PYRETHROIDS

The historical development of the synthetic pesticides called pyrethroids is based on the pyrethrins, which are derived from chrysanthemums. Pyrethrins are a "natural" environmental product that is of low toxicity to mammals. They are highly photolabile and degrade quickly in sunlight, and the cost of reapplying them has limited their widespread agricultural use. Pyrethroids have been synthesized to be similar to pyrethrins yet more stable in the environment. Evidence suggests that they have a very large margin of safety when used as directed by the label (Aldridge, 1990; Chen et al., 1991; Snodgrass, 1992).

Commercial pyrethroid products commonly use petroleum distillates as carriers. Some commercial products also contain OP or carbamate insecticides because the rapid paralytic effect of pyrethrins on insects ("quick knockdown") is not always lethal (Cheremisinoff and King, 1994). Pyrethroids are formulated as emulsifiable concentrates, wettable powders, granules, and concentrates for ULV application.

PERMETHRIN

General Information

Permethrin is a broad-spectrum pyrethroid insecticide. It is available in dusts, emulsifiable concentrates, smokes, ULV concentrates, and wettable-powder formulations. The chemical identity of permethrin is shown in Table 6.1, and Table 6.2 summarizes its physical and chemical properties.

Availability and Recommended Use of Permethrin During ODS/DS

Permethrin is part of the DoD Insect Repellent System[1] (Young and Evans, 1998) and was issued in the PGW as a ready-to-use insect repellent for clothing

[1]This system was known during the ODS/DS era as the DOD Repellent System. It later became known as the DOD Arthropod Repellent System and then the DOD Insect Repellent System. All

Table 6.1

Chemical Identity of Permethrin

Characteristic	Information
Chemical class	Pyrethroid
Chemical name	3-(2,2-Dichloroethenyl)-2,2-dimethylcyclopropanecarbobylic acid (3-phenoxyphenyl)methyl ester
Trade names	Ambush, Ectiban, FMC 33297, NIA 33297, NRDC 143, Permethrin, Pounce, PP557, S3151, SBP 1513, PT Wasp Freeze & Hornet Killer, Wasp & Hornet Killer II, Wasp Stopper II Plus
Chemical formula	$C_{21}H_{20}Cl_2O_3$
CAS Registry number	52645-53-1

Table 6.2

Physical and Chemical Properties of Permethrin

Property	Information
Molecular weight	391.29
Color/form	Colorless crystals to a pale yellow viscous liquid
Odor	Odorless
Water solubility at 30°C	0.2 mg/mL
Partition coefficient (K_{ow})	3.0×10^3
Vapor pressure at 25°C	3.4×10^{-7} mm Hg
EPA toxicity classification	Class II or III, depending on formulation
ACGIH TLV–TWA	NA, Pyrethrum[a]: 5 mg/m^3
NIOSH REL–TWA	NA, Pyrethrum: 5 mg/m^3
NIOSH REL–STEL	NA
NIOSH IDLH value	NA, Pyrethrum: 5,000 mg/m^3
OSHA PEL–TWA	NA, Pyrethrum: 5 mg/m^3
EPA IRIS RfD	5×10^{-2} mg/kg/day
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	NA, Pyrethrum: A4
EPA	NA
IARC	NA

NA = not available.

[a]Because occupational health standards and recommendations are largely unavailable for permethrin and *d*-phenothrin, these values are provided for pyrethrum for comparison. Pyrethrum is a botanical insecticide, and its active components are the pyrethrins (cinerins I and II, jasmolin I and II, and pyrethrins I and II).

describe essentially the same system; Young and Evans (1998) provide a good description of this system. This system was also described in Technical Guide 174, *Personal Protective Techniques Against Insects and Other Arthropods of Military Significance*, U.S. Army Environmental Hygiene Agency, June 1991. The use of permethrin and DEET had been emphasized earlier during ODS/DS in an electronic message to the services and geographic Commanders in Chief (CINC) from the U.S. Armed Forces Pest Management Board ("Availability of permethrin aerosol for treatment of the Battle Dress Uniform (BDU)," NSN 6840-01-278-1336, dated August 1, 1990).

application (Table 6.3). It is labeled for use on clothes such as the battle dress uniform (BDU) and bed netting, to be applied as an aerosol spray six to eight inches away from the target surface for 30 seconds, every six weeks or after six launderings. Treated clothing should not be worn for two to four hours after application.

Permethrin Residues

Studies show that most of the airborne residues of permethrin, dispensed with different types of applicators, are settled within four hours of application (Lindquist, 1987). Studies on the residues remaining in apparel fabrics after laundering indicate that while fabric fiber content does not affect the removal of permethrin residues, fabric weight may contribute to post-laundering residue retention. Heavier fabrics were found to prevent pesticide penetration more than lighter fabrics, but heavier fabrics retain more residues after laundering. The type of detergent—heavy-duty liquid or phosphate powdered—did not affect the fraction of permethrin removed (Laughlin, 1991).

