National Research Council (US) Subcommittee to Review Permethrin Toxicity from Military Uniforms. Health Effects of Permethrin-Impregnated Army Battle-Dress Uniforms. Washington (DC): National Academies Press (US); 1994.

4 Acute and Short-Term Toxicity of Permethrin

ACUTE TOXICITY

Human Studies

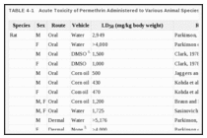
There are few human studies with permethrin. However, exposures to natural pyrethrins have been associated with dermal, pulmonary, and allergic responses. The allergic responses have been attributed to impurities in the pyrethrins. Most of the studies of synthetic pyrethroids involved workers applying the chemicals for fly control (Prinsen and van Sittert, 1978). Medical examinations, including extensive neurological and electrophysiological examinations, of these individuals failed to demonstrate any abnormality. Skin sensations and paresthesia have been reported in workers heavily exposed (dermally) to permethrin. These symptoms develop shortly after exposure (with a latent period as short as 30 min), peak by 8 hr, and disappear by 24 hr. Other symptoms that have been reported include numbness, itching, tingling, and a burning sensation.

Animal Studies

Synthetic pyrethroids, such as permethrin, are some of the least toxic insecticides to mammals, especially when compared with the more com monly used insecticides—organochlorine, organophosphorus, and methylcarbamate. Permethrin appears to be less toxic than other synthetic pyrethroids, such as cypermethrin and fenvalerate (NRCC, 1986). The acute (single dose) oral LD_{50} of technical-grade permethrin (purity 90.5-97.2% and consisting of mixtures of cis/trans isomers in various proportions) in animals (rats, mice, guinea pigs, and chickens) is in the range of 0.5-5 g/kg of body weight, depending on the vehicle used for administration. Permethrin is more toxic when formulated with corn oil, dimethyl sulfoxide, and propylene glycol than when in an aqueous suspension (perhaps because of greater solubility of permethrin in organic solvents than in water) (Table 4-1). Death in animals occurs within 3 days of exposure to permethrin. The cis/trans isomeric ratio also appears to affect toxicity, the cis isomer being more toxic than the trans isomer in animals (Table 4-2).

TABLE 4-1

Acute Toxicity of Permethrin Administered to Various Animal Species.



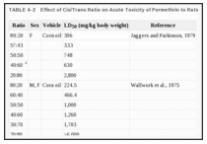


TABLE 4-2

Effect of Cis/Trans Ratio on Acute Toxicity of Permethrin to Rats.

Clinical signs of toxicity, when evident, occur within 2 hr and are associated with central nervous system functions. Permethrin belongs to the Type I group of pyrethroids, and exposure to permethrin is associated with tremors (T syndrome), convulsions, irregular breathing and increased respiratory rates, incoordination, ataxia, hyperactivity, prostration, and paralysis. Other signs that have been reported include hyperexcitability to external stimuli, lacrimation, occasional diarrhea, defecation, and urinary incontinence (Ishmael, 1989). Core body temperature is increased when clinical signs are severe. Signs of toxicity can last up to 3 days after acute exposure. None of the major permethrin metabolites shows greater toxicity than the parent compound.

Shapiro (1989a) administered the tick-repellent formulation (0.5% permethrin used on human clothing to repel arthropods) orally to rats at 5 g/kg of body weight 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 an air concentration of the tick-repellent formulation at 4.84 mg/L (774 mg/kg of body weight) (Ben-Dyke et al., 1987). Hemorrhaging or white or pale patches in the lungs were observed in 8 of 10 treated rats in this study during gross pathological examination.

Acute toxicity of permethrin from dermal exposure is lower than that from other routes of exposure in several animal species (Table 4-3). No deaths were observed when technical-grade permethrin was applied to the skin of rats at 2 g/kg of body weight, but tiptoe gait, upward curva ture of the spine, and urinary incontinence were observed in several animals (Robinson, 1989a). This dose of 2 g/kg was considered to be the lowest-observed-effect level (LOAEL). The no-observed-adverse-effect level (NOAEL) was estimated to be 200 mg/kg by dividing the LOAEL (2 g/kg) by an uncertainty factor of 10 (CEPA, 1992). The only sys temic signs seen when the tick-repellent formulation was applied topi cally to rabbits at 2 g/kg were weight loss and diarrhea in one animal on days 10-14 (Shapiro, 1989b).

