). Permethrin, 95.3%, 37.5:57.8, cis:trans; given orally to 20 per group at 0, 22.5, 71 or 225 mg/kg/day, days 6 - 16; maternal and developmental NOELs $\geq$ 225 mg/kg/day; unacceptable but upgradeable with submission of dosing analyses, evidence of maternal toxicity - dose selection based on a range-finding study in which 338 mg/kg/day was judged too toxic. Christopher, 6/19/85.
EPA 1-liner: No CORE grade. Not teratogenic at 225 mg/kg, maternal toxicity at 225 mg/kg.

008 013344, "Foetal Toxicity Study in the Rat given 21Z73 (NRDC 143) Orally", (Wellcome Research Labs., 5/74, BPAT/74/10). Permethrin, no purity stated; 22 - 23 females per group given 0 or 200 mg/kg/day by oral gavage, days 6 - 16; NOEL > 200 mg/kg/day; unacceptable (no maternal toxicity, single dose, no analysis of dosing solution, no purity stated, two deaths in dosed group but no cause given.) Christopher, 6/19/85.
EPA 1-liner: Minimum. Not teratogenic at 200 mg/kg. No definite maternal or fetotoxic effects evident.

382 071105, "Permethrin: Teratogenicity Study in the Rat", (ICI Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK, report CTL/P/2269, 9/20/88). Permethrin, 93.9%, batch # RS 78/E, 38:62 Cis:Trans ratio, was administered by gavage to groups of 24 pregnant Alpk:APfSD rats on days 7-16 of gestation at dose levels of 0 (corn oil vehicle control), 15, 50 or 150 mg/kg/day. Maternal toxicity (decreased food consumption and weight gain, tremors, and head flicks) was observed at 150 mg/kg/day. Intrauterine growth retardation (decreased fetal weight and delayed ossification) was also observed at the high dose. The fetal effects are considered to be secondary to the maternal effects, so **no adverse developmental effect is indicated. Maternal NOEL = 50 mg/kg/day (decreased weight gain and clinical signs); Developmental NOEL = 50 mg/kg/day (intrauterine growth retardation). The study, initially reviewed as unacceptable by H. Green and G. Chernoff (4/13/90), is upgraded to **ACCEPTABLE** with the submission of the cis:trans ratio data in record no. 087158 (G. Chernoff, 7/31/90).

412 087158, Supplemental information to record no. 071105, containing information on the cis:trans ratio.

TERATOGENICITY, RABBIT

008 013342, "Foetal Toxicity Study in the Rabbit given 21Z73 (NRDC 143) Orally", (Wellcome Research,, 1974, BPAT 74/19). Permethrin, no purity stated - 25/75, cis/trans; given orally to 6 - 7 Dutch Belted rabbits at 0 or 400 mg/kg, days 6 - 18; nominal maternal NOEL ≥ 400 mg/kg/day; unacceptable (inadequate number of pregnant females, single dose, no maternal toxicity reported, no purity stated, no analysis of dosing solution and no historical control data.) Not upgradeable. Christopher, 6/19/85.
EPA 1-liner: Minimum. Not teratogenic at 400 mg/kg. No definite maternal or fetotoxic effects evident.

341, 367, 388 057752, 066542, 073004, "Permethrin Teratogenicity Study in Rabbit - Individual Foetal Data Supplement, Skeletal Findings", (ICI, UK, 7/31/80; report no. CTL/P/523). Permethrin, 92.5%, cis:trans isomers 32.3%:60.2%; given by oral gavage to Dutch rabbits at 0, 600, 1200 or 1800 mg/kg body weight during days 6-18 of gestation; target of 18/group but some were lost due to misdosing or death; number of pregnant animals at day 29 were 15, 13, 14 and 13 for control, low, mid and high doses respectively; clinical observations of tremors at 1800 mg/kg and excessive fur in the stomach at 1200 and 1800 mg/kg; decreased weight gain during gestation at mid and high dose; embryotoxicity at 1200 and 1800 mg/kg with increase in post-implantation loss and decrease in mean fetal weight at 1800 mg/kg; no increase in malformations with treatment; maternal and developmental NOELS = 600 mg/kg. Reviewed twice as unacceptable due to missing data (Gee, 11/20/87; Gee, 9/16/88), upon receipt of individual fetal skeletal data, CDFA has all the information available on this study. The skeletal data were evaluated and found to be **acceptable. M. Silva, 11/16/89.

