Health Effects of Permethrin-Impregnated Army Battle-Dress Uniforms

Subcommittee to Review Permethrin Toxicity from Military Uniforms, Committee on Toxicology, Board on Environmental Studies and Toxicology,National Research Council

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Preface

Military personnel sometimes must be rapidly deployed to areas where life-threatening, insect-borne diseases are prevalent. This places such personnel at an increased risk of contracting diseases such as malaria, scrub typhus, leishmaniasis, and Lyme disease. The suddenness of deployments and movement after deployment often precludes the use of protection or control measures. To protect against specific disease risks from insect bites, the U.S. Army has formulated a clothing impregnant containing permethrin, a pyrethroid insecticide that is effective against disease vectors such as mosquitoes, ticks, and other arthropods. The Army proposes to use permethrin-impregnated fabric to manufacture battle-dress uniforms (BDUs). BDUs, made from either 100% cotton fabric or 50% nylon and 50% cotton fabric, are used to camouflage soldiers.

The U.S. Environmental Protection Agency has classified permethrin as a potential carcinogen, so there might be concern that soldiers wearing permethrin-impregnated BDUs would face an unacceptable level of cancer risk. In response to that potential concern, the Army requested that the National Research Council (NRC) review the toxicological and exposure data and make recommendations regarding long-term exposure to permethrin. This project was assigned to the NRC's Committee on Toxicology (COT). The Subcommittee on Permethrin Toxicity from Military Uniforms was established within COT to perform this task. The subcommittee reviewed the toxicity data as well as the exposure and pharmacokinetic data on permethrin and assessed the suitability of military personnel wearing permethrin-impregnated BDUs on a long-term basis. The report of the subcommittee is intended for use by the Army

in deciding whether to impregnate BDUs with permethrin to protect soldiers from arthropod-borne diseases. The subcommittee in this report also assessed the risk to garment workers who handle permethrin-impregnated fabric.

The subcommittee gratefully acknowledges Lieutenant Colonel Holly Doyne, Colonel Frederick Erdtmann, and Colonel Eric Evenson of the U.S. Army for their interest and support of the project. We also thank other persons who provided information for the subcommittee, including Major Stephen Berté, Lieutenant Colonel Phillip Pierce, Lieutenant Colonel Lyman Roberts, Hubert Snodgrass (all of the U.S. Army), and David Taplin (University of Miami).

We are grateful to the NRC's anonymous reviewers for their many helpful comments and suggestions that have resulted in improvements of the subcommittee's report. This report could not have been produced without the untiring efforts of the NRC staff, including James J. Reisa, director, Board on Environmental Studies and Toxicology; Richard D. Thomas, program director, COT; Ruth E. Crossgrove, editor; Wanda Smarr, project assistant; and Catherine Kubik, senior program assistant.

The subcommittee especially acknowledges its great debt to Kulbir S. Bakshi, who not only ably fulfilled the role of project director, but contributed substantially to the drafting and revision of the report. Without his skills and input, our task could never have been completed in the timely manner it has been.

Finally, we would like to thank all members of the subcommittee for their expertise, input, and support throughout our deliberations.

Ernest Eugene McConnell, *Chair*
Subcommittee to Review Permethrin
Toxicity from Military Uniforms
Rogene F. Henderson, *Chair*
Committee on Toxicology

Contents

Summary

More active military service days have been lost to diseases—many of them transmitted by insects—than to combat. In the Vietnam War and the Persian Gulf War, disease casualties (caused mostly by insect bites) outnumbered combat casualties. U.S. military personnel deployed on field operations all over the world face an increased risk of mortality or morbidity from insect-borne diseases. More than 60 diseases are spread between humans and animals by arthropod vectors such as mosquitoes, ticks, flies, and mites. The insect-borne diseases most often encountered by U.S. overseas troops are malaria, scrub typhus, leishmaniasis, and Congo-Crimean hemorrhagic fever. Three tick-borne diseases—Lyme disease, Rocky Mountain spotted fever, and Colorado tick fever—are often encountered by U.S. military personnel in the United States during stateside training exercises.

U.S. military personnel deployed overseas to insect-infested areas usually have not acquired natural immunity to insect-borne diseases and, therefore, are at increased risk of developing those diseases. Some insect-borne diseases are fatal if not diagnosed and treated promptly, and traditional chemoprophylactic and therapeutic treatments for these diseases are often inadequate. Vaccines are not available against many of the insect-transmitted diseases. Vector-control procedures have been effective in reducing, but not eradicating, insect and other arthropod populations and slowing the transmission of disease. However, rapidly

moving military units cannot wait for pesticide programs to be completed, and spraying is impossible in areas under enemy control.

Thus, personal protection methods are important alternatives for controlling insect-borne diseases. Such methods include the use of topical repellents and clothing impregnants to prevent contact with insects and other arthropods. Those products can be used separately or in combination to obtain up to 100% protection from biting arthropods.

N, N-diethyl-*m*-toluamide (DEET), a topical insect repellent, has proved to be effective against insects. It provides protection, especially against mosquitoes, for up to 8 hr. However, DEET has several drawbacks—it has a distinctive odor, it washes off easily and needs to be reapplied frequently, and it damages plastics.

Permethrin is a synthetic pyrethroid insecticide, used on vegetable and fruit crops for control of insects. Although highly toxic to insects and other arthropods, it is one of the least toxic insecticides to mammals. Controlled experiments in the laboratory and with human volunteers in the field show that clothing impregnated or sprayed with permethrin offers reliable protection against a wide range of vector insects and arthropods, such as mosquitoes, human body lice, tsetse flies, and ticks, including *Ixodes dammini,* the principal vector of Lyme disease and human babesiosis in the United States. Therefore, the U.S. Army has proposed using permethrin as a clothing impregnant in battle-dress uniforms (BDUs) to kill or repel insects, ticks, and mites.

Efficacy tests conducted by the U.S. Department of Agriculture and the U.S. Department of Defense show that the wearing of permethrin-impregnated BDUs in conjunction with application of DEET to areas of skin not covered by BDUs provides nearly 100% protection against bites from most insect vectors. (BDUs, made from either 100% cotton fabric or 50% nylon and 50% cotton fabric, are used to camouflage soldiers.)

Before introducing permethrin-impregnated BDUs for military personnel, the U.S. Army wanted a thorough and independent evaluation of the safety of wearing them or working with permethrin-impregnated fabric (as do garment workers) for long periods. Therefore, the Army requested that the National Research Council (NRC) review the toxicological and exposure data on permethrin to determine whether wearing BDUs impregnated with permethrin (at a concentration of 0.125 mg/cm^2 of fabric) 18 hr per day, 7 days per week, for up to 10 years is safe for soldiers,

and whether handling permethrin-impregnated fabric is safe for garment workers. The Army also asked the NRC to identify gaps in the permethrin toxicity data and make recommendations for future research.

In response to the Army's request, the NRC's Committee on Toxicology established the Subcommittee to Review Permethrin Toxicity from Military Uniforms, which prepared this report. The subcommittee based its evaluation of permethrin-impregnated BDUs on a detailed examination of current data on permethrin toxicity in animals and humans, pharmacokinetics, and potential exposure of military personnel and garment workers.

EXPOSURE ASSESSMENT

The subcommittee considered the dermal route to be the only significant route of exposure for soldiers wearing permethrin-impregnated BDUs. Because permethrin is solid at room temperature and has a relatively low vapor pressure, the subcommittee concluded that the inhalation route is probably insignificant and need not be considered. At present, there is no information to indicate that significant exposure to permethrin will occur by any route other than dermal absorption in soldiers wearing permethrin-impregnated BDUs.

Several conversion factors were used to translate the proposed fabric-impregnation concentration, 0.125 mg/cm^2, to an estimated internal dose for military personnel through dermal absorption. These factors were the time-weighted-average percentage of permethrin remaining in fabric through 50 washings (26%), percentage of permethrin migration from fabric to skin (0.49%/day), body-contact area (1.5 m^2), dermal absorption rate (2%/day), and adult body weight (70 kg).

To adjust for actual exposure conditions, it was assumed that military personnel would wear the permethrin-treated BDUs 18 hr per day for 10 years during a 75-year lifetime. Adjusting for the proportion of lifetime exposure resulted in a calculated average daily lifetime dose of 6.8×10^{-5} mg/kg per day. The only difference between field and nonfield military personnel is that field troops apply DEET topically to areas of the skin not normally covered by permethrin-treated BDUs. However, less than 5% of the skin would be expected to have overlapping exposure to

DEET and permethrin. Thus, no adjustment was made to distinguish between exposure patterns for military field personnel and nonfield personnel.

The average daily lifetime internal dose for garment workers was calculated to be 3.0×10^{-5} mg/kg per day—less than half the daily dose calculated for military personnel. That dose is only for dermal exposure from direct contact with permethrin-treated cloth and does not include possible exposure to permethrin by inhalation of permethrin-impregnated airborne particles from cutting and sewing the treated fabric. The subcommittee recommends that studies should be conducted to collect data on representative permethrin exposure factors to produce a more complete and accurate risk characterization for garment workers.

PHARMACOKINETICS

Following absorption, permethrin is extensively and rapidly metabolized. The two major pathways for metabolism are hydrolysis, which essentially splits the permethrin molecule in two, and oxidation, which occurs at a number of carbon atoms throughout the molecule. Both of these metabolic processes make the resulting permethrin metabolite more water soluble and more likely to be excreted in the urine. Thus, metabolism can be viewed as an important detoxification pathway for permethrin, because only the parent chemical exerts toxic effects.

Experiments with laboratory animals have shown that, upon absorption, permethrin is distributed throughout the body but appears to concentrate predominantly in fat. Solubility in fat might explain its high concentrations in brain and nervous tissue in comparison with other body organs.

Because dermal penetration of many chemicals is enhanced by DEET, use of DEET in combination with permethrin might also facilitate dermal absorption of permethrin. Research specifically on the interaction of DEET and permethrin has not been conducted. Facilitated absorption of permethrin by DEET represents an area of uncertainty in assessing risk for military personnel who wear permethrin-treated BDUs and apply DEET to uncovered areas of skin. Because the potential area of skin with overlapping coverage is small, the effect of DEET on the facilitated

absorption of permethrin is probably of minor importance and can be investigated easily.

The subcommittee recommends that military personnel consider minimizing areas of skin that are covered by both DEET and permethrin-treated uniforms to reduce potential interactive effects of DEET on permethrin absorption. The subcommittee also recommends that the Army conduct a human pharmacokinetic study with combined exposure to permethrin and DEET to determine whether this exposure increases the absorption of permethrin.

ACUTE TOXICITY

Although permethrin is highly toxic to insects and other arthropods, it is one of the least toxic insecticides to mammals. Its acute toxicity has been studied in several animal species and has been found to be more toxic by the oral route than by the dermal or inhalation routes. The oral LD_{50} (acute oral lethal dose for 50% of the subjects) of technical-grade permethrin in experimental animals is in the range of 0.5-5 g/kg of body weight. Aqueous suspensions of permethrin usually produced the least toxicity, with LD_{50} values ranging from 3 to 4 g/kg of body weight. Permethrin in corn oil suspensions yielded LD_{50} values of approximately 0.5 g/kg in most of the studies involving oral administration to rats and mice. The cis/trans isomer ratio also affects the toxicity, the cis isomer being more toxic than the trans isomer. Permethrin in BDU fabric would contain 60% cis isomer and 40% trans isomer.

The clinical signs of acute poisoning become evident within 2 hr of exposure to permethrin and are targeted to the central nervous system; symptoms are uncoordination, ataxia, hyperactivity, convulsions, and, finally, prostration, paralysis, and death.

SUBCHRONIC TOXICITY

The no-observed-effect level (NOEL) for permethrin in rats in 3- and 6-month feeding studies ranged from 20 to 1,500 mg/kg. Rats and mice have survived permethrin exposures as high as 10,000 mg/kg (in feed)

for 2-26 weeks, although clinical signs of toxicity were clearly evident. NOELs in dogs administered permethrin orally in gelatin capsules ranged from 5 mg/kg in a 3-month study to 250 mg/kg in a 6-month study. The primary target organ in subchronic toxicity studies in rodents is the liver (see section on liver toxicity).

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, as shown 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 permethrin dose for garment workers (3×10^{-5} mg/kg per day) is less than the daily dose for military personnel (6.8×10^{-5} mg/kg per day), the MOS for garment workers is even higher—approximately 168,000. Therefore, subchronic toxicity of permethrin should not be of concern when permethrin-treated BDUs are worn or permethrin-treated fabric is handled.

DERMAL TOXICITY

The dermal toxicity of permethrin has been studied in animals and humans. Single dermal application of permethrin failed to produce skin irritation in rabbits. Repeated dermal exposure to permethrin in rabbits has been shown to produce slight erythema. When cotton cloth impregnated with permethrin was applied to the clipped skin of rabbits for 21 days to mimic occupational exposure, no adverse effects were reported. Experiments with guinea pigs showed that permethrin might be a skin sensitizer at high doses. In photochemical irritation studies, permethrin did not cause phototoxicity in experimental animals.

In a study with 184 human subjects, a 21-day repeat patch test with a 40% permethrin solution did not cause any skin sensitization. However, several subjects described a transient burning, stinging, or itching sensation (subjective irritation). In a Swedish study of 87 plant nursery workers who were exposed to permethrin, itching and burning skin were reported.

Among 17 human volunteers exposed to 1% permethrin with skin patches for up to 9 days, two complained of mild erythema and skin irritation. Among 10 male volunteer soldiers who wore uniforms impregnated with an aqueous solution of 0.2% permethrin, none complained of skin irritation.

Permethrin preparations are the treatment of choice for insect-transmitted diseases such as crab lice and scabies. In studies of 1% permethrin cream rinse to treat head lice and 5% permethrin cream to treat scabies in humans, mild skin irritation occurred in a small percentage of those treated. The subcommittee estimated a MOS of 126,000 based on the studies that used 5% permethrin cream to treat scabies in humans.

The weight of evidence shows that permethrin is unlikely to be a skin irritant or skin sensitizer for military personnel who are exposed to it dermally from wearing permethrin-impregnated BDUs or for garment workers who sew permethrin-impregnated BDUs.

A few persons, however, might be hypersensitive to permethrin-treated BDUs and thus develop skin sensitization. Therefore, the subcommittee recommends that the Army should monitor for hypersensitivity when it begins to use permethrin-treated BDUs on a regular basis.

OCULAR TOXICITY

Several investigators have tested ocular toxicity of permethrin in rabbits. In one study, no eye irritation was observed when 0.1 mL of undiluted technical permethrin was instilled in the eyes of Japanese White rabbits. In other similar studies, minimal ocular effects were observed. The weight of evidence from ocular studies conducted to date suggests that permethrin is mildly irritating to the eyes only when high concentrations of permethrin are instilled in the eyes; therefore, wearing permethrin-treated BDUs or working with permethrin-impregnated fabric is not expected to produce eye irritation.

NEUROTOXICITY

Permethrin is neurotoxic at high doses. It produces a variety of neurotoxic

effects in animals. Some of these effects are tremors, salivation, paresthesia, splayed gait, depressed reflexes, and tiptoe gait; reversible axonal injury occurs at very high doses.

In one study, rats fed permethrin in diet at 6,000 mg/kg for 14 days showed fragmented and swollen sciatic nerve axons and myelin degeneration. In another study, rats fed permethrin at up to 9,000 mg/kg developed severe trembling but exhibited no consistent histological effects in nerve tissues. In other studies of neurotoxicity in rats, lesions caused by high concentrations of permethrin included swelling and increased vesiculation of unmyelinated nerves, hypertrophy of Schwann cells, fragmentation of myelinated axons, and demyelination of sciatic nerves.

In other studies, repeated oral administration of permethrin at doses of up to 9,000 mg/kg for 3 weeks or longer was not found to be neurotoxic in hens. A few studies on the effect of permethrin on neurobehavior of animals showed that permethrin exposure might have a weak effect on neurobehavior, but nerve conduction studies in 23 permethrin workers showed no evidence of nerve impairment associated with permethrin exposure.

Animal data show that permethrin is neurotoxic at high doses, but similar human data to verify that evidence are lacking. The estimated no-observed-adverse-effect level (NOAEL) for neurotoxicity by the dermal route in rats is 200 mg/kg. Based on that NOAEL from available neurotoxicity data, the MOS associated with daily human exposure from permethrin-treated BDUs at a level of 6.8×10^{-5} mg/kg per day is approximately 3 million.

$$\text{MOS} = \frac{200 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 3{,}000{,}000.$$

Because the daily dose for garment workers (3×10^{-5} mg/kg per day) is lower than that for military personnel, the MOS for garment workers is approximately 6.8 million. Therefore, neurotoxicity from wearing permethrin-impregnated BDUs or working with permethrin-treated fabric should not be a concern.

Although animal data clearly demonstrate the neurotoxic properties of high doses of permethrin, human data are needed to place these data in perspective. Therefore, the subcommittee recommends that data on neurotoxicity of permethrin in humans be collected from epidemiological studies of workers or from accidental human exposures.

LIVER TOXICITY

Extensive medical investigations of workers exposed to permethrin have not revealed any clinical chemistry changes that would suggest liver toxicity.