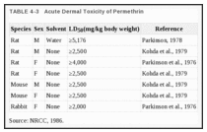


TABLE 4-3

Acute Dermal Toxicity of Permethrin.

Neurological effects typical of pyrethroids were observed when rats were exposed to technical-grade permethrin by the inhalation route at concentrations of 2,280 mg/m^3 for 4 hr (internal dose of 365 mg/kg), including paw flicking (probably paresthesias), splayed gait, tail erection, depressed reflexes, and tiptoe gait (Brammer, 1989). Those effects might reflect a higher internal dose rather than a route-specific effect (CEPA, 1992). Death occurred at air concentrations of 2,280 mg/m^3 (internal dose of 365 mg/kg) and higher. The LOEL was 240 μg/L (internal dose of 38 mg/kg). The NOEL was estimated to be 24 mg/m^3 (3.8 mg/kg) by dividing the LOEL by an uncertainty factor of 10 (CEPA, 1992).

SUBACUTE AND SUBCHRONIC TOXICITY

Oral Exposure

Mouse

Alderley Park mice (20 of each sex per group) were fed permethrin in the diet at concentrations of 0, 200, 400, 2,000, or 4,000 mg/kg of diet for 28 days. Mortality, growth, and food consumption were normal in all dose groups. One additional group (permethrin dose of 80 mg/kg for 2 weeks and 10,000 mg/kg for the final 2 weeks) showed weight loss and poor food consumption when permethrin feeding was begun at 10,000 mg/kg. Mice fed permethrin at 2,000 mg/kg of diet or more showed increased liver weight and liver-to-body-weight ratio. Higher weight and organ-to-body-weight ratios were also observed in the heart, kidney, and spleen of male mice in the 10,000-mg/kg dose group. Gross tissue changes were observed in female mice in the 2,000- and 10,000-mg/kg groups. Histopathological examination showed regenerating tubules in the renal cortex, hypertrophy of centrilobular hepatocytes with cytoplasmic eosinophilia, that were not dose related; these changes were observed in all the treated animals (Clapp et al., 1977a).

In another study, groups of six female mice were administered daily oral doses of permethrin (cis/trans ratio, 25:75) in corn oil at 0, 200, 400, 800, or 1,600 mg/kg of body weight for 10 consecutive days. Signs of acute toxicity, such as spasm and convulsion, were seen only in the animals in the highest dose group, half of which died after the initial dose. No significant changes were observed in hematology, clinical chemistry, or body weights after 11 doses. The mice administered permethrin at 800 and 1,600 mg/kg of body weight showed increased liver weights (Wallwork et al., 1974a).

Rat

In studies by Metker et al. (1977), Sprague-Dawley rats (six of each sex per group) were administered permethrin in the diet for 2 weeks at doses of 54, 108, 216, 432, 864, or 1,728 mg/kg of body weight per day. All rats surviving to term

were killed, and various tissues and organs were examined histopathologically. At the two highest doses (864 and 1,728 mg/kg of body weight), all animals died except one female in the 864-mg/kg group. Muscle tremors were observed in all animals in the 432-mg/kg group, but doses of 216 mg/kg or less produced no toxic signs in either male or female rats. Statistically significant increases in liver-to-body-weight ratios were seen at 432 mg/kg, but compound-related histological changes were not observed in any of the tissues or organs. The maximum NOEL in this study was 216 mg/kg.

Long-Evans rats (six of each sex per group) were also administered permethrin in the diet for 2 weeks at 0, 27, 54, 108, 216, or 432 mg/kg of body weight per day (Metker et al., 1977). All rats surviving to term were killed, and various tissues and organs were examined histopathologically. At 432 mg/kg, three of six females died in the first 5 days. Muscle tremors were observed in all surviving animals in the 216- and 432-mg/kg groups. A statistically significant increase was seen among female rats in the liver-to-body-weight ratio. Compound-related histological changes were not observed in any of the tissues or organs examined. The maximum dietary NOEL was calculated to be 108 mg/kg of body weight per day.

Clapp et al. (1977b) fed Wistar rats (eight of each sex per group) permethrin at 0, 200, 500, 1,000, 2,500, 5,000, or 10,000 mg/kg of diet for 4 weeks. All rats that received the highest dose died within 3 days. Mortality was seen at 5,000 mg/kg, and hyperexcitability was observed in animals that received 2,500 mg/kg. Food consumption and growth decreased in animals in the 5,000-mg/kg group. There was no effect on hematological values, clinical chemistry, or urinalysis except for a reduction in urinary protein excretion in male rats at 5,000 mg/kg. Liver weight and liver-to-body-weight ratios were increased in males at 2,500 mg/kg or greater and in females at 1,000 mg/kg or greater.