TERATOGENICITY, MOUSE

008 013343, "Foetal Toxicity Study in the Mouse given 21Z73 (NRDC 143) Orally", (Wellcome Research Labs, 1974, BPAT/74/12). Permethrin, no purity stated; given to mice, 20 - 23 per group, at 0 or 400 mg/kg/day, days 6 - 15 of gestation; NOEL > 400 mg/kg; unacceptable (no maternal toxicity, single dose level, no purity stated, no analysis of dosing solution). Christopher, 6/19/85.
EPA 1-liner: Minimum. Not teratogenic at 400 mg/kg. No maternal or fetotoxic effects evident.

GENE MUTATION

036 989589, "Permethrin Short-Term Predictive Tests for Carcinogenicity: Results from the Ames Test", (ICI, 11/76, Report no. CTL/P/301). Permethrin, 95.1%, 42% cis, 58% trans isomer; Salmonella strains TA1535, TA1538, TA98 and TA100, tested with and without activation at 0, 4, 20, 100, 500 or 2500 ug/plate, no evidence of mutagenicity; unacceptable (no individual plate counts but ±SD for 5 trials, no justification of high concentration with no cytotoxicity evident). Christopher, 6/18/85.

008 013341, "In Vitro Microbial Mutagenicity Study of an FMC Corporation Compound", (SRI, 1/76, Project LSC-4768). Permethrin, 95.7% - cis/trans, 44.7/55.3, tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without mouse liver activation; 0, 1, 50, 100, 250, 500 or 1000 ug/plate; single plate per concentration; no evidence of mutagenicity reported; unacceptable (single plate per concentration, marginal evidence of cytotoxicity or justification of high concentration.) Christopher, 6/17/85.

007 014896, "Mutagenicity Evaluation of Low Volatility Impurities in FMC 33297 (8531-114) Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). Chemistry of test article not described, amber liquid; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, with and without rat liver activation at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, apparently one plate per concentration, no retest; no evidence of mutagenicity or cytotoxicity in Salmonella, suggestion of cytotoxicity in Saccharomyces cerevisiae D4; unacceptable (no purity of test article, single plate and single trial.) Christopher, 6/17/85.

007 014895, "Mutagenicity Evaluation of Titanium Tetra-3-phenoxybenzoxide, Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). Titanium tetra-3-phenoxybenzoxide, viscous yellow liquid; no purity stated and no rationale for testing this compound; tested with Salmonella stains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation at 0, 0.001, 0.01, 0.1, 1.0 and 5.0 ul/plate, single plate, single trial; no evidence of increased reversion rate, cytotoxic at 5 ul; also tested Saccharomyces cerevisiae D4; unacceptable (test article not described, single plate, no repeat trial, no discussion of why this compound was tested.) Christopher, 6/17/85.

007 014894, "Mutagenicity Evaluation of FMC 30083MRT-501: Final Report", (Litton Bionetics, 7/77, LBI Project No. 2683). FMC 30083 MRT-501, no further identification, colorless liquid; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, also Saccharomyces cerevisiae D4, with and without rat liver activation, at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of increased reversion rate or mutagenicity; no evidence of cytotoxicity; unacceptable (no description of test article, single trial, single plate). Christopher, 6/17/85.

007 014893, "Mutagenicity Evaluation of FMC 47944; Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 47944, no description or further identification, viscous colorless liquid; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 as well as Saccharomyces cerevisiae D4; with and without rat liver activation; at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity or cytotoxicity; unacceptable (no description of test article, no repeat trial, single plate per concentration.) Christopher, 6/17/85.

007 014892, "Mutagenicity Evaluation of FMC 30094; Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 30094, no further identification, colorless liquid; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 as well as Saccharomyces cerevisiae D4; with and without rat liver activation; at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; no evidence of mutagenicity; marginal suggestion of cytotoxicity at 5 ul/plate; unacceptable (inadequate description of test article, no repeat trial, single plate.) Christopher, 6/17/85.

007 014891, "Mutagenicity Evaluation of FMC 30089, C-8117-20-cut-12; Final Report", (Litton Bionetics, 12/30/76. LBI Project No. 2683). FMC 30089, C-8117-20-cut 12, pale yellow liquid, no further description; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; single plate, single trial; no mutagenicity reported, cytotoxicity in several strains at 5 ul; unacceptable (test article not described, single plate, single trial except for retest with TA98 at 5.0 ul/plate - first trial showed a several-fold increase in revertants but was not confirmed.) Christopher, 6/17/85.