PHENOTHRIN

General Information

The compound *d*-phenothrin is labeled as an indoor-use aerosol insecticide, intended for purposes such as spraying bed netting (to kill insects trapped inside after installation) or spraying inside aircraft (to prevent transport of insects). The application rates are one 10-second spray per 1,000 ft^3 in aircraft and one 10-second spray per 1,000 ft^3 in buildings and tents; spraying should be done with a sweeping motion at least three feet away from surfaces. The indoor area should then stay closed for 30 minutes. Reapplication can be conducted as necessary. The chemical identity of *d*-phenothrin is shown in Table 6.4, and Table 6.5 summarizes its physical and chemical properties.

Table 6.3

Formulations of Permethrin Available During ODS/DS

NSN	Name	Form	Formulation (%)	Unit Size	Application Directions
6840-01-278-1336	Permethrin	Aerosol spray	0.5	6-oz can	Apply to battle dress uniforms, bed net, head net, and inside tent.

Table 6.4

Chemical Identity of *d*-Phenothrin

Characteristic	Information
Chemical class	Pyrethroid
Chemical name	2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid (3-phenoxyphenyl)methyl ester
Trade names	S-2539, Sumethrin, Sumitrin
Chemical formula	$C_{23}H_{26}O_3$
CAS Registry number	26002-80-2

Table 6.5

Physical and Chemical Properties of *d*-Phenothrin[2]

Property	Information
Molecular weight	350.46
Color/form	Pale yellow to yellow–brown liquid
Water solubility at 25°C	1.06 g/mL
Vapor pressure at 25°C	1.2×10^{-6} mm Hg
EPA toxicity classification	Class III
ACGIH TLV–TWA	NA
NIOSH REL–TWA	NA
NIOSH REL–STEL	NA
NIOSH IDLH value	NA
OSHA PEL–TWA	NA
EPA IRIS RfD	NA
EPA IRIS RfC	NA
Carcinogenicity classification	
ACGIH	NA
EPA	NA
IARC	NA

NA = not available.

Availability and Recommended Use of *d*-Phenothrin During ODS/DS

During ODS/DS, *d*-phenothrin was available as a ready-to-use aerosol insecticide, to be used according to the label directions (Table 6.6).

Environmental Characteristics of *d*-Phenothrin

Studies have shown that *d*-phenothrin displays slight to no soil mobility (Swann et al., 1983) and volatilizes slowly from water (Meylan and Howard, 1991), although it may also adsorb to sediments (Meylan et al., 1992). It can exist in

[2]See Table 6.2 for comparable information on pyrethrum.

Table 6.6

Formulations of *d*-Phenothrin Available During ODS/DS

NSN	Name	Form	Formulation (%)	Unit Size	Application Directions
6840-01-067-6674	*d*-phenothrin	Aerosol spray	2	6 oz	Spray preformulated aerosol to buildings, vans, tents, and aircraft

the atmosphere in its vapor and particulate phases, with estimated half-lives of from approximately one-half to three hours (Howard, 1991).

d-Phenothrin Residues

A recent study designed to determine the behavior of *d*-phenothrin sprayed in a room under various conditions found that the air concentrations depended mainly on ventilation rates but not on circulation (Matoba, 1998). The applications were done using a commercial 300-mL aerosol canister containing 0.9 g of *d*-phenothrin. Spraying occurred during an eight-week period every two weeks for 2.5 minutes (considerably longer than the rate recommended on the label). The air concentrations peaked after each spraying to about 750 $\mu g/m^3$ and decreased rapidly (the half-life in air is 20 minutes) to an eight-week concentration of 2.35 $\mu g/m^3$ and an annual mean of 0.43 $\mu g/m^3$. There was little difference in air concentrations between samples collected at different room heights, and airborne *d*-phenothrin in the room did not accumulate with repeated sprays (Matoba, 1998).

POTENTIAL HEALTH EFFECTS OF PYRETHROIDS

Synthetic pyrethroids are among the newest pesticides to enter the marketplace, and they account for a large percentage of the pesticides in use today. Despite their extensive use, few poisonings in humans have been reported (Morgan, 1989). When acute pyrethroid intoxication occurs in rats, two patterns of symptoms are observed, depending on the chemical configuration of the modified pyrethrins. The type I pyrethroids, lacking a cyano group, produce the T syndrome (tremors, aggressive sparring, and enhanced startle response). The type II variants, containing a cyano group, produce the CS syndrome that includes choreoathetosis, salivation, and seizures. Both types interact with the sodium channel on neuronal cell membranes, delaying closure of these channels. Type II pyrethroids also block the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

This review focuses on permethrin and *d*-phenothrin, both of which are classified as type I pyrethroid insecticides.