Bradbrook et al. (1977) studied the reversibility of hepatic changes in Wistar rats following short-term dietary administration of permethrin. Female Wistar rats (48 rats per group) were fed permethrin at 0 or 2,500 mg/kg of diet for 28 days. At the end of the feeding regimen, rats were either killed or maintained on control diets and sacrificed 1, 4, or 8 weeks after termination of dosing. None of the permethrin-treated rats died during the dosing period, but food consumption and body weights were reduced. However, the animals gained weight rapidly after the dosing period, and no differences in body weight between control and permethrin-treated animals were observed at the end of the study period. After 4 weeks of permethrin dosing, significantly higher absolute and relative liver weights were observed. During the 8-week recovery period, relative liver weights of permethrin-treated animals were significantly higher than liver weights of control animals, but absolute liver weights of control and test animals were similar. Oxidative enzyme activity in liver microsomes was significantly higher in permethrin-treated animals than in controls at the end of dosing and 1 week later. The activity of liver microsomal enzymes was normal 4 weeks after dosing in the permethrin-treated animals. The amount of smooth endoplasmic reticulum in rat liver cells was significantly increased as a result of

permethrin dosing, but within 4 weeks after dosing, no significant histological differences were observed in the livers of treated and control animals (Bradbrook et al., 1977).

Butterworth and Hend (1976) fed CD rats (six of each sex per group) permethrin at 0, 30, 100, 300, 1,000, or 3,000 mg/kg of diet for 5 weeks. Persistent tremors were seen in animals fed at 3,000 mg/kg, but none died. Growth was inhibited at that dose in both male and female rats. Relative liver weights were increased in male rats (groups fed 1,000 mg/kg of diet or higher) and female rats (fed 3,000 mg/kg). Histopathological examination of tissues and organs of the animals receiving the two highest doses did not show any adverse effects as a result of permethrin ingestion in the diet (Butterworth and Hend, 1976).

Killeen and Rapp (1976a) fed Long-Evans rats (10 of each sex per group) permethrin in the diet at 0, 20, 100, or 500 mg/kg of diet for 90 days. None died, and growth and food consumption of all animals were normal. The results of hematology, clinical chemistry, urinalysis, and ophthalmological examinations were also normal. Tremors were observed in some animals at the highest dose, mainly during the first week of treatment. Significant increases in absolute and relative liver weights were observed at the two highest doses. Those increases were consistent with data from microscopic examination of the liver showing compound-related centrilobular hepatocyte hypertrophy in both males and females. There were no significant effects at the 20-mg/kg dose, although slight hepatic effects were reported in a few of the male rats.

Sprague-Dawley rats (10 of each sex per group) were fed permethrin in the diet for 90 days at 0, 9, 27, 85, 270, or 850 mg/kg of body weight per day (Metker et al., 1977). All rats surviving to term were killed, and various tissues and organs from each animal were examined histopathologically. All male and female rats in the 850-mg/kg group died. An increase in the average liver-to-body-weight ratio was noted in both male and female rats fed 270 mg/kg. Compound-related histological changes were not observed in any of the tissues and organs examined. The minimum-effect dose was 270 mg/kg per day. At 85 mg/kg, no effects were observed.

Kadota et al. (1975) fed Sprague-Dawley rats (16 of each sex per group) permethrin in their diet at 0, 375, 750, 1,500, or 3,000 mg/kg of diet for 6 months. None died, and all animals exhibited normal growth and normal food and water consumption. Urinalysis and hematological and clinical biochemistry values were within normal limits. Signs of hyperexcitability and tremors were observed during the study in animals given 3,000 mg/kg, and their liver weights and liver-to-body-weight ratios were slightly increased. No significant histopathological findings were attributable to the presence of permethrin in the diet. The NOEL was 1,500 mg/kg (Kadota et al., 1975).