007 014890, "Mutagenicity Evaluation of Ten Coded Compounds: Final Report", (Litton Bionetics, 9/15/76, LBI Project No. 268). MR S936 FMC 39338 - C7925-62-4, clear liquid, and MR S928 FMC 30061 - C7967-15, pale yellowish clear liquid, were tested - no further identification of compounds; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100, also with Saccharomyces cerevisiae D4; with and without rat liver activation; tested at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, one plate per concentration except duplicates for TA98; single trial; unacceptable (test articles not described, single trial, single plates.) No evidence of mutagenicity. Suggestion of cytotoxicity at 5 ul/plate in several strains. Christopher, 6/17/85.

007 014899, "Mutagenicity Evaluation of FMC 30062: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 30062, yellow solid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4 with and without rat liver activation; 0, 0.1, 1.0, 10, 100 or 500 ug/plate; single plate, single trial; no evidence of mutagenicity; unacceptable (single plate, single trial, no justification of high concentration and no evidence of cytotoxicity.) Christopher, 6/17/85.

007 014900, "Mutagenicity Evaluation of 3-Phenoxybenzyl, 2-Methylbenzoate: Final Report", (Litton Bionetics, 9/77, LBI Project No. 20838). 3-Phenoxybenzyl 1,2-methylbenzoate, beige liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; single plate, single trial; no evidence of mutagenicity or cytotoxicity; unacceptable (single plate, single trial, inadequate description of test article.) Christopher, 6/17/85.

007 014901, "Mutagenicity Evaluation of 3-Phenoxybenzylbenzoate C-8531-115: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). 3-Phenoxybenzylbenzoate C-8531-115, amber liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity; suggestion of cytotoxicity at 5 ul with TA1535 and TA1537 strains; SR for TA100 rather high; unacceptable (inadequate description of test article, single trial, single plate.) Christopher, 6/17/85.

007 014902, "Mutagenicity Evaluation of Ethyl Benzoate: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). Ethyl benzoate, colorless liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; at 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; single plate, single trial; no evidence of mutagenicity, marginal cytotoxicity at 5.0 ul with TA1538; unacceptable (inadequate description of test article, single plate, single trial.) Christopher, 6/17/85.

007 014903, "Mutagenicity Evaluation of FMC 51046: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838.). FMC 51046, yellow liquid, no further description; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 or TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.0001, 0.001, 0.01, 0.1, or 1.0 ul/plate; single plate, single trial; no evidence of mutagenicity reported; cytotoxicity at 0.1 and 1.0 ul/plate; unacceptable (single plate, single trial, inadequate description of test article.) Christopher, 6/14/85.

007 014904, "Mutagenicity Evaluation of Diphenyl Ether: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). Diphenyl ether, colorless

liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity reported; cytotoxicity at 5.0 ul/plate in several strains; unacceptable (single plate, single trial, inadequate description of test article.) Christopher, 6/14/85.

007 014905, "Mutagenicity Evaluation of 2-Phenoxytoluene: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). 3-Phenoxytoluene, colorless liquid, no further description; tested with Salmonella strains TA1535, TA1537, TA1538, TA98 or TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity reported; cytotoxicity at 5 ul with several strains; unacceptable (single trial, single plate, inadequate description of test article.) Christopher, 6/14/85.

007 014898, "Mutagenicity Evaluation of FMC 51050: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 51050, colorless liquid, no further description; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate, single plate, single trial; no evidence of mutagenicity reported; suggestion of cytotoxicity in several strains at 5.0 ul/plate; unacceptable (single plate, single trial, inadequate description of test article and no justification for using compound.) Christopher, 6/14/85.

007 014897, "Mutagenicity Evaluation of FMC 30953: Final Report", (Litton Bionetics, 12/77, LBI Project No. 20838). FMC 30953, slightly viscous colorless liquid, no further description; tested in Salmonella strains TA1535, TA1537, TA1538, TA98 or TA100; also with Saccharomyces cerevisiae D4; with and without rat liver activation; 0, 0.001, 0.01, 0.1, 1.0 or 5.0 ul/plate; single plate, single trial; no evidence of mutagenicity reported, cytotoxicity at 5.0 ul/plate in all strains; unacceptable (single plate, single trial, inadequate description of test article.) Christopher, 6/14/85.