The most significant toxicological effect of permethrin involves the liver in rodents. It is characterized by an increase in absolute and relative liver weight in rodents. The weight increase requires several repeated high-dose exposures to become evident, and recovery is manifested after permethrin exposure is stopped. A significant increase in liver weight occurred in rats following ingestion of permethrin at 100 mg/kg per day for 26 weeks, the lowest dose that has been reported to cause such an effect.

The increase in liver weight in rats exposed to high doses of permethrin is due to hepatocellular hypertrophy. Necrotic foci, vacuolization, and increased eosinophilia also have been observed. Hepatocellular hypertrophy is characterized ultrastructurally by an increase in endoplasmic reticulum, which is functionally associated with an increase in microsomal activity and an increase in cytochrome-P-450-mediated enzymes. These changes are largely reversible after exposure to permethrin is stopped.

Dogs did not show morphological changes in the liver even when exposed to 2,000 mg/kg per day for 3 months. No significant toxic effects were seen in the liver in rabbits or cows administered high concentrations of permethrin for 10 or 28 days, respectively.

The NOAEL for hepatocellular hypertrophy in rats has been estimated to be 10 mg/kg per day. The subcommittee concluded that the NOAEL of 10 mg/kg per day from the available liver toxicity data and the daily exposure to permethrin at a level of 6.8×10^{-5} mg/kg per day from wearing treated BDUs provide a MOS of approximately 150,000 for liver toxicity.

$$\text{MOS} = \frac{10 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 150{,}000.$$

The MOS for garment workers is approximately 340,000. Therefore, liver toxicity from wearing permethrin-impregnated BDUs or working with treated fabric should not be a concern.

IMMUNOTOXICITY

No data are available to evaluate the immunotoxic potential of permethrin in humans. Only two laboratory studies are reported in the literature—an in vitro study of mouse lymphocytes and a study of chicks; both are inconclusive regarding the immunotoxological effects of permethrin.

The subcommittee recommends that immunotoxicological investigations be performed in laboratory animals to ascertain the immunotoxic properties, if any, of permethrin in mammalian species. The research should follow the guidelines presented in the 1992 NRC report *Biologic Markers in Immunotoxicology*.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data on reproductive and developmental toxicity of orally administered permethrin suggest that there are few toxic effects, and those tend to be limited to high doses. No reproductive or developmental toxicity data are available from dermal exposure studies, but dermal absorption is poor, and oral dosing would be expected to maximize any effects. Some studies involving oral exposures have reported reproductive or developmental toxicity effects, but the effects have not been confirmed in other similar studies. Also, there is disagreement among the studies regarding the doses at which such toxicity occurs. There were some differences in the strain of rat used in the studies, and the cis/trans ratio was not always specified; these factors might explain, in part, the inconsistencies in the data.

In studies of prenatal exposure only, NOAELs from the mouse and rabbit studies (400 mg/kg per day and 600 mg/kg per day, respectively) were much higher than those from the rat studies (20-50 mg/kg per day). In a three-generation reproductive toxicity study of permethrin, small increases in buphthalmos and persistent papillary membrane were observed in weanling rats following continuous exposure to permethrin at 1,000 and 2,500 ppm in diet (actual amounts of permethrin consumed were 50 and 125 mg/kg per day); the NOAEL was estimated to be 25 mg/kg per day. In contrast, another study reported no effects from

permethrin doses as high as 180 mg/kg per day given in the diet, but such effects might not have been observed because these changes are subtle and have a very low incidence.

No histopathological examinations were conducted or organ weights measured in any of the three-generation reproductive studies performed to determine the effect of permethrin on male reproductive function. Among the chronic exposure studies, one study in mice did note an effect on testis weight and testicular hypoplasia at permethrin doses of 75 and 300 mg/kg per day (NOAEL of 3 mg/kg per day). However, in other studies, no such effects were noted in rats or mice at permethrin doses of up to 250 mg/kg per day. Thus, information on male reproductive effects is minimal at best, and the most conservative NOAEL is 3 mg/kg per day.

The NOAEL of 3 mg/kg per day based on testicular effects and the permethrin intake of 6.8×10^{-5} mg/kg per day from wearing permethrin-impregnated BDUs provide a MOS of approximately 44,000.

$$\text{MOS} = \frac{3 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 44{,}000.$$

The MOS for garment workers is even higher—approximately 100,000. Given the lack of effects in most of the reproductive and developmental toxicity studies on permethrin and a MOS of approximately 44,000 from the most sensitive end point (decreased testicular weight), the possibility of male reproductive effects or other reproductive and developmental effects occurring from wearing permethrin-impregnated BDUs or working with permethrin-treated fabric is remote.

GENOTOXICITY

Studies conducted to determine the potential of permethrin to produce gene mutations were all negative. These studies included tests for gene mutations in microbial systems (Ames *Salmonella* reverse mutation assay, forward mutation assay using *Escherichia coli* WP_2, and *Drosophila* sex-linked recessive lethal test) and gene mutations in mammalian cells in culture (mouse lymphoma L5178Y cells and V79 Chinese hamster ovary cells).

Studies conducted to determine the potential of permethrin to produce chromosomal damage provided an array of results. Some were positive, some negative, and others deficient in information needed to draw a definitive conclusion. Of the two in vivo studies conducted in the micronucleus assay, one was negative and the other was inadequate because an insufficient number of animals were used and only one dose was tested. Three in vitro studies in which clastogenicity of permethrin was investigated provided evidence of potential clastogenicity of permethrin. Small statistically significant elevations in sister chomatid exchanges, micronuclei, and chromosomal aberrations in human lymphocyte cultures were reported. Chromosomal aberrations were also reported in Chinese hamster ovary cells. All three in vitro studies were performed in one laboratory by the same investigators.

Two studies were conducted with the dominant lethal test; both were considered deficient. In one study, there was no explanation of the deaths of at least 5% of the female animals, and the number of pregnant animals was insufficient. In the other study, only one dose was tested.

Other genotoxicity tests of permethrin (*E. coli* pol A assay, *Bacillus subtilis* rec assay, *Saccharomyces cerevisiae* D3 mitotic recombination assay, and unscheduled DNA synthesis assays) were negative.

The subcommittee believes that the weight of evidence suggests that permethrin does not produce gene mutations but is a potential clastogen in certain in vitro systems.

Three in vitro studies from one laboratory showed small statistically significant increases in clastogenic effects of permethrin. These results have not been independently confirmed by other investigators. The subcommittee recommends that these studies be repeated by other investigators to determine if the positive findings of permethrin's clastogenicity can be confirmed. If these findings are confirmed, the clastogenicity of permethrin should also be studied in vivo with an adequate number of animals and dosages of permethrin.

CARCINOGENICITY

There is no information in the literature on carcinogenic effects of permethrin in humans. Evidence of permethrin's possible carcinogenicity

in humans is derived from bioassays in rodents. Permethrin has been tested in seven chronic exposure studies in which permethrin was administered in the diet to rats in three studies and to mice in four studies.

The three rat studies were negative for carcinogenicity; however, permethrin concentrations were not high enough to adequately assess the oncogenic potential of permethrin. In spite of some deficiencies in the mouse studies, two showed evidence of carcinogenicity. In a 24-month study, permethrin was administered to male and female CD-1 mice. Permethrin doses were 0, 20, 500, and 2,000 ppm for males and 0, 20, 2,500 and 5,000 ppm for females. The primary findings were as follows: In males, statistically significant increases in liver adenomas at all doses were observed, as was a statistically significant dose-related trend. In females, statistically significant increases in lung adenomas and carcinomas combined were observed at mid and high doses, and the dose-related trend was also statistically significant. In addition, lung adenomas and carcinomas occurring separately showed statistically significant dose-related trends. In a 92-week study, permethrin was administered in the diet to male and female CFLP mice at doses of 0, 10, 50, and 250 mg/kg per day. There was a statistically significant increase in lung tumors in females at the highest dose, as well as a statistically significant dose-related trend.

Permethrin was also tested in the Shimkin mouse lung bioassay to determine if permethrin is a tumor promoter. This assay did not show any evidence that permethrin promoted lung tumors; however, the Shimkin assay is not a definitive mouse oncogenicity assay. Based on the weight of evidence from animal studies, the subcommittee concludes that permethrin is a possible human carcinogen. The subcommittee based its quantitative cancer risk assessment for permethrin on the 24-month chronic feeding study in CD-1 mice as described above. The oral carcinogenic potency factor (upper 95% confidence limit) was calculated on the basis of combined adenomas and carcinomas of the lungs in female mice. The subcommittee calculated a human-equivalent carcinogenic potency factor of 0.016 mg/kg per day, using the linearized multistage procedure, and extrapolated to humans on the basis of body weight to the 2/3 power.

An upper bound on the lifetime carcinogenic risk was estimated by multiplying the carcinogenic potency factor by the estimated average daily lifetime dose. For military personnel wearing permethrin-impregnated

BDUs, the upper bound on lifetime carcinogenic risk is estimated to be 1.6×10^{-6}. That same value applies to nonfield and field personnel and assumes that topically applied DEET does not enhance dermal absorption of permethrin.

As stated earlier, less than 5% of the skin would have overlapping exposure to DEET and permethrin. If the recommended pharmacokinetic studies are done and the results of those studies indicate an enhanced absorption of permethrin from simultaneous exposure to DEET and permethrin, that would mean that soldiers wearing permethrin-impregnated BDUs and applying DEET to skin areas not covered by BDUs are exposed to higher concentrations of permethrin. In that case, carcinogenic risk should be reevaluated to determine if the revised carcinogenic risk is acceptable.

The estimated upper-bound lifetime carcinogenic risk to garment workers, 6.9×10^{-7}, is less than half the calculated upper-bound risk to military personnel. That value does not reflect the possibility of workers being exposed to permethrin from airborne particles of permethrin-impregnated fabric, and it might not represent a true upper bound on the overall carcinogenic risk to garment workers. However, assuming that appropriate safety precautions are taken, it seems unlikely that the exposure of garment workers to airborne particles of permethrin-treated cloth would increase their overall exposure and thus their risk to the same level as military personnel.

The carcinogenic risk to field or nonfield military personnel or to garment workers from exposure to permethrin-impregnated fabric is very small—of the order of 10^{-6} or less. Therefore, the subcommittee concludes that premethrin-impregnation of BDUs is not a serious carcinogenic risk to field or nonfield military personnel or to garment workers.

CONCLUSIONS

The subcommittee analyzed the risk of adverse health effects to soldiers who wear permethrin-impregnated BDUs and the risk to garment workers who handle permethrin-treated fabric. Based on the review of the toxicity data on permethrin, the subcommittee concludes that soldiers who wear permethrin-impregnated BDUs are unlikely to experience adverse

health effects at the suggested permethrin exposure levels (fabric impregnation concentration of 0.125 mg/cm^2). The risk of adverse health effects in garment workers who handle permethrin-impregnated fabric is even smaller because their exposure to permethrin is estimated to be less than that of soldiers.

Permethrin-impregnated BDUs are effective in preventing insect-borne diseases in military personnel in insect-infested field areas. The most beneficial use of permethrin-impregnated BDUs will be in overseas field settings, where exposure to disease-bearing insects is substantial. The risk of vector-borne disease in the United States is considerably less but not zero. Military personnel wearing permethrin-impregnated BDUs in field operations in the United States will benefit from protection from tick and mosquito bites, which, in turn, will protect them from endemic diseases, such as Lyme disease, Rocky Mountain spotted fever, and viral encephalitis. They will also be protected from other routine insect bites that often become infected and require medical treatment.

The subcommittee notes that in situations where soldiers are in protected environments, such as offices, where insect contact is remote, there is no tangible benefit from wearing impregnated BDUs.

1

Introduction

In addition to being a nuisance, mosquitoes, ticks, biting flies, and other arthropods can be the bearers of disease—often debilitating, sometimes deadly. Throughout history, more active-soldier days have been lost to diseases—many of them transmitted by insects—than to combat. In the Vietnam War, disease casualties, mostly caused by insect bites, outnumbered combat casualties by more than two to one. In the United States and abroad, Lyme disease, vectored by deer ticks, is a serious concern for military and civilian populations. Public-health strategies rely on vector control to contain insect-borne diseases, but the military, because of its rapid deployment missions, must depend largely on personal protection methods, such as insect repellents. Recently, the U.S. Department of Defense (DOD) has focused on impregnating battle-dress uniforms (BDUs) with insect repellents to augment the protection provided by topically applied repellents. The most promising of the clothing treatments is the insecticide permethrin, a synthetic pyrethroid. Synthetic pyrethroids, such as permethrin, cypermethrin, and fenvalerate, are being considered as replacements for currently used insecticides (organochlorines, organophosphates, and methylcarbamates) because (1) they are more acutely toxic to target insects than other classes of available insecticides, and thus less insecticide is needed per application; and (2) they are less toxic than organochlorine, organophosphate, and methylcarbamate insecticides to mammals. Pyrethroids are more toxic to insects than mammals because of their more rapid absorption,

slower detoxification, and greater affinity for target sites in insects. Permethrin has insect-repellent as well as insecticidal properties. These insecticidal properties and those of other pyrethroids are due to their interference with the conductance of nerve impulses.

Pyrethroid insecticides are registered as insect controls for fruits and vegetables. Permethrin is used extensively by agriculture for control of food-crop pests. Pyrethroids are also used in greenhouses for control of whitefly and in livestock buildings (beef barns, dairy barns, and poultry houses) and stables for control of house and stable flies.

It is also the active ingredient (0.5%) in an aerosol spray formulation distributed for veterinary use and for human use in pediculocides (1%) and scabicides (5%) that have been approved by the Food and Drug Administration (FDA).

The physical and chemical properties of permethrin are shown in the following list (CEPA, 1992).

Common name:	Permethrin
Chemical name:	3-(phenoxyphenyl)methyl (±)-*cis, trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Tradenames:	Permanone, Ambush, Pounce, Ectiban, FMC 33297, PP557, BW-21-Z, NRDC 143
CAS registry no.:	52645-53-1
Molecular weight:	391.3
Empirical formula:	$C_{21}H_{20}Cl_2O_3$
Physical state:	Clear liquid
Color:	Medium to dark amber
Odor:	Moderate aromatic
Melting point:	55.7-56.3°C (cis) 45.7-46.3°C (trans)

Boiling point:	220°C at 0.05 mm Hg
Density:	1.0138 at 25°C
Solubility:	0.07 mg/L at 25°C in water Mixable with most organic solvents
Vapor pressure:	2.15×10^{-8} mm Hg at 25°C (cis) 0.69×10^{-8} mm Hg at 25°C (trans)
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). The cis isomer is more stable.
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)

Permethrin has been registered by the U.S. Environmental Protection Agency (EPA) as a clothing treatment to repel disease-transmitting and nuisance insects and other arthropods. Many studies have shown that permethrin-impregnated fabric is effective in repelling insects, ticks, and other arthropods (Schreck et al., 1978, 1980a,b, 1982a,b,c, 1984, 1986; Breeden et al., 1982; Mount and Snoddy, 1983; Dees et al., 1986; U.S. Army Natick Research, Development, and Engineering Center, 1987; Lillie et al., 1988; Sholdt et al., 1988, 1989; U.S. Army Environmental Hygiene Agency, 1988; Schreck and Kline, 1989; Schreck and McGovern, 1989; Evans et al., 1990). Studies have also shown that permethrin impregnation of BDUs at the concentration of 0.125 mg/cm^2 of cloth along with application of the insect repellent *N,N*-diethyl- *m*-toluamide (DEET) to exposed skin provides nearly 100% protection against bites of insects and other arthropods. Treatment at the approved dosage remains effective through 35 launderings of the uniform (i.e., beyond the combat life of the uniform) but can be removed by dry cleaning (U.S. Army, 1993).

A kit method and 2-gallon-sprayer method for permethrin impregnation

of BDUs have already been field tested, but both are more expensive than factory impregnation and require soldiers to perform the treatment. Short-notice deployments can result in units deploying without treated uniforms. According to the U.S. Army, application of permethrin to the BDU cloth at the time of manufacturing provides the most consistent treatment at the approved dosage and will relieve soldiers from the burden of treating BDUs.

EPA-registered aerosol cans of 0.5% permethrin are used by all services. Initial spraying of a BDU with the aerosol formulation provides a permethrin dosage approximately equal to that of an impregnated uniform that has been washed 25 times. However, pressurized cans in a combat environment are a potential problem.

The Army Clothing and Equipment Board has recommended factory permethrin treatment of all desert BDUs, which are worn by soldiers in such deployments as the Gulf War or by field units in rapid deployments. Permethrin-impregnated BDUs are recommended to be worn in garrison or nondeployment situations as well as in deployments. However, there is concern that long-term exposure to permethrin might result in adverse health effects, such as neurotoxicity or carcinogenicity.

In response to those concerns, the U.S. Army requested that the National Research Council's Board on Environmental Studies and Toxicology (BEST) review the toxicological and exposure data for permethrin and make recommendations regarding long-term exposure to permethrin. In response to the Army's request, this project was assigned to BEST's Committee on Toxicology. The Subcommittee on Permethrin Toxicity from Military Uniforms was established to review the current permethrin toxicity and exposure data and the appropriateness of long-term exposure to permethrin-impregnated BDUs.