Permethrin

Permethrin is a useful synthetic insecticide that has proven effective in a number of environmental and clinical settings. It appears to be more effective than DEET in protecting individuals from tick bites (either when sprayed or impregnated in battle uniforms) (Evans et al., 1990), but uniform impregnation alone was not found to be effective in preventing transmission of malaria in Thailand (Eamsila et al., 1994). In 1990, the U.S. military adopted permethrin as the standard clothing-application repellent, to be used as an adjunct to topical repellents (Young and Evans, 1998).

Permethrin exists in the *cis* and *trans* isomer forms. Studies demonstrate that the former is considerably more toxic to rats and mice than is the latter (Jaggers and Parkinson, 1979; Glickman et al., 1982). The majority of the literature regarding the health effects of permethrin consists of unpublished studies in the chemical and pesticide industries. These references are cited in the International Programme on Chemical Safety (IPCS), a joint effort undertaken by the United Nations, the International Labor Organization, and the World Health Organization (WHO, 1990). Discussions of the acute effects of permethrin exposure come from animal studies.

Acute Effects. The literature contains a limited number of references for permethrin, and those that are cited repeatedly describe the relative safety of this compound. A review of 573 cases of acute pyrethroid poisoning in the Chinese medical literature (He et al., 1989) focuses primarily on exposure to deltamethrin, fenvalerate, and cypermethrin, although it indicates that the spectrum of acute poisoning is similar for all pyrethroids. With occupational exposure, individuals experienced facial skin sensations (burning or itching), usually within a few hours of exposure. With ingestion, digestive symptoms included epigastric pain, nausea, and vomiting. Acute poisoning symptoms from all exposure routes are primarily related to the effects of pyrethroids on the nervous system and include dizziness, headache, nausea, anorexia, and fatigue. Muscle fasciculation and altered consciousness were reported in more severe cases with extensive exposures (He et al., 1989).

In a study using 10 volunteers (four men and six women), 30 percent of the subjects developed skin irritation after applying 1 percent permethrin to their skin (Farquhar et al., 1981b). Another study of dermal exposure showed minor skin irritation at approximately 30 minutes that peaked at eight hours and disappeared after one day (Flannigan and Tucker, 1985; Flannigan et al., 1985a,b). When their clothes were impregnated with 3.8 mg/day of permethrin, the vol-

unteers showed no signs of toxicity (Farquhar et al., 1981a). LeQuesne evaluated findings among 23 pest-control workers who were occupationally exposed to multiple compounds, including permethrin. Although the workers reported tingling, burning, and a rash starting 30 minutes after exposure and lasting up to eight hours, these findings were not exhibited among workers exposed to permethrin alone (LeQuesne et al., 1980).

After permethrin was introduced as an alternative treatment for head lice in humans, data were gathered regarding possible adverse effects from the use of a 1 percent permethrin creme rinse. Results on 18,950 individuals from 37 local public health departments showed few adverse reactions. The observed rate was approximately 2.2 adverse events per 1,000 administrations. Adverse events, although perhaps underreported in this post-marketing survey, were not clinically serious (Andrews et al., 1992). The most common adverse effects were itching and a rash. Other effects (e.g., shortness of breath, GI effects) occurred in only a few individuals.

Animal studies produce findings that support the effect of permethrin on the CNS. Poisoning was reported to start within two hours and to last up to three days following exposure. At very high levels, whole body tremors (mild to convulsive) occurred, sometimes with salivation. Additional evidence of poisoning included hyperactivity and hyperexcitability, urination, defecation, ataxia, and lacrimation (Parkinson, 1978; Litchfield, 1983). However, subjects in these studies were exposed to levels much higher than those that occur in occupational (pest-control operators), military (clothing impregnation), or clinical (treatment for lice) exposures. Acute effects of permethrin reported in three animal studies are shown in Table 6.7. Lethal exposure levels are given in Table 6.8.

The U.S. Army Environmental Hygiene Agency[3] evaluated the absorption of permethrin in individuals wearing permethrin-treated clothing (0.125 mg/cm^2) and found that the exposure dose is approximately 0.0006 mg/kg/day, orders of magnitude below levels that produced acute toxicity in animals (Snodgrass, 1992).

Chronic, Reproductive, Genetic, and Carcinogenic Effects. Data on chronic human exposure to permethrin come primarily from studies of pest-control workers and clinical evaluations of patients treated for scabies and lice infestations. Data again support the conclusion that permethrin is extremely safe when used in recommended applications (Table 6.9).