391 073022, "Permethrin: An Evaluation in the Salmonella Mutation Assay", (R. D. Callander, ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, report # CTL/P/2423, 2/22/89), permethrin technical, analysed purity 95.6% w/w, batch # P56; RS/38/F (Cis/Trans ratio of 38.6/61.4 - see 378-391, # 073018), liquid, 2 trials in triplicate with and without S9 (Aroclor induced male rat liver fraction) activation at 0 (strain only), 0 (DMSO), 1.6, 8.0, 40, 200, 1000, and 5000 mg/plate with Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100. Positive controls with activation: 2AA (all strains), without activation: MNNG (TA1535, TA100), daunorubicin (TA98), 4NPD (TA1538), acridine mutagen ICR191 (TA1537). **No statistically significant increase in revertants. **Acceptable**. (Gee, 4/11/90)

**008 013340, "Mutagenicity of BW 21Z73 in L5178Y/TK+/- Mouse Lymphoma Cells with and without Exogenous Metabolic Activation", (Burroughs Wellcome, 1/5/77, Doc. no. TTEP/77/001). Permethrin, no purity stated; tested for 4 hours with and without activation at 0, 31, 47, 62, 94 or 125 mg/ml; no evidence of mutagenicity reported; initially reviewed as unacceptable based on inadequate description of protocol and calculations by JPC, 6/17/85. Supplements in 278, #s 50809, 50810 and 50811 provide missing information and upgrade the study to acceptable status. Christopher, 6/17/85 and Gee, 1/8/87.

CHROMOSOME EFFECTS

** 036 989591 "Permethrin (PP557): Cytogenetic study in the Rat." (ICI, 11/76, Report no. CTL/P/294) Permethrin, 94%, 40.3:59.7 cis:trans; given by ip injection once or in 5 daily doses at 0, 600, 3000 or 6000 mg/kg to 12 males in control and 8 males per test group; sacrificed at 24 hours after the single dose, 6 hours after last dosing in multiple dosing; scored 50 cells per animal; initially reviewed as unacceptable (use of one sex must be justified, single sampling time, no data on toxicity - high dose stated to be near MTD but no data and no clinical observations presented.) Christopher, 6/18/85. A rebuttal was submitted (2-page letter) dated September 9, 1991, addressing the deficiencies noted above. Reconsidering the study, it is upgraded to acceptable status with some minor deficiencies. Gee, 10/3/91.

036 024952, "Dominant Lethal Study in Mice of 95.3% ICI-PP 557", (Inveresk Res. International, 11/76, IRI 406722). Permethrin, 95.3%, 37.5:57.8, cis:trans; given orally on five consecutive days to 15 male CD-1 mice per group at 0, 15, 48 or 150 mg/kg/day; mated 1 male:2 females, weekly for 8 consecutive weeks; unacceptable (no explanation for death of 54 females - 5% - with no time of death or clinical observations, inadequate number of pregnant mice per interval.) No evidence of dominant lethal effect. Christopher, 6/18/85.

008 013339, "21Z73, Dominant Lethal Study in Male Mice", (Wellcome Research Labs, 11/27/75, T. L. 37-75). Permethrin, no purity stated - 25/75, cis/trans; given orally to CD-1 male mice at 0 or 452 mg/kg in five daily doses; mated 1 male to 3 females weekly for 6 weeks; dose was 1/5 LD50/day; no evidence of dominant lethal effect; unacceptable (single dose level, inadequate number of pregnant females, variable fertility and number of dead implants making interpretation of results difficult.) Christopher, 6/17/85. EPA 1-liner: No CORE grade. Not mutagenic at 452 mg/kg.

472 121635; "Permethrin: an Evaluation in the Mouse Micronucleus Test"; Report No. CTL/P/3934; D. Fox and J.M. Mackay; Zeneca Central Toxicology Laboratory, Cheshire, UK; 3/5/93. A single oral dose of permethrin (batch no. P58/D7534/30, 93.1% w/w stated purity) in corn oil was given to 5 CD-1 mice/sex/dose/time point at 200 mg/kg for males and 320 mg/kg for females. Samples of femur marrow were taken 24 or 48 hours after dosing and prepared for microscopic examination. One thousand polychromatic erythrocytes per animal were examined for micronuclei and the ratio of polychromatic to normochromatic erythrocytes was determined in an additional 1,000 cells. There was no treatment-related increase in micronuclei. No adverse effect was indicated. The positive controls and doses were adequate. The study was not acceptable and not upgradeable because the stability and achieved concentrations of the test material were not determined by analysis (S. Morris, 6/22/93).

DNA DAMAGE

**372, 388 066477, 073009, "Permethrin: Assessment for the Induction of Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures", (Imperial Chemical Industries PLC, UK, Report No: CTL/P/1888, April 1988). Permethrin (purity = 93.5%) administered at concentrations 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8} and 10^{-9} molar to rat hepatocytes in culture (3 slides/dose for each of three (3) experiments). Permethrin did not induce DNA repair, as measured by unscheduled DNA synthesis, in primary cultures of rat hepatocytes exposed in vitro. Previously reviewed as unacceptable (Gee, 9/16/88), upon submission of the requested information (cytotoxicity data, unaltered and

damaged cell numbers, pyknotic nuclei data and number of cells scored), the study has been upgraded to **acceptable.** M. Silva, 11/20/89.