This report is the result of the subcommittee's detailed evaluation of possible adverse health effects associated with wearing permethrin-impregnated BDUs. The report examines the data on exposure assessment of permethrin in Chapter 2, pharmacokinetics in Chapter 3, acute toxicity in humans and animals in Chapter 4, dermal or ocular toxicity in Chapter 5, neurotoxicity in Chapter 6, liver and other organ toxicity in Chapter 7, immunotoxicity in Chapter 8, reproductive and developmental toxicity in Chapter 9, genotoxicity in Chapter 10, and carcinogenicity

in Chapter 11. Chapter 12 provides a summary of the subcommittee's conclusions and recommendations.

2

Exposure Assessment

Three exposure groups need to be considered in assessing the risk associated with a permethrin treatment concentration of 0.125 mg/cm^2 in fabric used to manufacture military battle-dress uniforms. These groups are (1) military nonfield personnel, (2) military field personnel, and (3) garment workers. The same basic information on carcinogenic potency can be used for all three groups, but with individualized exposure criteria being applied.

According to the U.S. Army (1993), nearly all permethrin lost from uniforms is lost in wash water, and little is transferred to other clothing laundered with the treated uniforms. Furthermore, only modest losses of permethrin from uniforms stored at extreme temperatures have been observed, suggesting low loss by volatilization in drying (U.S. Army, 1993). Thus, there appears to be little potential, if any, for either military or civilian personnel to become exposed as a result of the process of laundering impregnated uniforms.

MILITARY NONFIELD PERSONNEL

Because of permethrin's low volatilization, the U.S. Army and the subcommittee, considered the dermal route to be the only relevant route of exposure from impregnated uniforms. In a review of the Army's exposure assessment, EPA (1990a) concurred with the Army's position that

inhalation exposure to uniform wearers would probably be insignificant. At present, there is no information to indicate that exposure to uniform wearers will occur by any route other than dermal absorption.

Several conversion factors were used by the Army to translate the targeted fabric impregnation concentration, 0.125 mg/cm^2, to an internal dose for military personnel through dermal absorption. These factors were the time-weighted-average percentage of permethrin remaining in fabric through 50 washings (26%), percentage of migration from fabric to skin (0.49% per day; Snodgrass, 1992), body contact area (1.5 m^2), dermal absorption rate (2% per day; Bartelt and Hubbell, 1987), and adult body weight (70 kg). These conversion factors were reviewed by EPA (1990b). The only factor that was questioned by EPA was the assumed human dermal absorption rate of 2% per day for permethrin after being transferred from clothing to skin. EPA indicated that this rate should be increased from 2% to 7%, which would increase the Army's calculated exposure dose by a factor of 3.5. However, EPA's estimate of dermal absorption factor is based on studies of dermal absorption of permethrin in rabbits, whose skin is much more permeable to chemicals than human skin. The California EPA (CEPA), like the Army, used a dermal absorption rate of 2% for a 24-hr period (CEPA, 1992). This rate was established on the basis of a review of various in vivo and in vitro studies of permethrin applied to human skin (see Chapter 3, "Dermal Absorption," for details). Based on the available data cited by CEPA, the Army's assumed dermal absorption rate of 2% per day appears defensible.

To adjust for actual exposure conditions, the Army assumed that military personnel would wear the treated uniforms 16 hr per day for 6 years during a 75-year lifetime. Adjusting for the proportion of lifetime exposed resulted in a calculated average daily lifetime dose of 3.6×10^{-5} mg/kg per day. (Appendix A provides a detailed method for calculating exposure dose from wearing BDUs.) The Army has since indicated that an exposure scenario of 18 hr per day for 10 years should be used instead of 16 hr for 6 years (U.S. Army, 1993). That revision increases the Army's calculated average daily lifetime dose by a factor of 1.9, resulting in a final value of 6.8×10^{-5} mg/kg per day.

MILITARY FIELD PERSONNEL

The same considerations that led to calculation of the permethrin-exposure dose for military nonfield personnel would apply to field personnel. The only difference between field and nonfield personnel is that field troops apply DEET topically to areas of the skin not normally covered by the treated uniform. The application of DEET raises the possibility of DEET's facilitating the absorption of permethrin through the skin where DEET and permethrin overlap.

At present, there are insufficient data to evaluate the potential for DEET to enhance permethrin absorption. However, somewhat less than 5% of the skin would be expected to have overlapping exposure to DEET and permethrin. Thus, at present, no adjustment is being made to distinguish exposure patterns for military field and nonfield personnel. If subsequent data indicate that exposure to both permethrin and DEET is an important consideration, then the exposure assessment for field personnel can be modified.

GARMENT WORKERS

Estimation of dermal exposure to garment workers from handling impregnated fabric in the manufacture of uniforms requires that some of the factors used to convert the target impregnation concentration, 0.125 mg/cm^2, to an internal dose be different from those used for military personnel. Since washing of the uniform is not a consideration, it is assumed that 100% of the permethrin is available for transfer to the skin. The migration rate from fabric to skin is assumed to be the same as that for uniform wearers, 0.49% per day; although garment workers might handle many different pieces of fabric during a day, it is assumed that contact would be similar to contact with the same piece of fabric, as a uniform wearer would have. The body-surface area, hands and forearms, is conservatively assumed to be 1,600 cm^2, which is 10% of the body-surface area of an average female garment worker. The dermal absorption rate is assumed to be 2% per day, as it is for uniform wearers.

Adult female body weight is assumed to be 60 kg. According to a potential manufacturer of treated uniforms, hands and forearms of workers would be exposed to treated cloth 8 hr per day, 250 days per year (U.S. Army, 1993). It is assumed that exposure would last 30 years on average.

Putting all these factors together gives the average daily lifetime internal dose as

$(0.125\ \text{mg/cm}^2 \times 0.0049/\text{day} \times 1{,}600\ \text{cm}^2 \times 0.02/60\ \text{kg}) \times (8/24) \times (250/365) \times (30/75) = 3.0 \times 10^{-5}\ \text{mg/kg/day}.$

That dose is for dermal exposure to permethrin from direct contact only with treated cloth.

Depending on the degree of ventilation and dust removal in the cutting and sewing processes and the type of protective clothing and equipment worn by garment workers, airborne particles could constitute an additional source of exposure to permethrin. Such exposure could occur by inhalation and ingestion or by ocular and dermal routes. Thus, the above estimated internal dose of 3.0×10^{-5} mg/kg per day possibly represents a lower bound on the overall exposure of garment workers to permethrin. The subcommittee could not provide an estimate of the upper bound on permethrin exposure because data are not available on other potential routes of exposure. The lower bound might actually be an upper bound if other routes do not come into play.

RECOMMENDATIONS

The subcommittee recommends that studies should be conducted to collect data on the representative permethrin exposure factors to produce a more complete and accurate risk characterization for garment workers.

3

Pharmacokinetics of Permethrin

ABSORPTION OF PERMETHRIN

The two routes of exposure most relevant to evaluating permethrin toxicity from military uniforms are the oral and dermal routes. Consideration of oral absorption of permethrin in animals is necessary to estimate the absorbed dose in carcinogenicity studies, which were conducted by oral gavage. Dermal exposure, in contrast, is the most likely route of exposure to military personnel wearing uniforms impregnated with permethrin.

Oral Absorption

Oral absorption of permethrin was investigated in rats given permethrin in dimethyl sulfoxide at 1.6-4.8 mg/kg of body weight and was estimated to be about 70% for the cis/trans (35:65) isomer mix (CEPA, 1992). Only 3-6% of the dose was detected in feces as unmetabolized and, presumably, unabsorbed permethrin, suggesting that actual absorption might be higher than 70%. Likewise, Anadon et al. (1991) estimated bioavailability of permethrin to be 60% by comparing the "area under the curve" (AUC) for permethrin in blood after gavage with the AUC after intravenous injection. That low estimate could be due to first-pass biotransformation of permethrin by the liver following absorption.

Thus, although the precise gastrointestinal absorption of permethrin is not known, those two studies suggest that 70% is a conservative estimate of absorption by rats. That information is needed to estimate the actual absorbed dose in carcinogenicity studies in which permethrin is administered by gavage.

Dermal Absorption

The dermal absorption of permethrin is more relevant to human exposure and has been investigated in a number of laboratory animals, including rats (Shah et al., 1987), monkeys (Sidon et al., 1988), and mice (Shah et al., 1981). Limited studies on the dermal absorption of permethrin in humans have also been conducted. The percutaneous absorption of permethrin is generally lower in humans than in other mammalian species (CEPA, 1992). The results of several relevant studies are summarized below.

Absorption in Humans

The absorption of permethrin was determined in humans when the permethrin was applied to the scalp in a cream-rinse shampoo or applied to the entire body in a dermal cream (CEPA, 1992). The absorption rates in three studies were reported to be less than 1%. However, it was suggested that the hair rinse and cream vehicles might have hindered absorption. A fourth study was conducted in which isopropanol was used as the vehicle and ^{14}C-labeled permethrin (labeled in the carbonyl moiety) was applied to the shaved backs of volunteers (CEPA, 1992, ref. 16). (Studies with animals showed that when permethrin is labeled in this position, there is no loss of label through production of $^{14}CO_2$.) In the fourth study, from 0.3% to 2% of the applied dose of ^{14}C-label was excreted in urine in 5 days. This is not a precise estimate of dermal absorption because of the possibility of binding of permethrin to macromolecules or storage of permethrin in body tissues such as fat. Based on these studies, a dermal absorption rate of 2% was assumed for humans by the Medical Toxicology and Worker Health and Safety Branches of the Department of Pesticide Regulation of CEPA in their

risk characterization of permethrin (CEPA, 1992). Corresponding parenteral studies were not conducted; therefore, that absorption value can only be considered an estimate.

In another study, the transdermal absorption of permethrin, formulated in a cream at a 5% concentration, was reported (van der Rhee et al., 1989). Patients with scabies were treated with one application of that cream to the skin of the whole body, excluding the head and neck, for 8 hr, after which the patients were instructed to wash their skin. The degree of permethrin absorption was assessed indirectly by determination of conjugated and unconjugated cis/trans CVA (3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid, a metabolite of permethrin) excreted in urine. The results of these studies showed that permethrin could be absorbed through the skin, although they did not determine precisely how much was absorbed. They also demonstrated that excretion of CVA, which began within the first 7 hr, was at a maximum over the first 48 hr but continued at a low rate for at least 14 days, suggesting continued elimination of absorbed permethrin.

Estimates of permethrin absorption derived from metabolite excretion studies in healthy individuals suggested that the maximum absorbed by any one individual over the first 48 hr after application of 16 g of cream (800 mg of permethrin) was 18 mg and that the overall mean absorption by the group was 10 mg (unpublished data, cited by van der Rhee et al., 1989). Those studies with healthy volunteers were similar to the studies with scabies patients in that the amounts of permethrin absorption, as measured by the mass of urinary metabolites, are of the same order of magnitude in both studies.

In summary, although several dermal absorption studies were conducted in humans, these studies lacked corresponding parenteral controls and must be interpreted cautiously. In addition, no studies have been conducted in humans that focus on permethrin absorption under conditions of intended use by the Army, namely, dermal absorption of permethrin when applied to cloth.

Absorption in Animals

An acetone solution of permethrin was applied to the shaved backs of

mice to investigate dermal penetration (Shah et al., 1981). Of the 14 insecticides studied, permethrin penetrated the skin of mice most rapidly, the $T_{1/2}$ being 5.9 min. Within 5 min, 40% of the permethrin had moved from the site of application. Absorption of the insecticides did not appear to correlate with physicochemical factors, such as molecular weight, solubility, charge distribution, or partition coefficients (Shah et al., 1981). Those investigators also examined age dependence in dermal penetration of insecticides in young (33-day) and adult (82-day) female F344 rats. There was no age-related difference in the penetration of permethrin in young and adult rats. There was, however, a decreased absorption of permethrin with increasing dose (Shah et al., 1987).

The percutaneous absorption of cis/trans permethrin was determined in rhesus monkeys and rats (Sidon et al., 1988). Permethrin labeled at the alcohol or cyclopropyl portion of the molecule was applied to either the forehead or the forearm of rhesus monkeys or to the mid-lobosacral (back) region of the rat. Urine was collected for 7-14 days, and the recovered radioactivity in the urine was compared with that obtained after an intermuscular injection to determine the percent absorption. In monkeys, the forehead was more permeable than the forearm (14-28%, forehead; 5-12%, forearm). According to Siddon et al., the forehead is more absorbent than the forearms because the forehead is more glabrous (smooth and without hairs) and more highly vascularized than the forearms.

The investigators also noted that absorption of permethrin applied to the backs of rats was significantly greater than the forehead or the forearm in the monkey (rats, 43-46%). The interspecies difference supports the finding of higher permeability of rat skin demonstrated previously with other pharmaceutical compounds and underscores the importance of using caution in extrapolating the results of pesticide dermal absorption studies in nonprimate species to humans. Migration of permethrin from clothing to the skin surface is important for assessing the toxicity of permethrin when impregnated into uniforms. There are no human data on the absorption of permethrin from impregnated cloth rather than from direct application to skin. However, studies on the transfer of permethrin from treated cloth to skin surface have been conducted in rabbits (Snodgrass, 1992). In those studies, permethrin migration from cloth to skin was determined by measuring the fate of the ^{14}C label when swatches

of fabric impregnated with ^{14}C-labeled permethrin were applied to the backs of rabbits for 1 week. The results showed that fabric treated with permethrin at a rate of 0.125 mg/cm^2 lost the substance to the skin surface at an average rate of 0.49% per day. At the end of 7 days, about 3.2% of the available permethrin had reached the skin, 2% having been recovered from the excreta (absorbed) and 1.2% remaining on the skin surface. Other variables, such as temperature, fabric type, sweat, and prelaundering, had little effect on migration rate (Snodgrass, 1992). Although the rabbit studies do not address the important issue of absorption of permethrin through the skin of humans from permethrin-impregnated cloth, they can be used to estimate the rate of transfer of permethrin from cloth to the skin. Although absorption of permethrin through the skin of humans and rabbits is likely to be much different, physical transfer of permethrin from cloth to skin should be similar.

INTERACTIONS

A combination insecticide and repellent product (Hartz's Blockade) composed of 9% *N,N*-diethyl-*m* -toluamide (DEET) and 0.09% fenvalerate (a Type II pyrethroid insecticide) has been widely used for the control of fleas and other ectoparasites on dogs and cats. During 1987, the Illinois Animal Poison Information Center observed 200 times more poisonings in dogs or cats exposed to Blockade than to all other DEET-containing products. This report indirectly suggests that the use of DEET in combination with a pyrethroid insecticide increases the toxic response possibly by facilitating fenvalerate absorption (Dorman, 1990).

The possibility for enhancement of permethrin absorption by DEET is supported by a study on the use of DEET to enhance transdermal delivery of drugs. In in vitro diffusion studies using the hairless mouse skin as a barrier membrane, the absorption of a number of drugs (hydrocortisone, benzocaine, ibupropen, erythromycin, etc.) was studied (Windheuser et al., 1982). Although the diffusion cell results are not necessarily applicable to skin in vivo, they can demonstrate relative penetration enhancement. Enhancement of drug delivery is dramatic when DEET is present in the formulation. Drug diffusion, as expressed as a percent, increased from 1.6% to 35% for hydrocortisone and from not

detectable to 83% for erythromycin. These results suggest that DEET used in combination with permethrin might serve to facilitate the absorption of permethrin through the skin. The transdermal penetration of trisodium phosphonoformate (PFA) in the presence of sorption promoters, including DEET, was studied in excised rat skin. Ten-percent DEET doubled the amount of PFA in the skin, increased the amount permeated across the skin fourfold, and increased the flux fivefold (Hussain and Ritschel, 1988).

Other studies have shown that DEET enhances the dermal penetration of fenitrothion, an organophosphorus pesticide in rats and to a lesser extent in monkeys, when measured by recovery of absorbed fenitrothion in urine of exposed animals (Moody et al., 1987).

The U.S. Army conducted a study to determine the synergistic effect of permethrin and DEET combinations as measured by acute toxicity (Nelson, 1989). The results indicated a 25-40% potentiation of toxicity from the mixtures compared with single chemicals. In that study, the permethrin-DEET mixture was given orally, so the effect of DEET on transdermal absorption of permethrin could not be evaluated. However, the observed potentiation of permethrin toxicity by DEET is consistent with a facilitated absorption of permethrin by DEET across the gastrointestinal surfaces. Additional studies are recommended to assess the potential interactive effect on absorption (see "Recommendations" in this chapter for more details).

METABOLISM

Because permethrin is neurotoxic and carcinogenic in laboratory animals at high doses, an understanding of its metabolic fate after absorption, regardless of the route, is useful. As with other xenobiotics, it is most likely that the liver is quantitatively the most important site for permethrin biotransformation. Given what is known about the similarities in biotransformation enzymes in animals and humans, it is also likely that the metabolic pathway operant in animals will be present in humans.