Hart et al. (1977) conducted a study to evaluate liver hypertrophy. Groups of male and female Wistar rats were fed permethrin at 0, 20, 100, or 1,000 mg/kg of diet for 26 weeks. None died, and growth and food consumption were normal. Although the mean liver weight was increased at all doses, a significant increase was observed only at the

highest dose. The increase in liver weight at that dose was accompanied by an increase in the smooth endoplasmic reticulum and in biochemical changes associated with microsomal oxidative mechanisms. In the 100-mg/kg group, there were slight, insignificant increases in biochemical activities. No effects on any of the values were observed in animals receiving 20 mg/kg.

Dog

Killeen and Rapp (1976b) fed beagle dogs (four of each sex per group) permethrin in gelatin capsules daily for 3 months at doses of 0, 5, 50, or 500 mg/kg of body weight. None died, but clinical signs of poisoning were observed at various times in both males and females at the highest dose. Food consumption and growth as well as clinical chemistry, hematological, and urinalysis values were normal. The liver weights and liver-to-body-weight ratios of animals that received permethrin at 50 mg/kg or more were significantly increased. Histopathological examination did not show any adverse changes attributable to permethrin treatment (Killeen and Rapp, 1976b).

Beagle dogs (four of each sex per group) were administered permethrin in gelatin capsules daily for 13 weeks at doses of 0, 10, 100, and 2,000 mg/kg of body weight. Permethrin treatment did not result in increased mortality, but clinical signs of poisoning were observed in the dogs in the 2,000-mg/kg group. Hematological, clinical chemistry, and urinalysis values were within normal limits in all animals. There was a slight increase in the liver weight of animals receiving 2,000 mg/kg per day but no accompanying histopathological changes in the liver (Edwards et al., 1976).

Chesher et al. (1975a) administered two beagle dogs daily oral doses of permethrin (cis/trans ratio, 25:75) at 500 mg/kg of body weight for 14 days. No clinical signs of toxicity or significant effects of the treatment on body weight or on clinical chemistry or hematological values were observed.

Reynolds et al. (1978) administered beagle dogs (four males and four females in each group) encapsulated permethrin (cis/trans ratio, 25:75) at doses of 0, 10, 50, or 250 mg/kg of body weight for 6 months. No signs of toxicity and no effect on body weight were seen. No gross pathological or significant histopathological findings were seen. Hematological and clinical chemistry values were within normal limits.

Rabbit

Chesher and Malone (1974a) administered permethrin by gavage to groups of five female Dutch rabbits in 10 daily doses in corn oil at 0, 200, 400, or 800 mg/kg of body weight. The animals were killed on the 11th day. One rabbit, receiving 400 mg/kg of body weight, exhibited mild hyperactivity and muscular fasciculation, but only on days 6 and 7. Although all animals, including the controls, exhibited some degree of weight loss, it was most marked in the high-dose group. There were no significant hematological or clinical chemistry findings.

Cow

Edwards and Iswaran (1977) fed lactating cows (three per group) permethrin at 0, 0.2, 1.0, 10, or 50 mg/kg of diet for 28 days. No mortality was seen. Growth and milk production were normal, and no histopathological changes in the tissues were observed.

Dermal Exposure

Metker et al. (1977) applied technical-grade permethrin daily to the clipped skin of New Zealand White rabbits (eight males per group) at dose levels of 0, 0.10, 0.32, or 1.0 mg/kg of body weight for 21 consecutive days. The application site was abraded on the first test day in half (four) of the animals in each group. Blood samples were drawn weekly from the animals for clinical chemistry studies. All animals were killed on the tenth day after permethrin treatment was terminated. Various tissues and organs were removed from each animal and examined for microscopic lesions. A moderate primary irritation of the skin was produced by permethrin. No significant changes in body weight, organ weight, or clinical chemistry values were observed. No compound-related lesions in the skin or other tissues were observed.

Permethrin (dissolved in acetone) or acetone (as a control) was also applied on the skin twice a week for 3 weeks to six groups of 10 shaved male New Zealand White rabbits (Metker et al., 1977). Cotton cloth treated with permethrin (0.125 or 1.25 mg/cm^2) was applied to the skin over 1 mL of artificial sweat. The solution contained lactic acid, sodium chloride, urea, potassium chloride, glycine, glucose, ammonium hydroxide, and distilled water. In the case of other rabbits similarly treated, the sweat was omitted. In the control groups, acetone-treated cotton cloth with or without 1 mL of sweat was used. Blood samples were collected once a week for clinical chemistry determinations. All animals surviving to term were killed, and various tissues and organs from each animal were examined. No significant changes were noted in rabbit body weight or organ-to-body-weight ratios at the end of the 21-day test, and no skin irritation was observed. There were no significant changes in clinical chemistry values in the treated groups and no compound-related lesions on the skin or in other tissues and organs examined (Metker et al., 1977). Although the data on dermal toxicity from subacute exposures are scanty, the available information shows that subacute exposure to permethrin is unlikely to cause dermal effects.