NEUROTOXICITY

**009 013926, "Examination of Permethrin (PP 557) for Neurotoxicity in the Domestic Hen", (Huntingdon Research Centre, 9/30/77, ICI/157-NT?77468). Permethrin, 94.9%, 36.0:58.9, cis:trans; given orally to 10 in controls and 15 in dose group at 0 or approximately 12 g/kg, observed 21 days, then redosed; TOCP as positive control; no adverse effect with permethrin. Acceptable. Christopher, 6/17/85.
No EPA 1-liner.

SUPPLEMENTAL STUDIES

009 013934, "Preliminary investigation of the Neurological Effects in Rats Offered Diets Containing NRDC 143." (Wellcome Research Labs, 2/28/77). Permethrin, fed to Charles River Wistar rats, 10 females per group, at 6000 ppm, with 90, 40 or 25% cis and 10, 60 or 75% trans isomers; observed for 16 days; some acute neurotoxic symptoms seen, greatest with 90% cis isomer; unacceptable for acute delayed neuropathy test. J. Christopher, 6/18/85.

036 989469 "Effects of High Dietary Levels of PP557 on Clinical Behavior and Structure of Sciatic Nerves in the Rat." (ICI, 3/77, CTL/P/317) Permethrin, 40% cis: 60% trans, 90.4% purity, was fed to male SPF-derived Wistar rats for 14 days at 0 (diet), 2500, 3000, 3750, 4500, 5000 or 7500 ppm in two studies spaced 14 days apart, 10/group. Data were pooled. Only the sciatic nerve was examined although the brain, spinal cord, vagus nerve and gastrocnemius muscle were saved but not processed. Tremors of varying severity were seen in all treatment groups with decreasing severity with treatment time. Deaths occurred at 5000 and 7500 ppm. Nerves from the 2500, 4500 and 5000 ppm groups were examined by light and electron microscopy. The incidence of degenerating nerve fibers in the two 5000 ppm 14-day survivors was increased. Other minor changes were also noted. Nerves from the 2500 and 4500 ppm groups were similar to paired controls. No worksheet. Gee, 5/9/91.

009 013938 "Neurotoxic Effects of Some Synthetic Pyrethroids by Short-term Feeding in Rats." (Okuno, Y., Sumitomo Chemical Co., 11/10/76) NRDC 143 [permethrin], 93.3% purity - no further identification, was fed at 0 or 6000 ppm for 7 or 8 days to groups of 8/sex SD-SLC rats in control and 16/sex in the treated groups. Clinical signs were tremors and muscle twitch in the treated groups. Histological examination of 5/sex/group of the spinal cord and brain showed no abnormalities. The sciatic nerve showed swelling and, in 1/sex at 6000 ppm, degeneration. Demyelination occurred in 1/sex at 6000 ppm. No worksheet. Gee, 5/9/91.

APPENDIX B

HUMAN EXPOSURE ASSESSMENT

Estimation of Exposure of Persons in
California from Special Local Need Use
of Permethrin on Human Clothing

ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA FROM SPECIAL LOCAL NEED USE OF PERMETHRIN ON HUMAN CLOTHING

By

Tareq A. Formoli, Associate Pesticide Review Scientist

HS-1582 December 10, 1990
Revised May 6, 1991
Revised March 4, 1992

California Environmental Protection Agency
Department of Pesticide Regulation
Worker Health and Safety Branch
1220 N Street
Sacramento, California 95814

ABSTRACT

Permethrin is a contact insecticide which has a wide range of agricultural and non-agricultural uses. A formulated product containing 0.5 percent permethrin has been proposed for Special Local Need use on human clothing to repel and kill ticks, mosquitoes and chiggers as a preventive measure against vectors of Lyme disease. Only 11 illnesses/injuries have been reported during 1984-1988 that were associated with the use of permethrin. Human dermal absorption of permethrin is estimated to be about 2 percent. Absorbed Daily Dosage from dermal and inhalation exposure of a person to the spray and to the clothing sprayed with a 0.5 percent formulation of permethrin is estimated at 4.2 ug/kg/day for an adult human.

This report was prepared as Appendix B to the Department's risk assessment document for permethrin use on human clothing because of possible oncogenic and reproductive adverse effects observed in laboratory mice and rats, respectively.