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[3]Subsequently renamed the U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM).

Table 6.7

Acute Effects of Permethrin Reported in Animal Studies

Reference	Model	Concentration and Duration	Route	Effects
Okuno et al., 1976	Japanese white rabbits	0.5 mL technical grade to dorsal skin	Dermal	No irritation
Metker et al., 1977	Rabbits	0.05 mL 25% in ethanol	Dermal	No irritation
Okuno et al., 1976	Japanese white rabbits	0.1 mL technical grade washed at 5 min or 24 hr	Ocular	No irritation

Table 6.8

Lethal Exposure Levels of Permethrin Reported in Animal Studies

Reference	Model	Carrier	Route	LD_{50}
Parkinson et al., 1976	Female rabbit	None	Dermal	>2,000 mg/kg body weight
Parkinson et al., 1976	Female rats	None	Dermal	>4,000 mg/kg body weight
Parkinson, 1978	Male rats	Water	Dermal	>5,176 mg/kg body weight
Kohda et al., 1979	Mouse	None	Dermal	>2,500 mg/kg body weight
Clark, 1978	Rats	Xylene	Dermal	>750 mg/kg body weight
Kohda et al., 1979	Rats	None	Dermal	>2,500 mg/kg body weight
Sasinovich and Panshina, 1987	Rats	None	Dermal	2,000 mg/kg body weight
Parkinson et al., 1976	Rats	Water	Intraperitoneal	>3,200 mg/kg body weight
Parkinson et al., 1976	Female rabbit	Water	Oral	>4,000 mg/kg body weight
Parkinson et al., 1976	Female rats	Water	Oral	>4,000 mg/kg body weight
Piercy et al., 1976	Female Sprague Dawley rats	Corn oil	Oral	LD50 4,251 mg/kg body weight but 3,000 mg/kg for starved rats
Wallwork and Malone, 1974	Female Wistar rats	As is 40% in corn oil 40% in petroleum distillate 40% in DMSO 20% in glycerol	Oral	>20,000 mg/kg body weight 4,672 mg/kg body weight >8,000 mg/kg body weight >8,000 mg/kg body weight >5,048 mg/kg body weight
Millner and Butterworth, 1977	Hen		Oral	>1,500 mg/kg body weight
Jaggers and Parkinson, 1979	Male rats	Corn oil	Oral	500 mg/kg body weight
Parkinson, 1978	Male rats	Water	Oral	2,949 mg/kg body weight
Clark, 1978	Mouse	DMSO	Oral	250–500 mg/kg body weight

Table 6.8 (continued)

Reference	Model	Carrier	Route	LD_{50}
Kohda et al., 1979	Mouse	Corn oil	Oral	Male: 650 mg/kg body weight Female: 540 mg/kg body weight
Parkinson et al., 1976	Mouse	Water	Oral	>4,000 mg/kg body weight
Braun and Killeen, 1975	Rats	Corn oil	Oral	1,200 mg/kg body weight
Clark, 1978	Rats	DMSO	Oral	Male: 1,500 mg/kg body weight Female: 1,000 mg/kg body weight
Kohda et al., 1979	Rats	Corn oil	Oral	Male: 430 mg/kg body weight Female: 470 mg/kg body weight
Sasinovich and Panshina, 1987	Rats	Water	Oral	1,725 mg/kg body weight
Kohda et al., 1979	Mouse	Corn oil	Subcutaneous	>10,000 mg/kg body weight
Kohda et al., 1979	Rats	Corn oil	Subcutaneous	Male: 7,800 mg/kg body weight Female: 6,600 mg/kg body weight

DMSO = dimethyl sulfoxide.

Table 6.9

Subacute and Chronic Effects of Permethrin in Humans

Reference	Subjects	How Applied/Exposed	Absorption	Manifestations and Effects
Kolmodin-Hedman et al., 1982	6 forestry workers	2% aqueous emulsion, inhalation by occupational exposures	1 had detectable levels early	None.
Pegum and Doughty, 1978	17 volunteers	1% in soft paraffin, up to 9 days		2 of 17 developed mild erythema.
Wieseler et al., 1998	22 pest-control operators, 3 specifically exposed to permethrin	Normal commercial application of pyrethroid mix containing permethrin, 1-21 yr		No blood, heart, lung, liver, or nervous system abnormalities. No correlation between the number of complaints and pyrethroid metabolite concentration in urine. Only fatigue was more common in the pyrethroid exposed group. No specific pyrethroids were discussed.