The two major pathways for metabolism of permethrin are oxidation and hydrolysis (Hutson, 1979). Figure 3-1 and Figure 3-2 show the metabolic pathways and sites of metabolic attack. The relative contributions of the

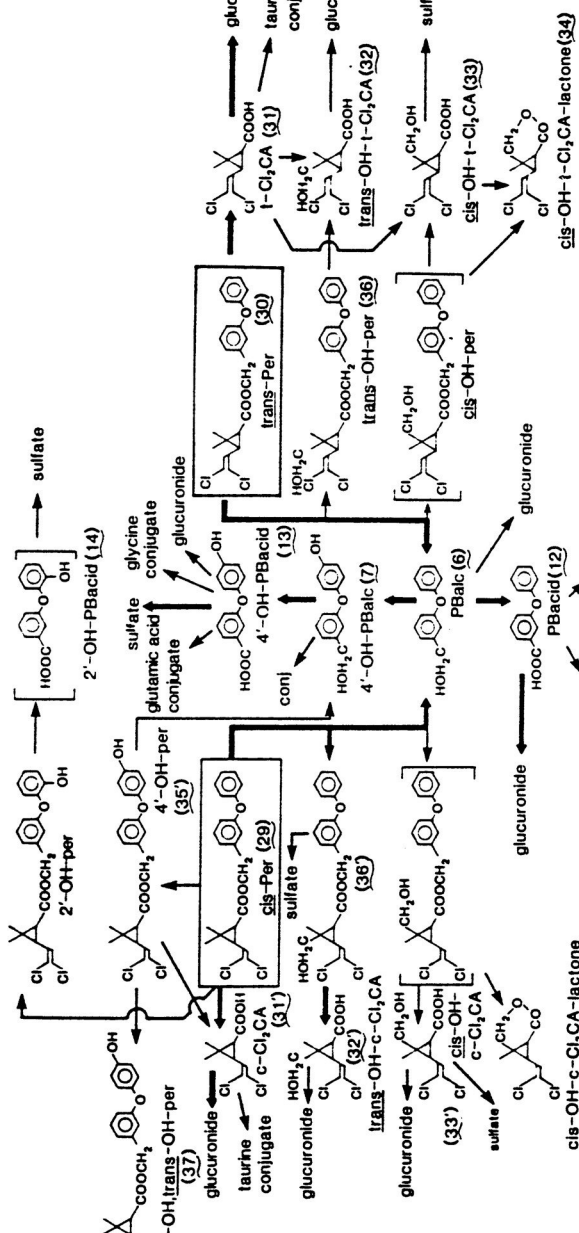

FIGURE 3-1 Metabolic pathways of permethrin in mammals. Source: IPCS, 1990. Reprinted with permission from *Permethrin*; copyright 1990, World Health Organization, Geneva, Switzerland.

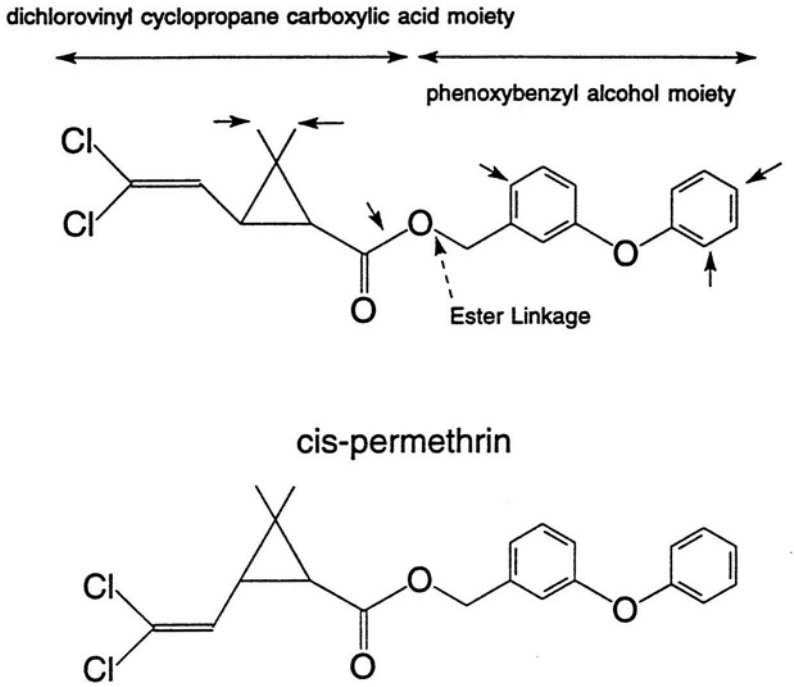

FIGURE 3-2 Chemical structures of cis- and trans-permethrin (3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylase) indicating the position of the ester linkage and the alcohol and acid portions of the molecule relative to the ester linkage. The small arrowheads designate known sites of metabolic attack.

esterase and oxidase in the in vitro hepatic metabolism of permethrin have been estimated for the R, S, cis, and trans isomers. As with other pyrethroids, trans isomer metabolism is dominated by hydrolysis and cis isomer metabolism is dominated by oxidation (Hutson, 1979).

HYDROLYSIS

The major pyrethroid hydrolyzing esterase is located in mammalian liver microsomes and is probably a carboxyl esterase (Hutson, 1979).

The cis and trans pyrethroid isomers show dramatic substrate specificity—the trans form being hydrolyzed up to 50 times faster than the cis form (Casida et al., 1976). Pyrethroid hydrolysis is inhibited by dialkylphosphorylating agents, such as organophosphorus pesticides, in vitro and in vivo (Hutson, 1979; Casida et al., 1983). That raises the question of hazard to pesticide users who might be exposed simultaneously or sequentially to the two types of pesticides. That situation is not likely under the field conditions proposed for use by the Army. However, nonfield military personnel who are wearing permethrin-treated uniforms might have occasion to use organophosphorus pesticides as part of their work duties. Therefore, the possibility of combined exposure should be taken into account when assessing potential risk of acute toxicity. The presence of a hydrolysis inhibitor should prolong the tissue distribution and retention of permethrin.

OXIDATION

Oxidation is also an important route of metabolism for pyrethroids and might be of paramount importance for the cis isomers, since they are less likely to be metabolized by hydrolysis (Glickman et al., 1981; Glickman and Lech, 1981). Oxidative reactions occur at the cyclopropane carboxylic acid moiety, at the alcohol moiety, and also probably in the proximity of the ester bond so that its cleavage is catalyzed. This later process might be very important for cis isomers, which are more resistant to hydrolysis. Additionally, oxidation at peripheral sites, while leaving the ester bond intact, affords points at which conjugation reactions occur, leading to biliary and fecal elimination of the esters (Hutson, 1979). The various c-hydroxylations are probably catalyzed by cytochrome P-450.

RELATIONSHIP TO TOXICITY

The rate of metabolism of a pyrethroid is profoundly important in its acute toxicity (Hutson, 1979). The trans isomers (rapidly hydrolyzed) are more rapidly eliminated and much less neurotoxic than their cis analogs. Inhibition of hydrolytic reactions enhances neurotoxicity. The inhibition of oxidative metabolism also increases neurotoxicity. Piperonyl

butoxide, the most important pyrethroid synergist and a classical mixed-function-oxidase (MFO) inhibitor, increases the toxicity of all pyrethroids to insects (Casida et al., 1976). It also increases the neurotoxicity of pyrethrins to mice. Induction of hepatic microsomal monooxygenases lowers the acute neurotoxicity of permethrin. These facts suggest that hydrolysis and oxidation are important in limiting acute toxicity, although they are not the only factors controlling acute toxicity (Hutson, 1979).

In summary, all of what is known about the metabolism of pyrethroids comes from studies conducted in laboratory animals and from in vitro studies using hepatic tissues. Information on the biotransformation of permethrin at the site of absorption (skin or gastrointestinal tract) or in the target tissue (nervous system) is lacking. Likewise, specific studies of the biotransformation by human tissues have not been conducted. However, the classes of enzymes responsible for permethrin metabolism are found in all mammalian systems, including humans, so it is likely that these pathways are operant in humans also. It is likely that biotransformation will serve to reduce the neurotoxic effects of permethrin in humans as it does in animals.

Several classes of biotransformation reactions might result in the formation of reactive intermediates. Epoxidation is one such biotransformation. Epoxidation can occur at the unsaturated side chains of the natural pyrethrins or at the dihalovinyl side chain of permethrin (Ruzo and Casida, 1977). Epoxides have been implicated in the carcinogenic action of such chemicals as vinyl chloride, styrene, ethylene oxide, and butadiene. However, in the metabolism studies conducted with permethrin reported so far, there has been no evidence of oxygenation at the dihalovinyl group (Hutson, 1979).

In summary, all of what is known about the metabolism of pyrethroids comes from studies conducted in laboratory animals and from in vitro studies using hepatic tissues. Information on the biotransformation of permethrin at the site of absorption (skin or gastrointestinal tract) or in the target tissue (nervous system) is lacking. Likewise, specific studies of the biotransformation by human tissues have not been conducted. However, the classes of enzymes responsible for permethrin metabolism are found in all mammalian systems, including humans, so it is likely that these pathways are operant in humans also. It is likely that biotrans

formation will serve to reduce the neurotoxic effects of permethrin in humans as it does in animals.

ELIMINATION

The pyrethrin metabolites are generally excreted as alcohols, phenols, or carboxylic acids and their glycine, sulfate, or glucuronide conjugates. At least 80 metabolites have been identified from cis and trans permethrin in various species and systems (IUPAC, 1981).

In a study by Gaughan et al. (1977), the 1R trans, 1RS trans, 1R cis, and 1RS cis isomers separately labeled in the acid and alcohol moieties were given orally to rats, and metabolites in urine and feces were identified. The results showed that there was no significant metabolic difference between 1R and 1RS isomers, although, as noted previously, cis permethrin isomers were more likely to undergo oxidative metabolism than the trans counterparts. Twelve days after administration, 97-100% of the radioactivity was recovered in urine and feces. Unchanged permethrin was detected only in the feces. Virtually no $^{14}CO_2$ was expired. Radioactivity from the cis isomers tended to be retained longer than that from the trans isomers and that from the alcohol label longer than that from the acid label. The most striking difference was that only 45-54% of the radiocarbon from the cis isomer appeared in the urine, whereas 81-90% of that from the trans isomer appeared in the urine. The more hydrolytically stable cis isomer resulted in metabolites that retained the ester bond, and these metabolites were excreted in the feces, presumably via the bile. The large molecular weight of permethrin (370) suggests that it would be an excellent candidate for biliary excretion. The major metabolites from both isomers were the sulfate and glucuronide conjugates of the phenoxybenzoic acid portion of the molecule and the glucuronide conjugate of the cyclopropane carboxylic acid portion.

Similar results were found in studies using rhesus monkeys (Sidon et al., 1988). As in the previous study, the position of the ^{14}C radiolabel on the permethrin (alcohol or cyclopropyl group) affected the radioactivity recovered in urine. In addition, a lower recovery of radiocarbon in urine was observed following an intramuscular injection of cis permethrin as compared with the recovery after injection of trans permethrin.

This observation is consistent with findings in other studies for intravenous or oral administration. Again, these results are most likely attributed to the more metabolically labile ester group of the trans isomer as compared with the cis isomer. However, they probably also reflect greater excretion of the cis residues via the fecal route or greater retention of the cis isomer in body tissues.

DISTRIBUTION

Tissue Concentrations

Pyrethroids are lipophilic molecules that generally undergo rapid absorption and distribution following ingestion by mammals (Hutson, 1979). Unless isolated in lipid depots, they are quickly metabolized and eliminated from the body. Permethrin persists longer in fat than in other tissues when measured in chickens, rats, goats, and cows (Casida et al., 1983). Cis permethrin is retained longer than its more metabolically labile trans isomer (Marei et al., 1982).

Although many factors combine to determine the toxicity of the chemical in a target organ, one of the major determinants is the tissue concentration of the chemical. In general, ^{14}C-labeled permethrin and its hydrolysis products are excreted from the body in a relatively short time. For example, the toxicokinetics of permethrin taken orally at 460 mg/kg or taken intravenously at 46 mg/kg was studied in male Sprague-Dawley rats (Anadon et al., 1991). The elimination half-time of permethrin was slower for the hippocampus, medulla oblongata, front cortex, and sciatic nerve (16-24 hr) than for plasma (12 hr). Higher amounts of permethrin were also found in those tissues than in plasma, indicating the accumulation of permethrin by nervous tissue. The metabolites of permethrin, *m*-phenoxy benzoalcohol and *m*-phenoxy benzoic acid, were detected in plasma and in all selected tissues for 48 hr after dosing.

Studies in Sprague-Dawley rats, in which a variety of pyrethroid insecticides were administered orally, demonstrated that the residues of permethrin in fat and brain were much higher and more persistent with cis permethrin than with trans permethrin (Marei et al., 1982). Fat and brain concentrations of the trans isomer but not the cis isomer were

greatly elevated on pretreatment with either esterase or oxidase inhibitors. Phenobarbital was moderately effective in lowering pyrethroid residues in fat most likely because of enhanced metabolism of permethrin.

Thus, although there is some information on the distribution of permethrin in tissues of mammals, the majority of this information has been obtained in rodents. There have been no studies conducted on the distribution of permethrin in the tissues of primates, including humans.

Protein Binding

The amount of the permethrin in the tissues is of some importance even at concentrations that are lower than the concentrations necessary to produce neurotoxicity. Studies using human skin fibroblast androgen receptors have demonstrated that nonsteroidal compounds, including permethrin, can interact competitively with human androgen receptors and the sex hormone binding globulin (Eil and Nisula, 1990). Those studies provide a mechanism by which chronic exposure of humans to pesticides containing nonsteroidal compounds might result in endocrine disturbances relating to androgen action. The competitive binding studies demonstrate that permethrin is a weak binder compared with other agents, such as R1888, a nonmetabolizable synthetic androgen. There is insufficient evidence, in vivo, to indicate whether these insecticides act as weak androgens, inhibitors of androgen activity, or a combination of both mechanisms.

SUMMARY AND CONCLUSIONS

In studies conducted in rodents, it has been shown that permethrin is extensively and rapidly metabolized following absorption. The two major pathways for metabolism are hydrolysis, essentially splitting the molecule in two, or oxidation at a number of carbon atoms throughout the molecule. Both of these metabolic processes result in a metabolite that is more water soluble than the parent compound and thus more likely to be excreted in the urine. Thus, one could view metabolism as an important detoxification pathway for permethrin, because it is the parent chemical

that exerts its neurotoxic effects. Given the similarities in xenobiotic metabolism in rodents and primates, metabolism can be assumed to be an important detoxification pathway for humans.

From studies conducted in rodents, permethrin, upon absorption, is found to be distributed throughout the body but appears to concentrate most predominantly in the fat. This observation might explain its high concentrations in brain and nervous tissue. One study has suggested that permethrin in vitro can weakly bind human androgen receptors. The toxicological implications of this binding are uncertain. There are no data on distribution of permethrin in human tissues.

The enhancement of dermal penetration of a variety of chemicals by DEET suggests that use of DEET in combination with permethrin might actually facilitate the dermal absorption of permethrin. Research specifically on the interaction of DEET and permethrin has not been conducted and represents an area of uncertainty regarding the dermal absorption of permethrin. Facilitated absorption of permethrin by DEET is a possible concern for the military personnel assigned to combat areas in which DEET applied to the skin is used in combination with permethrin-treated military uniforms. Dermal absorption might be enhanced on the surfaces of the skin that are not only covered with DEET cream but are also in contact with the military uniforms. Although the potential area of skin at risk is small, the magnitude of the effect is not known with certainty but is assumed to be of minor importance.

RECOMMENDATIONS

The subcommittee recommends that the Army conduct a human pharmacokinetic study with permethrin and DEET. Specifically, this study would involve three groups of volunteers: a group wearing untreated uniforms (control); a group wearing uniforms treated with permethrin (nonfield conditions); and a group wearing uniforms treated with permethrin and using DEET for skin protection (combat conditions). Urine samples would be collected from these individuals over a specified time, and the appearance of the permethrin metabolite CVA could be quantitated by mass spectrometry following the methods of van der Rhee et al. (1989). An increase in CVA in the urine of the DEET-permethrin

group would suggest a potent interactive effect. Similar values of CVA in the urine of the DEET-permethrin and permethrin-only groups would suggest no interactive effect under the Army's intended conditions of use. Military personnel should consider minimizing areas of skin that are covered by both DEET and the permethrin-treated uniforms to reduce potential interactive effects of DEET on permethrin absorption. In other words, the interactive effects could probably be minimized if the areas of the body covered by uniforms were not covered by DEET. DEET should be applied only to areas of skin not covered by uniforms.

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 commonly

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).