APPENDIX B

California Department of Food and Agriculture
Worker Health and Safety Branch

Human Exposure Assessment
Permethrin
For Use on Human Clothing

December 10, 1990
Revised May 6, 1991
Revised March 4, 1992

INTRODUCTION

Permethrin is a synthetic pyrethroid. Its chemical name is (3-phenoxyphenyl) methyl (±) cis, trans -3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate with various cis-trans isomer mixtures. Permethrin is an odorless, pale yellow liquid or colorless solid. It is almost insoluble in water (<1 ppm), but soluble in most organic solvents. It melts at approximately 35 ^{o}C. Its vapor pressure at 50 ^{o}C is < 1 X 10^{-6} mm Hg. Permethrin is used as a contact and residual insecticide.

EPA STATUS

A number of Special Local Need (SLN) registrations have been granted in several states pursuant to section 24(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for use of permethrin on human clothing. An SLN registration of a 0.5 percent permethrin product "Permanone Tick Repellent" has been requested for use on human clothing in California to repel and kill ticks, mosquitoes and chiggers. The application for registration of this SLN is currently under review in California.

USAGE

Permethrin has a wide range of agricultural and non-agricultural uses. About 181,000 pounds (lbs) of permethrin active ingredient (a.i) were sold in California in 1988 (1). The Annual Use Report indicates that approximately 140,000 lbs of ai were used in California in 1988, almost entirely for agricultural uses including livestock and livestock buildings (2). Only 3 lbs were reported as used for public health pest control. All users are not required to submit use reports for permethrin. This could be the reason for the discrepancy between the amount sold and the amount used in California in 1988. The proposed product for this SLN is currently registered for uses such as control of residential, industrial, garden, pet and livestock insects. It can also be used on premises, bedding, furniture and other infested inanimate objects. The primary purpose of this SLN is to use Permanone Tick Repellent on human clothing as a preventive measure against vectors of Lyme disease. Statements supportive of this SLN indicate the existence of the vectors of Lyme disease in California and the lack of any vaccine against Lyme disease (3, 4). The proposed SLN label instructs the user to spray clothing with a slow sweeping motion using one half content (85 grams) of an entire container. Treatment is to take about two minutes and must be made at least two hours prior to wearing the clothing.

FORMULATION

The product for the proposed SLN is an aerosol 0.5 percent permethrin formulation in pressurized 6-oz containers.

LABEL PRECAUTION

The product for the proposed SLN is a toxicity category III pesticide bearing the signal word "Caution". The label prohibits the use of this product in a manner such that it would come in direct contact with skin, face or eyes. The label instructs the user not to retreat clothing more than once every two weeks. Clothing must be laundered at least once before retreating. The label does not limit the use of this product to treat

one set of clothing once in two weeks. The product label alerts the user to avoid breathing vapors or spray mist. A statement of practical treatment on the label provides instruction in case of accidental exposure.

ILLNESS/INJURY REPORTS

A total of 11 illnesses/injuries (7 systemic and 4 skin) have been reported by physicians in California during 1984-1988 that were associated with exposure to permethrin or permethrin residues (5). These incidents were related to agricultural and non-agricultural uses of permethrin, involving five workers handling the pesticide or contacting pesticide residues, two home-residents, and four emergency response personnel (police and fire fighters). These incidents occurred as the result of permethrin uses that are not similar to the use that is proposed in this SLN. Skin, eye, or inhalation exposures resulted in reports of skin rashes, skin/eye irritation, watery eyes, coughing, laryngitis, headache, dryness of nasal and oral mucous membranes and stomach cramps.

DERMAL TOXICITY

Human skin contact with liquid or volatilized permethrin can induce paresthesia (stinging, burning and tingling, progressing to numbness) that is not allergic in nature (6, 7). Burning and itching felt at the site of application by persons treated with permethrin for louse and flea infestation are said to be mainly caused by the parasites themselves and is not typical of the paresthetic reaction mentioned above(7). A dermal irritation study of the formulated product (0.5% permethrin) has resulted in mild skin irritation in rabbits (8). No skin sensitization was observed in guinea pigs treated with this formulation (9).

DERMAL ABSORPTION

A number of dermal absorption studies of permethrin in human and laboratory animals, in vitro or in vivo, have recently been submitted to the Department. Animal percutaneous absorption studies have shown that dermal absorption varies among species and is generally higher than humans (10, 11, 12, 13). Different formulations of permethrin applied to human skin in vivo or in vitro have shown dermal absorption of generally below 2 percent in 24 hours or longer. However, it has been shown that hair, treated with permethrin creme rinse, retained a significant portion of the applied permethrin, thus contributing to reduced absorption of permethrin when applied to human hair and scalp (14). A human study of permethrin shampoo versus aerosol applied to the hair has revealed that permethrin was absorbed approximately 7 times more when treated as an aerosol compared to a shampoo (15). The absorption rate for either formulation was measured at less than one percent. In an in vitro study, human chest skin exposed to ^{14}C-labelled permethrin for 8 hours had a dermal absorption of 0.62 percent (12).