Animal studies of subacute and chronic exposure, even at high doses, generally fail to show any lasting effects (Table 6.10). Only at extremely high doses do animals begin to demonstrate evidence of neurologic impairment. Animal studies repeatedly conclude that the potential for permethrin to induce cancer, even at fairly high exposures, is weak at best (WHO, 1990). In vitro and in vivo tests fail to reveal a mutagenic potential for permethrin (Anderson and Richardson, 1976; Longstaff, 1976; McGregor and Wickramaratne, 1976; Miyamoto, 1976; Newell and Skinner, 1976; Simmon, 1976; Clive, 1977; Suzuki, 1977; Woodruff et al., 1983; Pluijmen et al., 1984; Surralles et al., 1995). Mouse studies with permethrin doses of up to 150 mg/kg body weight from day seven to day 12 of pregnancy failed to show any effect on the pregnant females or offspring (Kohda et al., 1976). Sprague Dawley rat findings were similar with doses of up to 50 mg/kg body weight from day nine to day 14 of pregnancy (Kohda et al., 1976).

Others reported similar findings when exposing CD rats (doses of up to 225 mg/kg, day six to day 16) (McGregor and Wickramaratne, 1976), Sprague Dawley rats (doses of up to 83 mg/kg diet, day six to day 16) (Metker et al., 1977), and Wistar rats (doses of up to 200 mg/kg body weight, day six to day 16) (James, 1974) to permethrin. Dutch rabbits were exposed to 600, 1,200, or 1,800 mg/kg body weight per day (Richards et al., 1980). At all levels, body weight gain decreased, and the two highest doses were embryotoxic but not teratogenic.

Reproductive studies also fail to show any attributable adverse effects from fairly high doses of permethrin: in Long-Evans rats (up to 100 mg/kg in the diet for three generations) (Schroeder and Rinehart, 1977); in Wistar rats (up to 2,500 mg/kg in the diet for 12 weeks [Hodge et al., 1977] or up to 180 mg/kg body weight for three generations [James, 1979]); and in Sprague Dawley rats (up to 4,000 mg/kg in the diet, day six to day 15 of pregnancy) (Spencer and Berhance, 1982).

d-Phenothrin

The literature cites very few references for *d*-phenothrin, and those that are cited repeatedly address the relative safety of this insecticide, and of the pyrethroids in general. The majority of the literature consists of unpublished studies from the chemical and pesticide industry. These references are cited in the International Programme on Chemical Safety (IPCS), a joint effort undertaken by the United Nations, the International Labor Organization, and the World Health Organization (IPCS, 1990).

Acute Effects. The acute effects of *d*-phenothrin on animals are summarized in Table 6.11. The studies cited show toxicity but only at extremely high doses and in routes inconsistent with conventional exposure in humans. Suzuki et al. (1981) failed to show genetic effects on bone marrow with high intraperitoneal doses at up to two days following exposure.

Table 6.10

Subacute and Chronic Effects of Permethrin in Animals

Reference	Model	Concentration and Duration	Exposure Route	Effects
Franz et al., 1996	Hartley male guinea pigs	2 mL 5% permethrin cream for 3 days to a 6 x 8 cm shaved skin	Dermal	Systemic exposure following dermal application was found to be 40 to 400 times lower for 5% permethrin than for 1% lindane.
Flannigan et al., 1985b	New Zealand white rabbits	0.13 mg/cm^2 for 16 days	Dermal	Slight erythema.
Metker et al., 1977	New Zealand white rabbits	0.10, 0.32, 1.0 g/kg body weight for 21 days	Dermal	No effect.
Metker et al., 1977	New Zealand white rabbits	1.25 or 0.125 mg/cm^2 to skin on cloth twice weekly for 3 wk	Dermal	No effect.
Metker, 1978	Beagle dogs	125, 250, or 500 mg/m^3, 6 hr/day, 5 days/wk for 13 wk	Inhalation	No effect.
Metker, 1978	Male Hartley guinea pigs	125, 250, or 500 mg/m^3, 6 hr/day, 5 days/wk for 13 wk	Inhalation	No effect.
Metker, 1978	Sprague Dawley rats	125 or 250 mg/m^3, 6 hr/day, 5 days/wk for 13 wk	Inhalation	No effect.
Metker, 1978	Sprague Dawley rats	500 mg/m^3, 6 hr/day, 5 days/wk for 13 wk	Inhalation	Shortened hexobarbital-induced sleeping time; tremors for first week.
Chesher and Malone, 1974b	New Zealand white rabbits	40% in corn oil 0.1 mL	Ocular	No effect.
Clapp et al., 1977b	Alderly Park mice	200, 400, 2,000, or 4,000 mg/kg diet for 28 days	Oral	No effect on mortality, growth, food utilization.
Clapp et al., 1977b	Alderly Park mice	80 mg/kg diet for 2 weeks, then 10,000 mg/kg for 2 wk	Oral	Weight loss and poor food utilization at 10,000 mg/kg start.
Chesher et al., 1975	Beagle dogs	500 mg/kg body weight for 14 days	Oral	No observed effect.
Killeen and Rapp, 1976a	Beagle dogs	5, 50 mg/kg body weight in gelatin capsules for 3 mo	Oral	No effect except increased liver weight at 50 mg/kg.