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 curvature

TABLE 4-1 Acute Toxicity of Permethrin Administered to Various Animal Species

Species	Sex	Route	Vehicle	LD_{50} (mg/kg body weight)	Reference
Rat	M	Oral	Water	2,949	Parkinson, 1978
	F	Oral	Water	>4,000	Parkinson et al., 1976
	M	Oral	DMSO[a]	1,500	Clark, 1978
	F	Oral	DMSO	1,000	Clark, 1978
	M	Oral	Corn oil	500	Jaggers and Parkinson, 1979
	M	Oral	Corn oil	430	Kohda et al., 1979
	F	Oral	Com oil	470	Kohda et al., 1979
	M, F	Oral	Corn oil	1,200	Braun and Killeen, 1975
	M, F	Oral	Water	1,725	Sasinovich and Panshina, 1987
	M	Dermal	Water	>5,176	Parkinson, 1978
	F	Dermal	None[b]	>4,000	Parkinson et al., 1976
	M	Dermal	None	>2,500	Khoda et al., 1979
	F	Dermal	None	>2,500	Khoda et al., 1979
	M, F	Dermal	Xylene	>750	Clark, 1978
	M, F	Dermal	None	2,000	Sasinovich and Panshina, 1987
	M	sc[c]	Corn oil	7,800	Khoda et al., 1979
	F	sc	Corn oil	6,600	Khoda et al., 1979
	M	ip[d]	Water	>3,200	Parkinson et al., 1976
	F	ip	Water	>3,200	Parkinson et al., 1976
	—	ip		463-1,725	Sasinovich and Panshina, 1987
	—	Inhalation	None	500 mg/m^3 (6 hr/d, 5 d/wk for 13 wk)	Metker, 1978
	—	Inhalation	None	2,280 (single 4-hr exposure)	Brammer, 1989

Mouse	F	Oral	Water	>4,000	Parkinson et al., 1976
	M, F	Oral	DMSO	250-500	Clark, 1978
	M	Oral	Corn oil	650	Kohda et al., 1979
	F	Oral	Corn oil	540	Kohda et al., 1979
	M	Dermal	None	>2,500	Kohda et al., 1979
	F	Dermal	None	>2,500	Kohda et al., 1979
	M	sc	Corn oil	>10,000	Kohda et al., 1979
	F	sc	Corn oil	10,000	Kohda et al., 1979
Rabbit	F	Oral	Water	>4,000	Parkinson et al., 1976
	F	Dermal	None	>2,000	Parkinson et al., 1976
Guinea pig	M	Oral	Water	>4,000	Parkinson et al., 1976
Hen	—	Oral	—	>1,500	Millner and Butterworth, 1977

[a]DMSO = dimethyl sulfoxide.
[b]Technical material applied without vehicle.
[c]sc = subcutaneous.
[d]ip = intraperitoneal.
Sources: IPCS, 1990; NRCC, 1986.

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 systemic

TABLE 4-2 Effect of Cis/Trans Ratio on Acute Toxicity of Permethrin to Rats

Ratio	Sex	Vehicle	LD_{50} (mg/kg body weight)	Reference
80:20	F	Corn oil	396	Jaggers and Parkinson, 1979
57:43			333	
50:50			748	
40:60[a]			630	
20:80			2,800	
80:20	M, F	Corn oil	224.5	Wallwork et al., 1975
60:40			466.4	
50:50			1,000	
40:60			1,260	
30:70			1,703	
20:80			≥6,000	

[a]Technical-grade permethrin consisting of a cis/trans isomer ratio of approximately 40:60.
Source: NRCC, 1986.

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).

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).

TABLE 4-3 Acute Dermal Toxicity of Permethrin

Species	Sex	Solvent	LD_{50}(mg/kg body weight)	Reference
Rat	M	Water	≥5,176	Parkinson, 1978
Rat	M	None	≥2,500	Kohda et al., 1979
Rat	F	None	≥4,000	Parkinson et al., 1976
Rat	F	None	≥2,500	Kohda et al., 1979
Mouse	M	None	≥2,500	Kohda et al., 1979
Mouse	F	None	≥2,500	Kohda et al., 1979
Rabbit	F	None	≥2,000	Parkinson et al., 1976

Source: NRCC, 1986.

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.

5

Dermal and Ocular Toxicity of Permethrin

DERMAL TOXICITY

To determine whether a compound is safe for application to human skin, a series of standard dermatological tests—namely, primary skin irritation, acute dermal irritation, 21-day dermal repeat application, photo-irritation, skin sensitization, and human 21-day repeat patch test—are usually conducted. The results of these toxicological evaluations are then summarized, and the compound is categorized according to its hazards.

Human Data

Little information exists on workers who manufacture permethrin. In a study of six Swedish forestry workers who handled seedlings immersed in a 2% aqueous solution of permethrin (Kolmodin-Hedman et al., 1982), airborne permethrin concentrations ranged from 0.01 to 0.09 mg/m^3 No adverse effects of those exposures were noted. In another study of 87 Swedish nursery workers who were studied 1-2 months after the planting season, symptoms of itching and burning skin and respiratory and eye irritation were reported. Symptoms were twice as prevalent among workers exposed to a permethrin mixture of cis/trans isomers in a ratio of 25:75 than to a mixture of 40:60; skin and respiratory irritation

was reported by 63% of those exposed to a cis/trans ratio of 25:75 and by 33% of those exposed to a ratio of 40:60. In addition, increased nasal secretions were noted among 13% of those exposed to the 25:75 mixture.

Staff involved with bagging, mixing, or spraying a 5% preparation of permethrin (cis/trans ratio, 25:75) in Nigeria were evaluated with a questionnaire and urinalysis (Rishikesh et al., 1978). Although substantial exposures and absorption occurred, as shown by urinary excretion studies, no adverse health effect could be attributed to permethrin exposures in this group.

Among 17 civilian volunteers exposed to 1% permethrin (cis/trans ratio, 25:75) via skin patches for up to 9 days, two complained of mild erythema and skin irritation (Pegum and Doughty, 1978).

A group of 10 male volunteer soldiers wore uniforms impregnated with an aqueous solution of 0.2% permethrin (cis/trans ratio, 25:75) (Farquhar et al., 1981). They were evaluated after 48 hr for their levels of permethrin exposure and for symptoms of toxicity. Their average exposure to permethrin was 3.8 mg/day, and none complained of skin irritation or other health problems.

The production of skin paresthesia by various pyrethroids, including permethrin, has been examined in human volunteers (Flannigan and Tucker, 1985; Flannigan et al., 1985a,b). Permethrin (0.13 mg/cm^2) was applied on five occasions to 4 cm^2 of an ear lobe; the other lobe had distilled water applied. Evaluation at 48 hr showed that all pyrethroids, including permethrin, produced altered skin sensation. Paresthesia typically developed within 30-60 min of application, was maximal within 8 hr, and slowly disappeared within 24 hr. The changes caused by permethrin were substantially less than those caused by pyrethroids that contained an α-cyano group.

Snodgrass (1986) performed a Draize repeat insult patch test with 184 subjects who represented both sexes, ranged in age from 18 to 80, and were from all races. A 40% permethrin solution (technical-grade permethrin, 92.5%, and ethanol, 95%) was used. A dose of 0.2 mL was applied to the upper arm or back of each subject and placed beneath an occluded patch 3 times per week for 3 weeks. The patches were kept dry and left on between applications. Two weeks after the induction period, a challenge application was made on a previously untreated site and removed 72 hr later. Responses were recorded at 96 hr. None of

the 184 test subjects showed evidence of allergic contact dermatitis. However, several subjects described a transient burning, stinging, or itching sensation.

Clinical Trials

Several clinical trials for the treatment of human ectoparasites have demonstrated the efficacy of permethrin in eradicating the organisms and its accompanying low toxicity to humans. The subcommittee reviewed a summary of clinical trials to date in which 1% permethrin cream rinse was used to treat body lice (650 subjects), head lice (3,041 subjects), and crab lice (56 subjects), and 5% permethrin dermal cream was used to treat scabies (2,068 subjects) and crab lice (28 subjects). Burroughs Wellcome, the manufacturer of permethrin, has published a summary of many of the studies (Andrews et al., 1992).

Of the clinical trials to date, several provided details of possible health effects attributable to permethrin. All published studies made some mention of the presence or absence of side effects, and some provided a systematic account of their methods and findings; these studies are summarized in Table 5-1.

Skin problems, ranging from mild itching to paresthesia and occasional erythematous or eczematous conditions, were reported in most of these trials; rates varied from none to 7% to an isolated rate of 70% among a group of 10 subjects treated intensively for scabies with 5% permethrin cream. In general, the reported skin effects of permethrin were uncommon and of a mild degree. Even the most pronounced skin effects were not disabling or a risk to the person's general health.

The 1% permethrin cream rinse for head lice is available over the counter under the brand name NIX. This product has been more thoroughly tested than any pediculicide ever introduced. More than 21,000 patients have been followed under controlled conditions, including 18,000 monitored during postmarketing surveillance. The overall reported adverse events were approximately 2.5 per 1,000 patients, which is extremely low for any topical medication. These events include reports of pruritus, which is difficult to evaluate, because pediculosis (head lice) is a pruritic condition (Taplin and Meinking, 1993).

The 5 % permethrin cream available only by a doctor's prescription

TABLE 5-1 Selected Clinical Trials of Permethrin with Detailed Possible Side Effects

Condition	Patients Treated, No.	Dose	Reactions	Reference
Head lice *(Pediculus humanus* var. *capitis)*	257	1% cream rinse for 10 min (25-50 mL applied)	Evaluated at 30-60 min, 24 hr, days 7 and 14: skin problems in 37/257 (12.9%)	Brandenburg et al., 1986
Head lice	659	1% cream rinse for 10 min (median 50 mL applied)	Evaluated at days 7 and 14: skin problems in 8/659 (1.2%)	Bowerman et al., 1987
Head lice	108	1% cream rinse for 10 min (25-50 mL applied)	Evaluated at 30-60 min, 24 hr, days 7 and 14: skin problems in 17/231 (7%)	DiNapoli et al., 1988
Human scabies	10	5% cream for 8 hr (mean weight applied, 25 g or 1.25 g of permethrin)	Evaluated at 1 hr, 24 hr, days 7, 14, and 28: mild-to-moderate eczema in 7/10 (70%)	van der Rhee et al., 1989
Human scabies	202 (scabies) 793 (contacts)	5% cream for 8-14 hr (mean weight applied, 25 g or 1.25 g of permethrin)	Evaluated at 30 min, days 14 and 28: skin problems in 28/995 (2.8%)	Yonkosky et al., 1990
Human scabies	234	5% cream for 8-14 hr (mean weight applied, 25 g or 1.25 g of permethrin)	Evaluated at days 7 and 14: skin problems in 8/659 (1.2%)	Schultz et al., 1990

under the brand name Elimite is used for the treatment of scabies. This product has an excellent record of safety. Most adverse reactions have been associated with localized burning, irritation, or tingling sensations, but these should be considered in light of the fact that the product is often applied to skin already damaged by the effects of the scabies mite. The preservative in Elimite is formaldehyde, which is expected to cause some cases of allergic contact dermatitis. In practice, the reported incidence of allergic skin reactions has been extremely low—about two patient reports for every 500,000 units distributed (Taplin and Meinking, 1993).

To treat scabies, 60 g of 5% permethrin cream is applied to the entire human body (head to toe) for 12 hr. This treatment has no adverse effects in healthy individuals, although it might cause minor skin problems in persons with scabies. The margin of safety (MOS) is calculated as follows:

60 g of 5% permethrin cream applied to humans (70 kg) = 43 mg/kg of body weight.

This level presumably includes a safety factor of at least 10. Therefore,

NOAEL = 43 mg/kg/day × 10 = 430 mg/kg.

The NOAEL of 430 mg/kg based on treatment of scabies with 5% permethrin cream and the daily intake of 3.4×10^{-3} ($6.8 \times 10^{-5}/0.02$) mg/kg per day from wearing permethrin-impregnated BDUs provide a MOS of approximately 126,000 as shown below:

$$\text{MOS} = \frac{430 \text{ mg/kg/day}}{3.4 \times 10^{-3} \text{ mg/kg/day}} \approx 126{,}000.$$

Since 60 g of 5 % permethrin cream provides a MOS of 6 million, 56 g of 1% permethrin cream rinse used for head lice would also provide a sufficient MOS.

Animal Data

Acute and Subchronic Effects

Dermal Irritation Robinson (1989b) showed permethrin to be a

moderate skin irritant on the intact and abraded skin of rabbits (Category III). In an acute dermal toxicity test in rats, Robinson (1989a) found an LD50 greater than 200 mg/kg but also observed desquamation, edema, thickening, scab, or skin eruptions in 9 of 10 rats. These skin changes persisted in a few animals up to 10 days (Category III). In the rabbit study, Robinson (1989b) evaluated the skin irritation responses to several concentrations of permethrin. The author observed erythema and edema at a concentration of approximately 80 mg/cm^2. The California Environmental Protection Agency (CEPA, 1992) concluded that the NOEL would be approximately 8 mg/cm^2 (using an uncertainty factor of 10). The subcommittee believes that the CEPA's estimated NOEL of 8 mg/cm^2 is appropriate.

When a permethrin formulation was applied to the clipped dorsal surface (0.13 mg/cm^2) of six New Zealand White rabbits (three of each sex) once a day for 16 days, a slight erythema appeared, which correlated with increased cutaneous blood flow. No significant histopathological changes were detected (Flannigan et al., 1985).

Single applications of up to 0.5-mL[a] permethrin produced only mild, localized irritation (McCreesh, 1977). The treated area showed focal acanthosis and hyperkeratosis of the epidermis. Those pathological conditions are common skin reactions to nonspecific irritant chemicals.

When 0.5 mL of undiluted technical permethrin (91.3 % purity) was applied to the clipped dorsal surface of Japanese White rabbits, there was no irritation (Okuno et al., 1976a).

In occupational settings, dermal contact is one of the main routes of exposure to pesticides. To simulate human dermal contact, rabbits were clipped free of hair and dressed with cotton cloth impregnated with permethrin. After 21 days of exposure, the animals were necropsied. Tissues examined were skin, brain, eye, stomach, small intestine, large intestine, cecum, lung, heart, thyroid, liver, pancreas, adrenal gland, kidney, testes, urinary bladder, skeletal muscle, bone, bone marrow, and trachea. SGOT, SGPT, LDH, glucose, BUN, bilirubin, total protein,

[a]0.5 mL was equivalent to 0.3 mg/kg of body weight, assuming the permethrin was 100% pure and had a specific gravity of 1.214. The body weight of the rabbit was taken as 2 kg.

Na^+, and K^+ were determined. No abnormalities in any of the values were observed (McCreesh, 1977).

Dermal Sensitization In a study by Parkinson et al. (1976), guinea pigs were dermally administered permethrin as a 10% solution in dimethylformamide for 3 consecutive days. This was followed 4 days later by challenge doses of 0.1%, 1%, and 10% solutions of permethrin in dimethylformamide. Only very slight erythema was observed. Permethrin was therefore considered to be either nonsensitizing or only mildly so.

In studies conducted by the U.S. Army Environmental Hygiene Agency (AEHA), guinea pigs (10 per group) were initially injected intradermally with 0.1-mL permethrin solution, and 14 days later were challenged with an intradermal injection (0.1 mL) of either a 0.1% solution of permethrin or dinitrochlorobenzene (DNCB). Five other animals per group received intradermally a challenge dose of 0.1% permethrin or DNCB without a prior sensitizing dose. The positive control substance (DNCB) elicited sensitization reactions in all guinea pigs when examined 24 and 48 hr after the challenge dose, whereas permethrin did not cause any sensitization reactions (Metker et al., 1977; Metker, 1978).

Permethrin (cis/trans ratio, 25:75) in corn oil (1% wt/vol) or Freund's complete adjuvant (1% wt/vol) did not produce dermal irritation or sensitization in groups of 10 male guinea pigs when applied as a 25% dispersion in petrolatum. The positive control, DNCB (5% wt/vol), in petrolatum produced marked sensitization (Chesher and Malone, 1974b).

Employing the guinea pig maximization test, Leah (1989a) reported permethrin to be a moderate skin sensitizer. In this study, 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 a 30% solution in corn oil and with the undiluted test material, which were applied topically. Slight to moderate erythema was observed in 6 of 20 animals. However, the subcommittee believes that in the absence of supporting data from studies conducted by using current knowledge, the results of Leah (1989a) might have yielded a false positive response.

Photochemical Irritation

Irradiation of permethrin-pretreated guinea pigs with UV light (365 nm) for 30 min at a distance of 10-15 cm did not cause a photochemical irritation reaction (McCreesh, 1977).

Single applications of 0.05 mL of 25% (wt/vol) permethrin (in 95% ethanol) or 10% (wt/vol) oil of bergamot solution (in 95% ethanol) (positive control) were applied to the intact skin of six rabbits. Five minutes later, some of the rabbits were exposed to UV light (365 nm) at a distance of 10-15 cm for 30 min (the intensity of UV light was not specified). Skin treated with the positive control solution and irradiated exhibited a greater irritation reaction than did nonirradiated skin. Permethrin did not cause any irritation reaction under the test conditions with or without irradiation (Metker et al., 1977).

OCULAR TOXICITY

The ocular irritation of permethrin has been tested by several investigators in rabbits. Okuno et al. (1976) instilled 0.1 mL of undiluted technical permethrin (91.3% pure) into the eyes of Japanese White rabbits. The eyes were washed with distilled water 5 min or 24 hr after the application of permethrin. No eye irritation was observed in the rabbits.

Parkinson et al. (1976) applied undiluted permethrin to the eyes of female rabbits. Application of permethrin only caused minimal pain, redness, or chemosis of the conjunctiva; there was a slight discharge.

Chesher and Malone (1974a) applied 0.1 mL (dissolved in corn oil and containing a 25:75 ratio of cis/trans isomers) of 40% permethrin into the ocular sac of New Zealand White rabbits. No ocular effects were seen.

Leah (1989b) instilled 0.1 mL of permethrin in the conjunctival sac of rabbits and observed conjunctival erythema, chemosis and discharge. However, no corneal or iridial effects were seen.

Shapiro (1989b) instilled 0.1 mL of the tick-repellent formulation in the conjunctival sac of rabbits and observed mild conjunctival erythema, chemosis, and discharge.

CONCLUSIONS

Ocular Toxicity

The results of the ocular toxicity studies also show that permethrin in BDUs should not be a problem at the intended-use concentrations.