Inhalation Exposure

Metker (1978) evaluated the inhalation toxicity of technical-grade permethrin in guinea pigs, Sprague-Dawley rats, and beagle dogs. The animals were exposed to an aerosol of permethrin at concentrations of 125, 250, or 500 mg/m^3, 6 hr per day, 5 days per week for 13 weeks. At 500 mg/m^3, tremors and convulsions were observed in the rats during the first

week of exposure but disappeared in the second week. Urine metabolite studies indicated that permethrin was rapidly metabolized and excreted. Post-exposure experiments in male rats showed that the hexabarbital-induced sleeping time was significantly shortened after exposures at 500 mg/m^3 but not at lower doses. No clinical signs of permethrin toxicity were observed in the guinea pigs and dogs when exposed to aerosols of permethrin under similar conditions. Pulmonary function, clinical chemistry values, and blood-cell counts were normal. No compound-related gross or microscopic pathological changes were observed in the dogs, rats, or guinea pigs as a result of permethrin inhalation (Metker, 1978).

CONCLUSIONS

Permethrin is acutely toxic at high doses in animals and humans (LD_{50} for animals is greater than 1 g/kg); the toxicity varies with the cis/trans ratio—the cis isomer being more toxic than the trans isomer. Acute signs of toxicity to the central nervous system include incoordination, ataxia, hyperactivity, convulsions, and finally prostration, paralysis, and death. Permethrin can be an ocular irritant following direct application to the eye, but that would not result from its intended use in BDUs. It can also be a skin irritant and sensitizer after dermal exposure at high concentrations, but permethrin in BDUs at the intended concentrations is not likely to result in skin irritation or skin sensitization.

There is little evidence that short-term (up to 13 weeks), repeated exposures are highly toxic to mammals; the NOEL in feeding studies of rats ranged from 20 to 1,500 mg/kg of diet in 3- and 6-month studies. Rats and mice have survived exposures as high as 10,000 mg/kg (in feed) for 2-26 weeks, although clinical signs of toxicity were clearly evident (IPCS, 1990). NOELs in dogs ranged from 5 mg/kg per day in a 3-month study to 250 mg/kg per day in a 6-month study (IPCS, 1990). Therefore, the lowest LOEL (5 mg/kg) was selected for risk calculations.

In most studies, no effects were observed in hematological or serum chemistry values, even at exposures that produced clinical signs of toxicity. However, at near lethal doses in rats, increases in serum aspartate aminotransaminase (SGOT), alanine aminotransaminase (GTP), and lactic dehydrogenase (LDH) enzymes were reported, which suggest some liver toxicity.

The primary organ showing morphological changes is the liver. In most studies in rodents, livers were enlarged (absolute and relative to body weight) but only at clearly toxic doses, and they returned close to normal after exposure ceased. Microscopically, hepatocellular swelling occurred, which has been attributed to increased microsomal activity resulting in a proliferation of endoplasmic reticulum. No morphological changes in the liver of dogs were observed at exposures of up to 2,000 mg/kg per day (in gelatin capsules) for 3 months, although a slight increase in liver weight was observed at doses above 50 mg/kg. No significant toxic effects were seen in rabbits or cows administered permethrin for 10 or 28 days, respectively.

The lowest NOEL from subchronic toxicity studies of permethrin was estimated to be 5 mg/kg per day in dogs. That NOEL and the daily exposure to permethrin of 6.8×10^{-5} mg/kg per day from wearing permethrin-impregnated BDUs provide a margin of safety (MOS) of approximately 74,000 in the following equation:

$$\text{MOS} = \frac{\text{NOEL}}{\text{Daily Intake}} = \frac{5 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 74{,}000.$$

Because the daily lifetime dose for garment workers is less than the daily dose for military personnel (3×10^{-5} mg/kg per day), the MOS for garment workers is even higher—168,000. Therefore, the acute or subchronic toxicity of permethrin should not be a concern when soldiers wear permethrin-treated BDUs or workers handle permethrin-treated fabric.

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