Table 6.10 (continued)

Reference	Model	Concentration and Duration	Exposure Route	Effects
Killeen and Rapp, 1976a	Beagle dogs	500 mg/kg body weight in gelatin capsules for 3 mo	Oral	Clinical evidence of poisoning. Normal growth, food consumption, and laboratory parameters.
Reynolds et al., 1978	Beagle dogs	Up to 250 mg/kg body weight for 6 mo	Oral	No observed effect.
Hogan and Rinehart, 1977; Rapp, 1978	CD-1 mice	20 mg/kg diet for 2 yr	Oral	No effect.
Hogan and Rinehart, 1977; Rapp, 1978	CD-1 mice	500 mg/kg diet to wk 19, 5,000 mg/kg next 2 wk, 500 mg/kg rest of 2 yr	Oral	Increased liver weight. No neoplastic effect or laboratory parameter abnormalities.
Hogan and Rinehart, 1977; Rapp, 1978	CD-1 mice	100 mg/kg diet to wk 21, 4,000 mg/kg diet thereafter	Oral	Decreased glucose but no other laboratory finding. No oncogenic effects.
Butterworth and Hend, 1976	Charles River (CD) rats	30, 100, 300 mg/kg diet for 5 wk	Oral	No effect.
Butterworth and Hend, 1976	Charles River (CD) rats	1,000 mg/kg diet for 5 wk	Oral	Increased liver weight in males.
Butterworth and Hend, 1976	Charles River (CD) rats	3,000 mg/kg diet for 5 wk	Oral	Increased liver weight in females. In all: persistent tremors, growth inhibition. No mortality. Slight increase in prothrombin time.
Hend and Butterworth, 1977	Charles River rats	6,000 mg/kg diet up to 14 days	Oral	11 of 12 died. Histologically there were frequent fragmented, swollen sciatic nerve axons and myelin degeneration.
Clapp et al., 1977b	Female Alderly Park mice	At least 2,000 mg/kg diet	Oral	Increased liver, kidney, heart, and spleen weight.
Chesher and Malone, 1974a	Female Dutch rabbits	200, 400, 800 mg/kg body weight	Oral	No significant laboratory abnormalities although more marked weight loss at the 800 mg/kg dose.
Wallwork et al., 1974	Female mice	200, 400, 800, 1,600 mg/kg body weight for 10 days in corn oil	Oral	Spasm and convulsion only in 1,600 mg/kg dose with 50% mortality. No hematology, chemistry, or body weight differences.
Millner and Butterworth, 1977	Hens	1 g/kg 40% solution in DMSO for 5 days	Oral	No delayed neurotoxic effect at 3 wk following exposure.

Table 6.10 (continued)

Reference	Model	Concentration and Duration	Exposure Route	Effects
Ross and Prentice, 1977	Hens	9 g/kg body weight day 1 and 9	Oral	No neurologic signs or histopathologic changes in nervous system at 21 days after the last dose.
Edwards and Iswaran, 1977	Lactating cows	0, 0.2, 1.0, 10, or 50 mg/kg diet for 28 days	Oral	No effect.
Killeen and Rapp, 1976b	Long-Evans rats	0, 20, 100, 500 mg/kg diet for 90 days	Oral	No abnormal laboratory results or mortality. Tremors mostly during first week with 500 mg/kg dose. 100 and 500 mg/kg doses showed increased liver weight.
Braun and Rinehart, 1977; Billups, 1978a; Billups, 1978b	Long-Evans rats	0, 20, 100, 500 mg/kg diet for 2 yr	Oral	No oncogenic potential, no mortality, growth, or food consumption effect. No ophthalmology or laboratory effects except increased glucose at 18 months in females and 24 months in males.
Dyck et al., 1984	Long-Evans rats	Up to 500 mg/kg diet for 2 yr and up to 100 mg/kg diet for 3 generations	Oral	No nerve morphological changes related to feeding of permethrin.
Metker et al., 1977	Long-Evans rats	27, 54, 108 mg/kg body weight for 14 days	Oral	No effect.
Metker et al., 1977	Long-Evans rats	216 and 432 mg/kg body weight for 14 days	Oral	Muscle tremors.
Metker et al., 1977	Long-Evans rats	432 mg/kg body weight for 14 days	Oral	50% of females died.
Clapp et al., 1977b	Male Alderly Park mice	At least 10,000 mg/kg diet	Oral	Increased liver, kidney, heart, and spleen weight.
Glaister et al., 1977	Male Wistar rats	2,500, 3,000, 3,750, 4,500, 5,000, and 7,000 mg/kg diet for 14 days	Oral	Poisoning and death at two highest doses. At lowest doses, signs and symptoms disappeared after a week. Ultrastructural changes were present at the highest 2 doses, including vacuolation and swelling of unmyelinated fibers and Schwann cell hypertrophy.
Ishmael and Litchfield, 1988	SPF Alderly Park strain mice	250 mg/kg diet for 2 yr	Oral	No effect.