Dermal Toxicity

Review of the available information on dermal toxicity of permethrin indicates that permethrin might be a skin sensitizer at high doses in guinea pigs, although the Draize repeat insult patch test in 184 human subjects did not cause any dermal sensitization. However, several subjects described a transient burning, stinging, or itching sensation. The results of the photochemical irritation studies described above showed that permethrin does not cause phototoxicity (photochemical irritation). The weight of evidence indicates that exposure to permethrin from wearing permethrin-impregnated BDUs at the recommended concentrations is unlikely to cause skin sensitization or other skin effects in humans.

Recommendation

The Army needs to be aware that a few persons might be hypersensitive to permethrin-treated BDUs and thus develop skin sensitization. The Army should monitor for hypersensitivity when they begin to use permethrin-treated BDUs on a regular basis.

6

Neurotoxicity of Permethrin

Permethrin is neurotoxic at high doses. It produces a variety of clinical neurotoxic effects in animals. Some of those effects are tremors, salivation, paresthesia, splayed gait, depressed reflexes, and tiptoe gait; reversible axonal injury occurs at high doses (Brammer, 1989; Robinson, 1989a,b). These symptoms appear to be universal for pyrethroids.

The primary action of pyrethroids on the peripheral nervous system is to induce pronounced repetitive activity—i.e., continuous rather than single nerve impulses (van den Bercken, 1977; van den Bercken et al., 1979). Pyrethroids interact with a fraction of the voltage-dependent sodium channels in excitable membranes that produce a prolongation of the inward sodium current during excitation in which the channels remain open much longer than normal (see review by Vijverberg and van den Bercken, 1990). Membrane depolarization might also occur, resulting in enhanced neurotransmitter release and eventually blockage of excitation. Although postsynaptic neurotransmitter responses can be suppressed by pyrethroids, doses must be higher than those that produce effects on sodium channels. Pyrethroids also increase concentrations of β-glucuronidase and β-galactosidase, which are thought to be associated with repair process, in peripheral nerves (Aldridge, 1990).

HUMAN DATA

A paucity of data are available on the neurotoxic effects of pyrethroids in humans—especially for permethrin. However, in a review of 573 cases of acute pyrethroid poisonings of humans in China (229 occupational and 344 accidental; cases mainly involved deltamethrin (325), fenvalerate (196), and cypermethrin (45)), the initial symptoms from occupational exposures were burning, itching, or tingling sensation (subjective irritation) of the face or dizziness that usually developed after 4-6 hr of exposure (He et al., 1989). Systemic symptoms that occurred in the most serious cases were mainly digestive, including epigastric pain, nausea, and vomiting. Vijverberg and van den Bercken (1990) in their review of pyrethroid insecticides report that the systemic symptoms in humans are burning, itching, or tingling sensation of the face, epigastric pain, anoxemia, nausea, vomiting, dizziness, headache, fatigue, convulsions, and coma.

Nerve conduction studies and interviews of 23 laboratory technicians involved with several pyrethroids in field trials, formulation, or other laboratory work showed no evidence of nerve impairment associated with exposure to permethrin (Le Quesne et al., 1980). Symptoms of facial paresthesia and occasional pruritic rashes were reported among those workers, but symptoms were not clearly related to permethrin.

Staff involved with bagging, mixing, or spraying a 5% preparation of permethrin (cis/trans ratio, 25:75) in Nigeria were evaluated with a questionnaire and urinalysis (Rishikesh et al., 1978). Regardless of the protective equipment worn by spraymen, only 2 mg of permethrin was absorbed after exposure to 6 kg of permethrin, which was excreted in 24 hr.

ANIMAL DATA

Neurotoxic Effects

Rats

Peripheral nerve damage has been reported to occur in laboratory animals at near lethal doses of pyrethroids (Aldridge, 1990; Vijverberg and van den Bercken, 1990).

In an acute dermal toxicity study, Robinson (1989a) exposed rats to permethrin at 2 g/kg and observed neurotoxic signs such as tip-toe gait, upward curvature of the spine, and urinary incontinence in some of the exposed animals. Based on these results, Robinson (1989a) estimated the LOAEL to be 2 g/kg and also estimated the NOAEL to be 200 mg/kg by using an uncertainty factor of 10 to the LOAEL.

Hend and Butterworth (1977) fed permethrin to male and female Charles River rats (six of each sex per group) in diet at concentrations of 0 or 6,000 mg/kg for up to 14 days. Severe clinical signs of poisoning were seen in all the permethrin-treated rats. Only one permethrin-treated male survived the 14-day trial. Histological examination showed fragmented and swollen sciatic nerve axons and myelin degeneration in four of five permethrin-treated animals.

Dayan (1980) fed permethrin (cis/trans ratio, 25:75) (94.5% pure) to groups of 10 male and 10 female Sprague-Dawley rats at 4,000, 6,000, or 9,000 mg/kg for 21 days. All animals developed severe trembling and lost weight. Some rats of each sex in the 9,000-mg/kg group died. Histopathological examination of brain, spinal cord, trigeminal and dorsal root ganglia, proximal and distal root trunks, and terminal motor and sensory nerves showed no consistent abnormalities.

Groups of 10 Wistar rats that were administered permethrin in their diet at concentrations of 0, 2,500, 3,000, 3,750, 4,500, 5,000, or 7,500 ppm (1, 125, 150, 187.5, 225, 250, or 375 mg/kg per day) for 14 days developed peripheral nerve toxicities (Glaister et al., 1977). Deaths occurred among the animals administered 5,000 or 7,500 ppm, and minor histological and ultrastructural changes occurred in the sciatic nerves of the animals in the 5,000-ppm group. The lesions included swelling and increased vesiculation of unmyelinated nerves, hypertrophy of Schwann's cells, contraction of axoplasm and formulation of myelin whorls in residual spaces, and fragmentation of myelinated axons. Similarly, swelling, nodal demyelination, and disintegration of the sciatic nerves were observed in rats fed permethrin at 6,000 ppm (300 mg/kg per day) for 8 days (Okuno et al., 1976b). In another study (James et al., 1977), vacuolation of myelinated nerve fibers occurred in rats fed permethrin at 6,000 ppm (300 mg/kg per day) for 18 days.

Dyck et al. (1984) conducted a detailed morphological evaluation of the nervous system of rats in two chronic feeding studies of permethrin. In the first study, Long-Evans rats were fed diets containing permethrin

at concentrations of 0, 20, 100, or 500 mg/kg for 2 years, and five male and five female animals (randomly selected) from each dose group were examined. In the second study, Long-Evans rats were fed diets containing permethrin at concentrations of 0, 20, or 100 mg/kg for three successive generations, and five male and five female rats from each group were randomly selected from the third-generation parental animals. Examination of central and peripheral nerves, teased myelinated fibers of distal sural and tibial nerves, and the maxillary division of the fifth cranial nerve did not show any changes attributable to the feeding of the permethrin (Dyck et al., 1984).

Hens

Millner and Butterworth (1977) administered permethrin orally (cis/trans ratio, 50:50) as a 40% wt/vol solution in dimethylsulfoxide to hens at daily doses of 1 g/kg of body weight for 5 days. After 3 weeks, the dosing regimen was repeated, and the hens were maintained for an additional 3 weeks before being killed. No signs of neurological disturbance were seen, and there was no mortality. All hens treated with tri-*ortho*-cresyl phosphate (TOCP) (positive control chemical) showed clinical and histopathological evidence of neurotoxicity; none of the hens treated with permethrin showed signs of neurotoxicity. Histological examination of nerve tissues revealed no abnormalities. Permethrin was considered to have no delayed neurotoxic potential such as that seen with certain organophosphates (Millner and Butterworth, 1977).

Ross and Prentice (1977) orally administered permethrin to 15 hens at 9 g/kg of body weight and again 21 days later. After an additional 21 days, the hens were killed. All positive control animals (given TOCP at 500 mg/kg) manifested signs of delayed neurotoxicity ranging from slight muscular incoordination to paralysis. No signs of ataxia were seen in any of the hens in the permethrin-treated or negative control animals. Histopathological examination of the nervous tissues of permethrin-treated animals showed none of the degenerative changes observed in the tissues of the animals from positive control groups.

Neurobehavioral Effects

Pyrethroids can affect behavior patterns. Mice exposed to Ambush (25.6% permethrin) at 0.5, 5.0, or 50 mg/kg orally or 30 or 300 mg/kg dermally displayed an increase in activity (Digiscan optimal animal activity monitor) at the 50- and 300-mg/kg oral and dermal doses, respectively (Mitchel et al., 1988). Additional behavioral studies are necessary to further evaluate the behavioral effects of permethrin.

Sherman (1979) studied the behavior of immature male Sprague-Dawley rats that were habituated to inhalation of permethrin aerosols. Habituation of rats was achieved by exposing three groups of rats (five per group) to aerosols of permethrin at 500 mg/m^3 for 21 days and then again at 1,000 mg/m^3 for an additional 21 days. Three other groups of rats (five per group) served as controls; they were similarly treated but were not exposed to permethrin. At the end of this conditioning period, all rats, including the control animals, were exposed to a permethrin aerosol at 5,000 mg/m^3 for 4 hr. At the end of the habituation period, there were no differences in retention of avoidance training or the ability to learn the same task between control animals and permethrin-exposed groups. However, after exposure to permethrin at 5,000 mg/m^3, retention capacity was significantly lower among nonhabituated control rats than among habituated rats. The nonhabituated control rats also showed decreases in coordination and balance and a higher incidence of conflict behavior and tremors. The performance of the rats in the habituated groups was not changed (Sherman, 1979).

CONCLUSIONS

Permethrin is neurotoxic in animals at high doses. The neurotoxic symptoms of pyrethroid toxicity in humans appear to mimic those observed in animals. The estimated NOEL for neurotoxicity in rats by dermal route is 200 mg/kg (Robinson, 1989a). In the committee's judgment, 125 mg/kg is the LOAEL for permethrin from oral exposure in rats (Glaister et al., 1977; ICI, 1984).

Based on a NOAEL of 200 mg/kg per day from the available neurotoxicity

data, the margin of safety (MOS) associated with daily human exposure to permethrin from permethrin-treated BDUs at a level of 6.8×10^{-5} mg/kg per day is approximately 3 million.

$$\text{MOS} = \frac{200 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 3{,}000{,}000.$$

Because the daily lifetime dose for garment workers (3×10^{-5} mg/kg per day) is less than the daily dose for military personnel, the MOS for garment workers is even higher—6.8 million.

$$\text{MOS} = \frac{200 \text{ mg/kg/day}}{3 \times 10^{-5} \text{ mg/kg/day}} \approx 6{,}800{,}000.$$

Therefore, neurotoxicity that could result from wearing permethrin-impregnated BDUs or working with treated fabric should not be a concern.

RECOMMENDATIONS

Animal data clearly demonstrate the neurotoxic properties of permethrin; however, human data are lacking and need to be substantiated in epidemiological or case studies. The subcommittee recommends that data should be collected on neurotoxicity of permethrin in humans from epidemiological studies of workers or from studies of accidental human exposures.

7

Liver and Other Organ Toxicity of Permethrin

LIVER TOXICITY

Human Data

Specific studies of human liver changes have not been conducted, although extensive medical investigations of workers exposed to permethrin did not reveal any clinical chemistry changes (serum enzymes) that would suggest liver toxicity (Prinsen and van Sittert, 1978).

Animal Data

The most significant (morphologically recognizable) toxicological effect of permethrin involves the liver. It is characterized by an increase (absolute and relative) in weight, but takes several repeated exposures to be evident. The lowest dose that has been reported to cause a significant increase in liver weight occurred after animals ingested 100 mg/kg for 26 weeks. Sex-related differences in liver enlargement have been reported but are not consistent. Female rats exhibited an increase in liver weight and in liver-to-body-weight ratio when fed a diet containing permethrin at 1,000 mg/kg of diet, whereas that effect was observed in male rats at 2,500 mg/kg of diet (Clapp et al., 1977b). However, in another

study, increase in relative liver weight was observed at 1,000 mg/kg of diet in male rats and at 3,000 mg/kg of diet in female rats (Butterworth and Hend, 1976). The increase in liver weight is due to hepatocellular hypertrophy. Necrotic foci, vacuolization, and increased eosinophilia also have been observed. Hepatocellular hypertrophy is characterized ultrastructurally by an increase in endoplasmic reticulum, which is functionally associated with increased microsomal activity and an increase in cytochrome-P-450-mediated enzymes (Bradbrook et al., 1977) (see Chapter 4). These changes are largely reversible after ceasing exposure, although microsomal activity is still slightly increased. An increase in specific liver-related enzymes (SGOT, GPT, and LDH) has been observed in blood serum of rats at clearly toxic doses (near the LD_{50}) (Wallwork et al., 1974a).

In a reproductive toxicity study, 12 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 per day) for three generations with two litters per generation (Hodge et al., 1977). Hepatic centrilobular hypertrophy, evaluated histologically only in F3b weanlings, was observed at all doses. This liver effect was not considered an adverse reproductive or developmental effect but rather a systemic effect similar to that observed in adult rats at high doses in the studies on chronic toxicity and oncogenicity of permethrin. Liver effects observed in chronic carcinogenicity studies are discussed in Chapter 11.

The NOEL for hepatocellular hypertrophy in rats has been estimated to be 10 mg/kg per day on the basis of a LOEL of 50 mg/kg after 2 years of oral exposure (in feed); the NOEL for hepatic enzyme induction was estimated to be 25 mg/kg and the LOEL to be 50 mg/kg (CEPA, 1992).

OTHER ORGAN TOXICITY

Human Data

No organs have been identified as showing lesions related to permethrin exposure. Clinical signs and symptoms of central nervous system intoxication have been reported (see Chapter 6).

Animal Data

Lesions in other organs in response to permethrin exposure have been observed only at very high doses. Dogs exposed to 500 or 2,000 mg/kg (orally) for 3 months showed only significant liver enlargement (Killeen and Rapp, 1976a), but when exposed to 250 mg/kg for 6 months more, overt changes were a decrease in food intake; relative increase in liver, heart, and kidney weight; and perturbations in hematological and serum chemistry values (Reynolds et al., 1978).

CONCLUSIONS

The liver is the only organ to consistently show evidence of change after chronic permethrin exposure. There is an increase in liver weight characterized microscopically by hepatocellular swelling. Ultrastructurally, there is an increase in endoplasmic reticulum, which is reflected in an increase in microsomal enzymes and serum enzymes specific to the liver.

The NOAEL for hepatocellular hypertrophy in rats has been estimated to be 10 mg/kg per day based on a LOEL of 50 mg/kg after 2 years of dietary exposure, and the NOEL for hepatic enzyme induction has been estimated to be 25 mg/kg based on a LOEL of 50 mg/kg.

The subcommittee concluded that the NOAEL of 10 mg/kg per day from the available liver toxicity data shows that daily exposure to permethrin-impregnated uniforms at a level of 6.8×10^{-5} mg/kg per day provides a MOS of approximately 150,000 for liver toxicity.

$$\text{MOS} = \frac{10 \text{ mg/kg/day}}{6.8 \times 10^{-6} \text{ mg/kg/day}} \approx 150{,}000.$$

Because the daily lifetime dose for garment workers (3×10^{-5} mg/day) is less than the daily dose for the military personnel, the MOS for garment workers is higher.

$$\text{MOS} = \frac{10 \text{ mg/kg/day}}{3 \times 10^{-5} \text{ mg/kg/day}} \approx 340{,}000.$$

Therefore, liver toxicity that might result from wearing permethrin-impregnated BDUs or working with treated fabric should not be a concern.

The subcommittee recognizes the limitations of extrapolating from oral toxicity studies to effects expected from dermal exposures, because such an extrapolation can introduce quantitative errors if the underlying assumptions are not true. However, in the absence of data from dermal exposure studies, extrapolation from other routes is done by default. In general the dermal toxicity of chemical contaminants is less than the oral toxicity, because less chemical is absorbed dermally than orally. Furthermore, in light of the very high LD_{50} of permethrin by the dermal route in acute exposure studies—greater than 2,500 mg/kg—the possibility of dermal toxicity from low-level exposures is remote.

8

Immunotoxicity of Permethrin

The immune system is the first line of defense to protect animals and humans from disease. Suppression of the immune response can result in an increase in susceptibility to infectious and carcinogenic agents, and an increased response can provoke allergies and autoimmunity. In some instances, the immune system can be the primary target organ of toxic chemicals.

No data are available in the literature on the immunotoxic potential of permethrin in humans.

Two immunotoxicity studies have been conducted with permethrin. In an in vitro study (Stelzer and Gordon, 1984), permethrin at a concentration of approximately 10^{-5} to 10^{-6} M inhibited the mitogenic response of murine immune lymphocytes. Although permethrin inhibited the mitogenic response of murine lymphocytes in vitro, mitogenic responses in in vitro exposures do not represent functional immunity, nor do they simulate in vivo reactions.

McCorkle et al. (1980) fed 1-day-old chicks permethrin at 0.01, 0.1, or 1 ppm for 6 weeks. The antibody titers to a T-cell-dependent antigen (sheep red blood cells) were elevated, and titers to a T-cell-independent antigen (*Brucella abortus*) were depressed. The contrasting, elevated and suppressed, antibody responses to antigen do not reflect a consistent immunotoxicological effect. Immunotoxicological data for most chemicals have been acquired in laboratory mice and rats; therefore, additional studies need to be performed in those species to determine the immunotoxic

potential of permethrin. Few immunotoxicological data from laboratory animal exposures are available for permethrin or other pyrethroids.