In a dermal absorption study of permethrin in humans, ^{14}C-permethrin was applied to the shaved back of six volunteers at the rate of 8 ug/cm^2 (2040 ug/256 cm^2) using isopropanol (20 %) as a carrier (16). The treated area was covered with a dressing and washing was avoided for 5 days. The dressing was changed every 24 hours. A part of the treated skin was stripped with 20 pieces of adhesive tape at each dressing change. Plasma at specific times and cumulative urine and feces were obtained continuously and kept frozen until shipped to the laboratory. Plasma radiocarbon levels appeared to peak about 24 hours after the treatment with the highest level measured at 0.31 ng/mL and then rapidly declined. The majority of excreted radiocarbon was found in urine, ranging from 0.29 to 2.00 percent of the applied dose in 5 days. Fecal radiocarbon levels were negligible (<4% of the excreted ^{14}C). After 24 hours of treatment, 14 C levels on skin measured by tape stripping averaged 8.1 percent of the applied dose. Skin ^{14}C levels declined each day to mean values of 3.2, 0.6, 0.1 and 0.03 percent of the applied dose for days 2, 3, 4, and 5 after the application, respectively.

Although the absorption rate in the above study (0.29 to 2.00 percent) is from five days of exposure and the absorption rate of the human skin in vitro study (0.62 percent) is from 8 hours of exposure, the confounding effects of hair and cream vehicles have been eliminated in these two studies. Based on these observations, a dermal absorption of 2 percent will be assumed in calculating Absorbed Daily Dosage (ADD).

HUMAN EXPOSURE

The use directions for this SLN are such that the product is sprayed with a slow sweeping motion to moisten the outer surface of clothing from a distance of 6 to 8 inches before the clothing is worn. The efficacy data suggest a range of 15 to 60 seconds of spraying time with 0.5 percent permethrin for effective

control of ticks (17). The amount of permethrin (a.i.) on clothing was estimated in the range of 4 to 12.8 ug/cm^2 (17, 18, 19). However, the product label for this SLN suggests a total of 120 seconds of spraying time, using 85 g of the product. Assuming that 10 percent of this amount disperses in the air, the remaining 76.5 g (382 mg a.i.) of the actual spray (formulated pesticide product) would reach the clothing of 18,000 cm^2 surface area. This is equal to 21.2 ug a.i./cm^2 clothing.

Laundering permethrin impregnated fabrics in a complete wash cycle removed 20 - 33 percent of the permethrin present in the clothing (20). Subsequent laundering removed only an additional 6 percent of permethrin in the second laundering. A steady loss of 2 to 3 percent per wash was observed in the third to tenth laundering. The same study indicated that rabbits wearing contaminated fabrics for seven days absorbed about 1.8 percent of the dose remaining after laundering.

Based on a biweekly retreatment and weekly laundering schedule in a six month period, the average accumulated residues on clothing would be 66.0 ug/cm^2 for the weeks treatments were made and 52.8 ug/cm^2 for the weeks that no treatments were made (Table 1).

Table 1

Permethrin Accumulation
on Treated clothes

Week	Applied (ug/cm^2)	Accumulated (ug/cm^2)	Lost (%)
1st	21.2	21.2	-20
2nd		17.0	-6
3rd	21.2	37.2	-20
4th		9.7	-6
25th	21.2	83.4	-20
26th		66.7	-6

Formoli, WH&S, 1992

Residue migration studies of permethrin from treated fabrics to rabbit skin have demonstrated 4.5% or 2.8% migration in the first week or the second week of continuous dermal exposure, respectively (21). The migration was generally higher during the first few days of the week. The migration was calculated at 0.9%/day during the first week and 0.56%/day during the second week. The average amount of accumulated permethrin (a.i.) available for daily dermal absorption could be 0.59 ug/cm^2 in a week that a treatment was made and 0.30 ug/cm^2 in the following week that no treatment was made.

Approximately 18,000 cm^2 of an adult human body surface area can be covered with normal clothing such as long-sleeved shirt and long pants. Consequently, the total amount of permethrin (a.i.) available for dermal absorption would be 10.7 mg/person/day in a week that a treatment was made and 5.3 mg/person/day in the following week that no treatment was made.