Table 6.10 (continued)

Reference	Model	Concentration and Duration	Exposure Route	Effects
Ishmael and Litchfield, 1988	SPF Alderly Park strain mice	1,000, 2,500 mg/kg diet for 2 yr	Oral	No mortality effect. No carcinogenic effect. Liver showed proliferation of smooth endoplasmic reticulum on ultrastructural examination.
Kadota et al., 1975	Sprague Dawley rats	0, 375, 750, 1,500 mg/kg diet for 6 mo	Oral	No effect.
Kadota et al., 1975	Sprague Dawley rats	3,000 mg/kg diet for 6 mo	Oral	No clinical laboratory abnormalities. Hyperexcitability and tremors occurred.
Metker et al., 1977	Sprague Dawley rats	54, 108, 216 mg/kg body weight for 14 days	Oral	No effect.
Metker et al., 1977	Sprague Dawley rats	432, 864, or 1,728 mg/kg body weight for 14 days	Oral	Muscle tremors.
Metker et al., 1977	Sprague Dawley rats	1,728 mg/kg body weight for 14 days	Oral	23 of 24 died.
Dayan, 1980	Sprague Dawley rats	Up to 9,000 mg/kg diet for 21 days	Oral	Severe trembling and weight loss. However, evaluation of brain, spinal cord, trigeminal and dorsal root ganglia, proximal and distal root trunks, and terminal motor and sensory nerves did not demonstrate consistent histopathology.
Clapp et al., 1977a	Wistar rats	0, 200, 500 mg/kg diet for 4 wk	Oral	No effect.
Clapp et al., 1977a	Wistar rats	1,000 mg/kg diet for 4 wk	Oral	Nonspecific signs of poisoning.
Clapp et al., 1977a	Wistar rats	2,500 mg/kg diet for 4 wk	Oral	Hyperexcitability and increased liver weight.
Clapp et al., 1977a	Wistar rats	5,000 mg/kg diet for 4 wk	Oral	Decreased food consumption. No significant change in lab parameters.
Clapp et al., 1977a	Wistar rats	10,000 mg/kg diet	Oral	All died within 3 days.
Ishmael and Litchfield, 1988	Wistar rats	500, 1,000 mg/kg diet for 2 yr	Oral	Increased liver and kidney weight at both levels; increased smooth endoplasmic reticulum at 1 yr but not at 2 yr.
Ishmael and Litchfield, 1988	Wistar rats	2,500 mg/kg diet for 2 yr	Oral	Tremors and hyperexcitability for 2 wk. No related mortality; no change in growth or food consumption. No laboratory abnormalities. Increased smooth endoplasmic reticulum.

Table 6.11

Acute Effects of *d*-Phenothrin in Animals

Reference	Model	Concentration/ Duration	Route of Exposure	Manifestations and Effects
Segawa, 1979b	Sprague Dawley rats	>10,000 mg/kg body weight	Oral, subcutaneous, dermal, intraperitoneal	LD_{50}.
Segawa, 1979a	DdY mice	>10,000 mg/kg body weight	Oral, subcutaneous, intraperitoneal	LD_{50}.
Segawa, 1979a	DdY mice	>5,000 mg/kg body weight	Dermal	LD_{50}.
Kohda et al., 1979	Sprague Dawley rats	>3,760 mg/m^3	Inhalation	4-hr LC_{50}; no neurotoxicity observed.
Kohda et al., 1979	ICR mice	>1,180 mg/ m^3	Inhalation	4-hr LC_{50}.
Hiromori et al., 1984	ICR mice	265-315 mg/kg	Intravenous	LD_{50}.
Okuno et al., 1978	Sprague Dawley rats	5,000 mg/kg body weight per day for 5 days	Oral	1 of 10 females died after 4 doses. Signs of toxicity (piloerection, urinary incontinence) appeared but rapidly resolved after discontinuation.
Suzuki et al., 1981	ICR mice	2,500, 5,000, or 10,000 mg/kg once, then bone marrow examined at 6, 24, and 48 hr	Intraperitoneal	No chromosomal aberrations.