CONCLUSIONS

No human data are available to evaluate the immunotoxic potential of permethrin in humans. The two laboratory studies (an in vitro study with lymphocytes and a study in chicks) are inconclusive to assess the immunotoxicological effects of permethrin.

RECOMMENDATIONS

Little immunotoxicological information is available for permethrin. Immunotoxicological investigations need to be performed in laboratory animals to ascertain the immunotoxic properties, if any, of permethrin in mammalian species. These studies should follow the guidelines presented in the National Research Council's report *Biologic Markers in Immunotoxicology* (NRC, 1992).

9

Reproductive and Developmental Toxicity Of Permethrin

Several reproductive and developmental toxicity studies have been conducted with permethrin administration in diet or by gavage. No studies were found that used dermal exposure, but any effect would be expected to be less because of lower absorption in dermal exposure than in oral exposure. The oral studies include six experiments in rats, two in mice, and two in rabbits in which permethrin was given during part or all of organogenesis, and fetuses were examined at term or, in some cases, postnatally. Three three-generation reproduction studies were conducted in rats. Several chronic toxicity studies were also reviewed for information on reproductive organ weight or histopathology. As a whole, the data available suggest little or no effect of permethrin on developmental or reproductive end points, except at fairly high doses. There were observations of developmental or reproductive effects in single studies, but those alterations were not confirmed in other similar studies.

Most of the following descriptions of studies were developed from information in the World Health Organization's (WHO's) Environmental Health Criteria (IPCS, 1990) and the California Environmental Protection Agency's Risk Characterization Document (CEPA, 1992). In addition, clarifying information on several studies was obtained from Dr. John Doherty, Office of Pesticide Programs, U.S. Environmental Protection Agency (EPA), who reviewed many of the original studies on permethrin for that office.

RAT STUDIES

Kohda et al. (1976a) treated Sprague-Dawley rats with permethrin at 0, 10, 20, or 50 mg/kg per day orally on gestation days (GDs) 9-14. Two-thirds of the animals were killed on GD 20, and the rest were allowed to deliver, were weaned, and then killed at 6 weeks of age. Parental females fed 50 mg/kg showed neurotoxicity and slight body-weight decreases, but no mortality. Fetal loss at the high dose was also slightly increased, and there was an increase in nonossified sternebrae. No other effects were seen either prenatally or postnatally.

McGregor and Wickramaratne (1976a) treated CD rats with permethrin at 0, 22.5, 71, or 225 mg/kg per day on GDs 6-16. No effects on any maternal or developmental end points were seen at GD 20 when animals were killed and uterine contents examined.

Metker et al. (1977) treated Sprague-Dawley rats with 4, 41, or 83 ppm in the diet on GDs 6-16. Animals were killed on GD 20, and no effects on adults or offspring were noted.

James (1974a) administered permethrin (cis/trans ratio, 25:75) to Wistar rats by gavage at 0 or 200 mg/kg on GDs 6-16. Animals were killed on GD 20; no effects were seen in either maternal or developmental end points.

Hodge (1988) administered permethrin dissolved in corn oil by gavage to Alpk:Apf Sprague-Dawley rats (24 in each group) at doses of 0, 15, 50 or 150 mg/kg per day on GDs 7-16. Maternal toxicity was seen at 150 mg/kg, and reduced fetal body weight and delayed ossification were seen at 150 mg/kg. The maternal and developmental NOAELs were 50 mg/kg.

Spencer and Berhane (1982) treated Sprague-Dawley rats (five to eight in each group) with 0, 500, 1,000, 1,500, 2,000, 2,500, 3,000, 3,500, or 4,000 ppm in the diet on GDs 6-15. Laparotomies were done on GD 6 to count implantation sites (after iv injection with Chicago blue dye), and animals were killed on GD 20. Other animals were treated similarly and killed on GD 16 for assay of placental protein and glycogen content. Although a reduction in placental glycogen content was seen at 2,000 ppm and above and protein content was reduced at 2,500, 3,000 and 4,000 ppm, there was no consistent dose-related effect in offspring observed on GD 20. There was an increase in the

resorption rate in all treated groups, but the increase was not dose-related and might have been due to an unusually low incidence in controls.

Schroeder and Rinehart (1977) conducted a three-generation reproduction study in Long-Evans rats (10 males and 20 females in each group) with two litters in each generation. Animals were exposed to permethrin at 0, 20, or 100 ppm (cis/trans ratio, 40:60) in the diet (0, 1, or 5 mg/kg per day). The only observation was a decrease in the F2 mating index in both controls and treated groups, but no dose-related effects were seen in the study. No histopathological examination was done in this study.

Hodge et al. (1977) also conducted a three-generation study (two litters per generation) in Wistar rats (12 males and 24 females in each group) with 0, 500, 1,000, or 2,500 ppm in the diet (0, 25, 50, or 125 mg/kg). Tremors and other clinical signs were seen mostly in the high-dose group or F0 females. In both generations, there was a dose-related increase in the occurrence of buphthalmos (enlargement of the eye) and pupillary membrane (a mesodermal layer attached to the iris during embryonic development) in offspring at weaning. The pupillary-membrane incidence in the 0-, 500-, 1,000-, and 2,500-ppm groups was 0 of 1,252, 2 of 1,241, 18 of 1,383, and 19 of 1,408, respectively, and the buphthalmos incidence was 0 of 121, 1 of 120, 14 of 130, and 15 of 131, respectively. The incidence was significantly increased at 1,000 and 2,500 ppm, although the highest incidence was less than 2% of pups, approximately 11% of litters. These effects were similar to those seen in adult animals exposed to permethrin (see Chapter 7). The earliest litter affected was the second F2 at 500 ppm, the first F2 at 1,000 ppm, and the second F1 at 2,500 ppm. Thus, there was some progression toward earlier litters affected as the dose was increased. The CEPA document noted that this defect can be genetically determined, but no evidence for that was found in the pedigree of the animals used in the study. However, they did not rule out a genetic-chemical interaction. In F3b offspring, dose-related centrilobular hypertrophy and cytoplasmic eosinophilia were seen in the liver at all doses (looked at only in the F3b offspring). No other effects of permethrin exposure were seen. No histopathological examination was performed in this study.

A third three-generation study with two litters in each generation was

conducted by James (1979) in Wistar COBS rats. Twenty males and 20 females in each group were fed permethrin (cis/trans ratio, 25:75) in the diet at doses of 0, 5, 30, and 180 mg/kg of body weight. No effects were reported in any group. No histopathological examination was performed in this study.

MOUSE STUDIES

Kohda et al. (1976b) treated ICR mice with 0, 15, 50, or 150 mg/kg orally on GDs 7-12. Two-thirds of the animals were killed on GD 18, and the rest went to term, delivered, and weaned their young; pups were killed at 6 weeks of age. No effects were seen on any maternal, developmental, or postnatal end points.

James (1974b) treated CD-1 mice with 0 or 400 mg/kg per day by oral gavage on GDs 6-15, and killed the animals on GD 18 to examine the offspring. No effects were seen.

RABBIT STUDIES

Richards et al. (1980) treated Dutch rabbits by gavage with permethrin at 0, 600, 1,200, or 1,800 mg/kg in 0.5% Tween 80 on GDs 6-18 and killed the animals on GD 29. Maternal body-weight gain was reduced, and there was increased hair loss at 1,200 and 1,800 mg/kg. Embryo lethality was also increased at the two highest doses, and fetal weight was decreased at 1,800 mg/kg.

James (1974c) treated Dutch belted rabbits (six to seven per group) with permethrin at 0 or 400 mg/kg per day in a corn oil gavage on GDs 6-18. No effects were noted in the permethrin-exposed animals.

OTHER STUDIES

Since the multigenerational studies did not include data on specific reproductive toxicity, such as organ weights, histopathology, or semen measurements, other data were reviewed to determine whether there

might be more specific effects of permethrin, particularly on male reproductive function. Data summaries of the chronic toxicity studies and the dominant-lethal-effects studies using permethrin exposure were reviewed in an attempt to find more specific information. There are several issues that should be considered in evaluating these data, however. In the chronic toxicity studies, data were usually collected at the end of 1-2 years when pathology of aging is often seen in the testis. Also, histopathological examinations at the time these studies were done were most likely conducted after formalin fixation, which does not result in adequate testicular morphology. Current procedures recommend Bouin's fixation for testes. The following summarizes data available from these studies.

Ishmael and Litchfield (1988) conducted chronic toxicity studies in Alpk:AP (Wistar-derived) rats and Swiss-derived mice fed permethrin (cis/trans ratio, 40:60) in the diet for 104 weeks. The concentrations used for rats were 0, 500, 1,000, or 2,500 ppm, and those used for mice were 0, 250, 1,000, or 2,500 ppm. Testis weights were recorded at 52 and 104 weeks in rats and at 26, 52, and 98 weeks in mice; no effects were noted. It is not clear from the paper whether testis histopathological examination was done.

A chronic toxicity study was conducted by Tierney and Rinehart (1979) in CD-1 mice (75 of each sex per group) (see Table 9-1). Permethrin was given at 0, 20, 500, or 2,000 ppm in the diet to male mice and 0, 20, 2,500, or 5,000 ppm in the diet to female mice. At the end of the 2-year study, testis weight was reduced and testicular hypoplasia histologically was noted; increased mortality occurred in males at the 2,000-ppm (300-mg/kg) dose. There was also reduced testis weight and increased mortality in males at 500 ppm (75 mg/kg); testis weight was not significantly reduced at 20 ppm (3 mg/kg), but there was a clear dose-related change among the three permethrin doses. The study was considered unacceptable by CEPA because of poor animal husbandry, but EPA audited the study and found it acceptable.

Another chronic toxicity study submitted to EPA by Wellcome (Life Science Research, 1980) was a dietary feeding study in which Charles River Wistar rats were fed permethrin at 0, 10, 50 and 250 mg/kg of body weight per day (cis/trans ratio, 25:75). At the end of the study (104 weeks), histopathological examination was performed on a number

TABLE 9-1 Reproductive and Developmental Toxicity in Tierney and Rinehart Study

	% Reduction Relative to Controls		
Testis Weight Reduction	20-ppm Group	500-ppm Group	2,000-ppm Group
Absolute	7	15	38
Relative to body weight	7	12	35

of tissues, including male and female reproductive organs (using H & E staining and presumably formalin fixation). No effects were noted.

Several subacute and subchronic toxicity studies are cited in the WHO document (IPCS, 1990), and several other chronic toxicity studies are reviewed in the WHO document (IPCS, 1990) and the CEPA document (CEPA, 1992). These reviews do not indicate testis-weight or histopathological results, but very little detail of what was done in the studies is given.

Two dominant-lethal-effects studies were performed in mice, and both were negative but poorly conducted. One study had small numbers of animals in each group (McGregor and Wickramaratne, 1976b), and the other study used only a single dose (Chesher et al., 1975b).

CONCLUSIONS

Data on the reproductive and developmental toxicity of orally administered permethrin suggest that there are few toxic effects and that these tend to be at high doses. No data are available from dermal exposure studies, but oral dosing would be expected to maximize any effects, since dermal absorption is poor. Where toxic effects have been reported, other similar studies have not confirmed those effects. There is also disagreement among the studies on the doses at which toxicity was observed. In the rat developmental toxicity studies, for example, Kohda et al. (1976a) reported maternal and developmental toxicity at 50 mg/kg per day on GDs 9-14 and a NOAEL of 20 mg/kg per day. On the other hand, Hodge (1988) reported maternal and developmental toxicity at 150 mg/kg per day (given orally on GDs 7-16) and a NOAEL of 50 mg/kg

per day, and McGregor and Wickramaratne (1976a) reported no effects at doses as high as 225 mg/kg per day on GDs 6-16. There were some differences in the strain of rat used in these studies, and the cis/trans mixture was not always specified; that might explain in part the inconsistencies in the data. NOAELs from the mouse and rabbit studies (400 mg/kg per day and 600 mg/kg per day, respectively) were much higher than those from the rat studies.

In the three-generation studies, Hodge et al. (1977) reported an increase (albeit small) in buphthalmos and persistent papillary membrane in weanling rats following continuous exposure to permethrin at 1,000 and 2,500 ppm (50 and 125 mg/kg per day); the NOAEL was 500 ppm (25 mg/kg per day). In contrast, James (1979) reported no effects from doses as high as 180 mg/kg per day given in the diet. It is possible that buphthalmos and persistent papillary membrane might have occurred in the James (1979) study but were not observed because they are subtle changes and have a very low incidence. Schroeder and Rinehart (1977) used such low doses (5 mg/kg per day was the highest dose used) that the defects were unlikely to have occurred in their study. Given the available data and the uncertainties concerning possible differences in observation of pups among the studies, the NOAEL of 25 mg/kg per day from the Hodge et al. (1977) study will be used as the NOAEL for developmental toxicity on the basis of the three-generation studies. Liver hypertrophy similar to that seen after adult exposures (see Chapter 7) was not considered a developmental effect but was significantly increased in F3b weanling pups at all doses in the Hodge et al. (1977) study (the LOAEL was 25 mg/kg per day).

As for the possibility of an effect of permethrin on male reproductive function, few data are available. No histopathological examinations were done in any of the three-generation studies, and there was no indication that organ weights were measured. Few data on testis weight and histopathology were available from chronic toxicity studies (usually at the end of the 2-year study when pathology due to aging is often seen). Also, it is assumed that formalin fixation and H & E staining were probably used for histological examination because the studies were conducted in the late ‘70s and early ‘80s, when this was the standard procedure. Current procedures include Bouin's fixation of testes to obtain good histological results. One chronic toxicity study in mice (Tierney

and Rinehart, 1979) did note an effect on testis weight and testicular hypoplasia at doses of 500 and 2,000 ppm (75 and 300 mg/kg per day; NOAEL of 20 ppm or 3 mg/kg per day). There was also increased mortality at the two higher doses. However, no such effects in rats or mice were noted by Ishmael and Litchfield (1988) using concentrations of permethrin up to 2,500 ppm in feed. The Life Science Research (1980) study also reported no effects of permethrin in rats on testis weight or histopathology at doses of up to 250 mg/kg per day. Thus, information on male reproductive effects is minimal at best, and the most conservative NOAEL was 3 mg/kg per day.

The NOAEL of 3 mg/kg per day based on testicular effects and the daily intake of 6.8×10^{-5} mg/kg per day from wearing permethrin-impregnated BDUs provide a MOS of approximately 44,000.

$$\text{MOS} = \frac{3 \text{ mg/kg/day}}{6.8 \times 10^{-5} \text{ mg/kg/day}} \approx 44{,}000.$$

Because the daily lifetime dose for garment workers is less than that for military personnel (3×10^{-5} mg/kg per day), the MOS for garment workers is 100,000.

$$\text{MOS} = \frac{3 \text{ mg/kg/day}}{3 \times 10^{-5} \text{ mg/kg/day}} \approx 100{,}000.$$

Given the lack of reproductive or other types of toxicity (except for the liver) in most of the reproductive and developmental toxicity studies available on permethrin and a MOS of approximately 44,000 or more from the most sensitive toxic end point (decreased testicular weight), the possibility of male reproductive effects or other reproductive and development effects occurring from wearing permethrin-impregnated BDUs or working with treated fabric seems remote. It should be noted, however, that no data are available from dermal exposure studies. Furthermore, there is disagreement among different studies on the doses at which toxicity was observed, and there are no specific studies on either male reproductive effects or human reproductive toxicity.

10

Genotoxicity of Permethrin

No data are available in the literature on the genotoxicity of permethrin in humans.

GENE MUTATIONS

Several investigators have tested permethrin for its ability to produce mutations in Ames reverse mutation assay using *Salmonella typhimurium* tester strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100, with and without metabolic activation (Litton Bionetics, 1975; Longstaff, 1976; Simmon, 1976; Callander, 1989). The concentrations of permethrin tested ranged from 1 to 2,500 μg per plate. The results of these studies showed that permethrin was not mutagenic in the Ames *Salmonella* test. Permethrin was also not mutagenic in *Escherichia coli* WP_2 uvrA mutation assay (Newell and Skinner, 1976; Simmon, 1976). In one host-mediated assay, permethrin (200 mg/kg of body weight) was orally administered to ICR mice, and the indicator organisms, *S. typhimurium* G46, were injected intraperitoneally and harvested from the abdominal cavity of mice 3 hr after treatment. The study did not reveal any mutagenic effect (Shirasu et al., 1979). In another host-mediated assay employing a similar test system, trans-permethrin at 600 and 3,000 mg/kg of body weight and cis-permethrin at 21 and 54 mg/kg of body weight gave negative results (Miyamoto, 1976).

Permethrin has also been tested for its genotoxicity with *Saccharomyces cerevisiae* D4, with or without metabolic activation, at concentrations ranging from 0.0001 to 5.0 μg per plate, and the results showed that permethrin was not mutagenic to *S. cerevisiae* D4 (Litton Bionetics, 1975).

Permethrin was not mutagenic in *Drosophila melanogaster* sex-linked recessive lethal mutation assay (Mehr et al., 1988).