The potential for inhalation exposure occurs during the application (approximately 120 seconds). Assuming that during this period 90 percent of the spray reaches the target (76.5 g) and the remaining 10 percent (8.5 g) disperses in a volume of 2.5 m^3 of the air in the user's breathing zone, approximately 0.5 mg/person/day (7 ug/kg/day) permethrin may be inhaled in 120 seconds of exposure. This estimate is calculated based on the EPA's human breathing rate of 29 liters per minute, and a 50 percent respiration uptake (22, 23). The label instructs users to avoid breathing vapors or mist to reduce the potential for inhalation exposure. This instruction to avoid breathing the mist coupled with an estimate for inhalation rate during light work (actual inhalation rate during spraying is probably closer to rest or less than half of the work rate) causes this

estimate to be very conservative. Potential inhalation exposure, if any, during the period that the clothing is worn, is expected to be negligible due to the very low vapor pressure of permethrin.

Fall and winter are reported to be the periods of greatest adult I pacificus tick activity in north coastal California, while deer ticks that also may cause Lyme disease are generally acknowledged to be active from April to October (19, 24). The following scenario was assumed as a logical extreme case that could occur without violating label instructions: Using 5 sets of laundered clothing, a person treats and wears one set of clothing each day for 5 days in the first week. After laundering all 5 sets of worn clothing, the same person wears (no retreatment) one set of laundered clothing each day for 5 days in the next week. This two-week cycle is repeated in a sequence that each set of clothing is retreated only once in two weeks during six months in a year. Calculated Absorbed Daily Dosage (ADD), Annual Average Daily Dosage (AADD), and Lifetime Average Daily Dosage (LADD) for a person spraying and then wearing the clothing as described in the extreme case scenario are shown in Table 2.

Table 2
Estimated Exposure of a Person to Permethrin as a
Result of Its SLN Use on Human Clothing

Week of	Calculated Exposure Dermal (mg/person/day)	Inhalation (mg/person/day)	ADD[a] (ug/kg/day)	AADD[b] (ug/kg/day)	LADD[c] (ug/kg/day)
Treatment	10.7	1.0	7.3		
No Treatment	5.3	0.0	1.1		
Average	8.0	0.5	4.2	2.1	1.2

a - Assuming dermal absorption of 2 percent, respiration uptake of 50 percent, 5 applications every two weeks, five working days a week, body weight of 70 kg.
b - Six months use season in a year. c - Forty years of working exposure.

Formoli, WH&S, 1991

As it was shown (Snodgrass, 1988), little (2-3 percent in third to tenth laundering) permethrin could be removed in laundry. Thus, it should be noted that it is likely that more leaching would occur under laundering conditions than under the conditions which clothing are worn, resulting in negligible off season exposure.

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5. Illness/injuries associated with exposure to permethrin, 1984 - 1988 (1990). California Pesticide Illness Surveillance Program, Worker Health and Safety Branch, California Department of Food and Agriculture, Sacramento, CA.

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APPENDIX C

Oncogenicity Computer Model Printout

ONCOGENIC POTENCY ESTIMATION FOR PERMETHRIN
Using the Multistage Model, GLOBAL86

Based on the Incidence of Lung Tumors in Female Mice
from the Second Reading of the Pathology Slides
for the Bio/dynamics Mouse II Study

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=O)
CHI-SQUARE TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	.000000	15/ 71	20.42
2	.495000	24/ 65	18.82
3	61.8750	35/ 68	33.96
4	123.750	44/ 69	44.72

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 4.1195

P-VALUE FOR THE CHI-SQ TEST WITH 2 DEGREES
OF FREEDOM IS .1274851559

FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-QO - Ql * D - Q2 * D^2)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = .339116165053
Q(1) = 5.700935694744E-03
Q(2) = .000000000000

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -173.774499388

CALCULATIONS ARE BASED UPON EXTRA RISK

GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.00000E-06	1.75410E-04	1.27555E-04	95.0%	Q(0) = .30401 Q(1) = 7.83974E-03 Q(2) = .00000

GLOBAL 86 UPPER CONFIDENCE LIMITS ON RISK FOR FIXED DOSE
****

DOSE	MLE DOSE	UPPER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.0000	5.68472E-03	7.80909E-03	95.0%	Q(0) = .30401
				Q(1) = 7.83974E-03
				Q(2) = .00000

NORMAL COMPLETION!

APPENDIX D

EXPOSURE MITIGATION

Appendix D

MITIGATION OF PERMANONE EXPOSURE

It is not possible to mitigate exposure to the general public for this consumer applied aerosol which is intentionally applied to clothing under the current use scenario.