The literature does not provide evidence of *d*-phenothrin toxicity to humans. Hashimoto et al. (1980) found no adverse effects (dermal irritation, clinical signs, blood chemistry, or hematology) following dermal exposure of volunteers at concentrations of 0.44 to 0.67 mg/kg body weight per day for three days. Matoba modeled the risk assessment following residual spraying of *d*-phenothrin; and with aerosolization of 0.9 g *d*-phenothrin (and 1.1 g d-tetramethrin) in a 300 mL container, there was a 24,400 margin of safety (21,300 for infants) even under the worst conditions (windows closed, contrary to label instructions) (Matoba et al., 1998). The margin of safety is defined as the NOEL/exposure; the study used animal data to estimate the NOEL.[4]

[4]The no observable effect level (NOEL) is the lowest administered dose or exposure that results in no statistically significant difference from control.

Table 6.12

Chronic Effects of *d*-Phenothrin in Animals

References	Model	Concentration/ Duration	Route of Exposure	Manifestations and Effects
Murakami et al., 1981	Sprague Dawley rats	Up to 10,000 mg/kg per day for 6 mo	Oral	No effect on mortality, clinical signs, ophthalmology, urinalysis, or histopathology. NOEL M:F reported to be 55.4:63.3 mg/kg/day.
Martin et al., 1987	Fisher-344 rats	Up to 3,000 mg/kg per day for 105-118 days	Oral	No clinical signs, mortality, or food and water consumption, ophthalmology, blood biochemistry, urinalysis, or hematology changes. No oncogenic activity. NOEL M:F reported to be 47:56 mg/kg/day.
Amyes et al., 1987	B6C3F$_1$ hybrid mice	Up to 3,000 mg/kg per day for 2 yr	Oral	No clinical signs, mortality, ophthalmology, blood, urinalysis, or hematology changes. No tumor profile changes. NOEL M:F reported to be 40:164 mg/kg/day.
Pence et al., 1981	Beagle dogs	Up to 1,000 mg/kg in diet for 26 wk	Oral	No effects on mortality, clinical signs, body weight, food consumption, ophthalmology, histopathology, hematology, or urinalysis. NOEL reported to be 300 mg/kg diet per day.
Cox et al., 1987	Beagle dogs	Up to 1,000 mg/kg in diet per day for 1 yr	Oral	No effects on clinical signs, body weight, food consumption, ophthalmology, or urinalysis. NOEL M:F reported to be 8.24:26.77 mg/kg body weight/day.
Cox et al., 1987	Beagle dogs	3,000 mg/kg in diet per day for 1 yr	Oral	Decreased erythrocyte count, hemoglobin, and hematocrit, decreased total protein, increased liver weight, histopathological changes in adrenal and liver in some animals.
Rutter, 1974	New Zealand white rabbits	0, 10, 100, or 1,000 mg/kg body weight days 6-18 of gestation, sacrificed at day 29 or 30	Oral	No abnormalities in the does or fetuses (implantation sites, corpora lutea, resorption sites, weight, condition, viability). No effects on gestation.
Nakamoto et al., 1973	ICR mice	0, 30, 300, 3,000 mg/kg body weight days 7–12 of gestation, sacrificed on day 18 of gestation	Oral	No adverse effects as indicated by maternal growth, fetal mortality, and external and internal examination of fetuses for teratogenic or embryotoxic effects.
Nakamoto et al., 1973	ICR mice	0, 300, 3,000 mg/kg body weight days 7-12 of gestation, pups examined 29 days after delivery	Oral	No adverse effects as indicated by maternal growth, fetal mortality, and external and internal examination of fetuses for teratogenic or embryotoxic effects.
Tesh et al., 1987	Charles River CD rats	Up to 1,000 mg/kg diet for 3 generations	Oral	No effect on mortality, somatic growth, development, or reproductive performance. NOEL stated to be 1,000 mg/kg diet.
Tesh et al., 1987	Charles River CD rats	3,000 mg/kg diet for 3 generations	Oral	No effect on mortality, body weight, reproductive performance. Third generation normal. Slight increase in liver weight for first two generations.

Chronic, Reproductive, Genetic, and Carcinogenic Effects. The chronic effects of *d*-phenothrin on animals are summarized in Table 6.12. The studies cited show toxicity but only at extremely high oral doses that are inconsistent with conventional human exposure. Even at these high exposures, reproductive, genetic, and carcinogenic effects were not observed.

The literature does not provide evidence of chronic *d*-phenothrin toxicity to humans.

SYNTHESIS

Pyrethroids, particularly permethrin and *d*-phenothrin, are safe and effective when used in recommended applications. Studies show that these compounds are potentially toxic at extremely high exposures; however, when used in conventional ways, only minor skin irritation in sensitive individuals results. Clinical manifestations subside after short periods when the inciting exposure is discontinued.