Clive (1977) studied the mutagenicity of permethrin (purity not stated) in mouse lymphoma L5178Y TK^+/TK^- assay at concentrations ranging from 1 to 125 mg/mL, with and without metabolic activation. There was no evidence of mutagenicity in this study.

Pluijmen et al. (1984) showed that permethrin was not mutagenic to V79 Chinese hamster cells, with or without metabolic activation.

CHROMOSOMAL EFFECTS

The results of investigations of clastogenic effects of permethrin are inconsistent. In one study, *D. melanogaster* males were administered permethrin in a feeding solution at 5 ppm for 3 days before mating with untreated mus-302 DNA-repair defective females. The F1 male progeny were screened for partial or complete chromosomal loss. The results of this investigation were negative (Woodruff et al., 1983). The utility of this study is questionable because the assay is not commonly used for chromosomal aberrations and its sensitivity is unknown. Furthermore, the findings are questionable because only low doses of permethrin were tested.

Anderson and Richardson (1976) tested permethrin for its ability to induce micronuclei in Alderley Park rats. Male rats (12 controls and 8 per treatment group) were injected intraperitoneally with permethrin (94% pure, cis/trans ratio, 40:60) once or in five daily doses of 0, 600, 3,000, or 6,000 mg/kg. There were eight animals per test group and 12 animals in the control group. Rats were killed 24 hr after the single injection and 6 hr after the final dose with multiple injections. Bone-marrow cells from each animal were analyzed, and the results of this investigation showed that permethrin was not clastogenic.

Hoellinger et al. (1987) reported a slight but significant ($p < 0.01$)

increase in micronuclei in bone-marrow cells (1,000 cells analyzed) of female Sprague-Dawley rats (0.71% vs. 0.25%) that were administered permethrin by gavage at doses of 139 mg/kg (purity, 91%; cis/trans ratio unknown). The subcommittee considers this study inadequate because only one dose was tested in six animals.

In another study, 10 male CFLP mice per group were administered permethrin (purity unknown; cis/trans ratio unknown) orally once at 150 mg/kg or in five daily doses at 45.2 mg/kg (Paldy, 1981). The animals were killed 24 hr after the final dose but only 100 bone-marrow cells from each animal were examined (the standard practice is to analyze 1,000 bone-marrow cells) for chromosomal aberrations—breaks, chromatid-type gaps, isogaps, and chromosome-type deletions with acentric fragments and translocations. The results showed that single and repeated administration produced these chromosomal effects. In both experiments, permethrin produced chromosomal aberrations in 5% of the cells as compared with 2% in controls. According to Paldy (1981), this result is on the borderline of statistical significance; the "p" value was not provided, however. The subcommittee considers the study to be inadequate because the study is published only as an abstract without details of protocols. Furthermore, only 100 bone-marrow cells were examined and the investigator observed mainly chromatid gaps and breaks; their significance is unknown.

Barrueco et al. (1992) tested permethrin for its ability to induce sister chromatid exchanges (SCEs), micronuclei, and chromosomal aberrations in cultured human peripheral blood lymphocytes from two human donors. Permethrin was tested at concentrations of 5-200 μg/mL in the absence and presence of rat liver S9 mix. Small increases in the SCE frequencies were found that were statistically significant, but they might not be biologically meaningful since there was no dose-effect relationship and the increase in SCEs was not always reproducible.

Permethrin increased the occurrence of micronuclei over controls when it was assayed at concentrations of 10-100 μg/mL in the absence of S9 mix. The effect was statistically significant. However, in the presence of S9 mix, the increase in micronuclei was not statistically significant in lymphocytes from both human donors.

Permethrin was found to increase the frequency of chromosomal aberrations at concentrations of 75-150 μg/mL in the absence of S9 mix. In

the presence of S9 mix, the increase in frequency of chromosomal aberrations was not statistically significant. The chromosomal aberrations induced by permethrin in this study were mainly chromosome type. The authors concluded that permethrin did not induce SCEs and recommended that additional studies should be conducted to confirm the positive results in the chromosomal-aberration and micronuclei assays using the cultured human lymphocyte. Additional studies should consider the influence of the metabolic activation system and the duration of treatment on the induction of clastogenic effects of permethrin (Barrueco et al., 1992).

Herrera et al. (1992) studied the induction of SCEs in cultured human lymphocytes from two human donors. They found that permethrin at concentrations of 50 or 100 μg/mL induced SCEs in the absence of rat liver S9 mix; however, the increases in frequency of SCEs were not dose-related. There were differences between the two donors in the SCE assays carried out in the presence of liver S9 mix—one showed no increase in SCEs and the other showed an increase in SCEs that was not dose-related. The authors concluded from this that "permethrin induces a slight genotoxic effect that cannot always be detected."

Herrera et al. (1992) also studied the induction of micronuclei in cultured human lymphocytes of two human donors. The lymphocytes were exposed to permethrin at concentrations of 0, 10, 25, or 50 μg/mL in the absence of S9 mix. Permethrin was positive in the micronucleus test when it was assayed in the absence of S9 mix. However, in the presence of S9 mix and permethrin concentrations of 0, 25, 50, 75, 100, or 200 μg/mL, the increase in number of micronuclei, observed in some cases, was not statistically significant. The authors concluded that "a definitive conclusion on the genotoxicity of the pyrethroid insecticide can only be possible when more experimental tests are available."

Barrueco et al. (1994) tested permethrin for its ability to induce structural chromosomal aberrations in human lymphocyte cultures and Chinese hamster ovary (CHO) cells. Permethrin was tested in the range of 50-200 μg/mL in human lymphocyte cultures and in the range of 20-100 μg/mL in CHO cells. A short-term (2-3 hr) exposure and a long-term (20-24 hr) exposure were used in each study. The short-term exposure was conducted in the presence and absence of S9 mix. Permethrin induced dose-dependent increases in chromosomal aberrations in human lymphocytes and CHO cells in the absence of S9 mix. In the presence of

S9 mix, the clastogenicity was not statistically significant. In both cultures, permethrin induced primarily chromosome-type aberrations.

Permethrin has been studied for dominant lethal effects in two studies. In one study, 15 male CD-1 mice in each group were administered permethrin (purity, 95.3%; cis/trans ratio, 40:60) orally on GDs 7-12 at 0, 15, 48, or 150 mg/kg per day. Each male was mated with two virgin females weekly for 8 consecutive weeks. The pregnant mice were killed on GD 12. There was no dose-related effect on pregnancy or early fetal deaths. Thus, permethrin had no dominant lethal effect on male mice (McGregor and Wickramaratne, 1976b). However, this study was flawed because there was no explanation for deaths of 5% of the females and the number of pregnant females per interval was insufficient. In the second dominant-lethal-effects study, 10 male CD-1 mice in each group were administered permethrin (purity unknown; cis/trans ratio, 25:75) orally at 0 or 452 m/g kg per day ($1/5\ LD_{50}$) for 5 days. Each male was mated with three virgin females weekly for 6 weeks. The results of the investigation showed no evidence of dominant lethal effect of permethrin (Chesher et al., 1975b).

OTHER GENOTOXIC EFFECTS

In DNA damage studies, Trueman (1988) studied the induction of unscheduled DNA synthesis in primary rat hepatocytes in culture. Rat hepatocytes were exposed to 93.5% permethrin at concentrations of 10^{-9}-10^{-2} molar. There was no evidence of induced DNA repair as measured by unscheduled DNA synthesis in primary cultures of rat hepatocytes exposed in vitro. Permethrin was negative in the *E. coli* pol A assay, the *Bacilus subtilis* rec assay, the *S. cerevisiae* D3 mitotic recombination assay, and the unscheduled DNA synthesis in human lung fibroblasts (Garrett et al., 1986).

CONCLUSIONS

Studies conducted to determine the potential of permethrin to produce gene mutations in microbial and mammalian systems were all negative.

Studies conducted to determine the potential of permethrin to produce

chromosomal damage provided an array of results. Of the two in vivo studies conducted in the micronucleus assay, one was negative and the other was inadequate. Three in vitro studies in which clastogenicity of permethrin was investigated provided evidence of potential clastogenicity of permethrin. Small, statistically significant elevations in sister chomatid exchanges, micronuclei, and chromosomal aberrations in human lymphocyte cultures were reported. Chromosomal aberrations were also reported in Chinese hamster ovary cells. All three in vitro studies were performed in one laboratory by the same investigators.

Other genotoxicity tests of permethrin (dominant lethal test and tests for DNA damage in microbial and mammalian cells) were negative.

The subcommittee believes that the weight of evidence suggests that permethrin does not produce gene mutations but is a potential clastogen in certain in vitro systems.

Three in vitro studies from one laboratory showed small, statistically significant increases in clastogenic effects of permethrin. The subcommittee recommends that these studies be repeated by other investigators to determine if the positive findings of permethrin's clastogenicity can be confirmed. If these findings are confirmed, the clastogenicity of permethrin should also be studied in vivo with an adequate number of animals and dosages of permethrin.

11

Carcinogenicity of Permethrin

No data are available in the literature on the carcinogenicity of permethrin in humans.

Evidence of permethrin's possible carcinogenicity in humans is derived from bioassays in rodents. Permethrin has been tested for its carcinogenicity in seven chronic carcinogenicity studies using mice and rats. These studies have been reviewed in detail by the U.S. Environmental Protection Agency (EPA, 1989a) and the California Environmental Protection Agency (CEPA, 1992).

CARCINOGENICITY STUDIES IN MICE

Four mouse carcinogenicity studies have been conducted with permethrin; in all four studies, permethrin was administered to mice in their diet.

ICI Mouse Study

Hart and co-workers (1977) conducted a chronic carcinogenicity study for Imperial Chemical Industries (ICI). Seventy Alderley Park (Swiss-derived) mice of each sex per group were administered permethrin (purity, 94.0-98.9%; cis/trans ratio, 40:60) at 0, 250, 1,000, or 2,500 ppm

(0, 37.5, 150, or 375 mg/kg of body weight per day) for 98 weeks. A slight increase was reported in lung adenomas in males at the highest dose tested (2,500 ppm), which was not statistically significant. There were no carcinomas observed in any of the male groups; in female mice, one carcinoma was reported in each treatment group.

Table 11-1 presents the lung adenoma incidences for this study. There was a slight decrease in growth of animals administered the two highest doses of permethrin.

Nononcogenic effects noted at doses of 1,000 ppm and above included minimal changes in liver enzyme activity, increases in liver weight, and histopathological changes in the liver (eosinophilia of hepatocytes). Hepatic aminopyrine *N*-demethylase activity increased significantly in male and female mice in the highest-dose group. A decrease in vacuolation of the proximal tubular epithelium of the kidney was also noted at all doses of permethrin in male mice. At the highest dose tested (2,500 ppm), mortality increased in both sexes. This study was conducted at an adequate dose for determining the oncogenic potential of permethrin.

EPA determined that the NOEL for this study was 250 ppm (37.5 mg/kg per day) on the basis of the liver effects. The subcommittee concluded that this study is negative for carcinogenicity.

FMC Mouse Studies

A mouse carcinogenicity study was conducted for FMC Corporation by Bio-Dynamics Laboratory (Hogan and Rinehart, 1977; Rapp, 1978). CD-1 mice (75 of each sex per group) were fed permethrin (purity unknown; cis/trans ratio, 40:60) for 2 years. During the first 5 months,

TABLE 11-1 Adenomas in Mouse Lungs in ICI Mouse Study

Dose, ppm in diet (mg/kg/day)	Males		Females	
	Incidence	Percent	Incidence	Percent
0 (0)	11/70	15.7	11/70	15.7
250 (37.5)	6/70	8.6	8/70	11.4
1,000 (150)	13/70	18.6	10/70	14.3
2,500 (375)	17/70[a]	24.3	15/70	21.4

[a] Fisher's exact test $p = 0.145$ (not significant).

two dose changes were made. From weeks 1 to 19, the animals were fed permethrin at 0, 20, 100, and 500 ppm of diet. At week 19, the 500-ppm dose was increased to 5,000 ppm and maintained for 2 weeks before returning to 500 ppm. At week 21, the 100-ppm dose was increased to 4,000 ppm and maintained for the remainder of the dosing period. Table 11-2 shows the doses used in this study. Because of the changes in dosing, 506 animals were not classified correctly. There was a statistically significant increase in mortality in male and female mice at the highest dose (4,000 ppm). In surviving male animals, growth was inhibited at 4,000 ppm.

The liver weight was higher than it was in control animals in both male and female animals at a dose of 500 ppm of diet or more. Although there was no direct effect with respect to hepatic neoplasms, it was noted that hepatocellular hypertrophy, pleomorphism, and degeneration occurred in treated mice with increased frequency and appeared to show a dose-response relationship. No oncogenic effects were observed in the test animals.

EPA (1989a) determined that this study was invalid because of test-diet feeding errors for a significant portion of the study and because of misplaced animals and failure to positively identify misplaced animals.

In the second FMC mouse study, permethrin (purity, 94.5-96.7%; cis/trans ratio, 40:60) was administered to groups of 75 male and 75 female Charles River CD-1 mice for 2 years (Tierney and Rinehart, 1979; Rapp, 1980). Male mice were fed permethrin at 0, 20, 500, or 2,000 ppm in diet (equivalent to 0, 3, 71, or 286 mg/kg per day); female mice were fed permethrin at 0, 20, 2,500, or 5,000 ppm (0, 3, 357, or 714 mg/kg per day).

Survival decreased at high doses in male mice, and liver weight increased at both mid and high doses. The sporadic histopathological changes observed were not deemed to be related to the test substance.

TABLE 11-2 Permethrin Dosage Regimen in FMC Mouse Study 1

	Permethrin Oral Dose, mg/kg of diet			
Week	Control	Group 1	Group 2	Group 3
1	0	20	100	500
19	0	20	100	5,000
21	0	20	4,000	500

The evidence of carcinogenicity was strongest in this study (Table 11-3). The following results were reported:

- Statistically significant increases in liver adenomas in male mice at all doses and a significant dose-related trend; statistically significant increases in combined liver adenomas and carcinomas at mid and high doses in males were also observed.
- Highly statistically significant increases in liver adenomas in female mice at mid and high doses (both were outside historical control range) and a significant dose-related trend; statistically significant increases in combined liver adenomas and carcinomas at mid and high doses and a significant dose-related trend.
- Statistically significant increases in lung adenomas and combined adenomas and carcinomas at all doses in females; carcinomas were significantly increased at the highest dose tested only, but were increased at all doses. Significant dose-related trends for lung adenomas, carcinomas, and combined adenomas and carcinomas in females were observed.
- Incidences of lung tumors in male mice (adenomas, carcinomas, or both) not statistically significant at any dose and no dose-related trend.

Burroughs Wellcome Mouse Study

In the Burroughs Wellcome study, permethrin (cis/trans ratio, 25:75) was administered to groups of 75 male and 75 female (100 mice of each sex for control) CFLP-strain Swiss-derived mice at 0, 10, 50, or 250 mg/kg per day for 92 weeks (James et al., 1980).

There were statistically significant increases in benign lung tumors at the highest dose in females and a significant dose-related trend. Malignant lung tumors were observed in treated animals (one in the mid- and two in the high-dose group), and none were seen in controls. The tumor incidences were, however, within the historical range (Table 11-4).

Non-neoplastic effects noted at the highest dose tested (250 mg/kg per day) were slightly increased liver and kidney weights. However, these mice were not tested at a high enough dose to assess the carcinogenic potential of permethrin. The NOEL for chronic toxicity in this study was 250 mg/kg per day (EPA, 1989a; CEPA, 1992).

TABLE 11-3 Incidence of Lung and Liver Tumors in the FMC Mouse 2 Study After Administering Permethrin in the Diet for 2 Years[a,b]

	Male				Female			
Tumor	0 ppm	20 ppm	500 ppm	2,000 ppm	0 ppm	20 ppm	2,500 ppm	5,000 ppm
Alveolar cell adenoma	16/72 (22%)[c]	15/69 (22%)	15/67 (22%)	17/68 (25%)	9/71[d] (13%)	17/65[e] (26%)	24/68[f] (35%)	29/69[g] (42%)
Alveolar cell carcinoma	7/48 (15%)	5/53 (9%)	13/54 (24%)	4/31 (13%)	6/66[h] (9%)	7/61 (11%)	11/59 (19%)	15/62[e] (24%)
Lung tumors combined	23/72 (32%)	20/69 (29%)	28/67 (42%)	21/68 (31%)	15/71[d] (21%)	24/65[e] (37%)	35/68[g] (51%)	44/69[g] (64%)
Hepatocellular adenoma	6/64[h] (9%)	17/63[f] (27%)	15/63[e] (24%)	17/56[f] (30%)	2/64[d] (3%)	4/60 (7%)	22/61[g] (36%)	28/65[g] (43%)
Hepatocellular carcinoma	16/67 (24%)	12/64 (19%)	19/64 (30%)	8/59 (14%)	4/49 (8%)	3/54 (6%)	3/47 (6%)	2/50 (4%)
Liver tumors combined	22/67 (33%)	29/64 (45%)	34/64[e] (53%)	25/59 (42%)	6/64[d] (9%)	7/60 (12%)	25/61[g] (41%)	30/65[g] (46%)

[a]The incidence was expressed as the number of tumor-bearing animals per animals at risk.
[b]The Army used different denominators for risk assessment.
[c]The number in parentheses is the incidence in percentage.
[d]Significant trend at $p < 0.001$ based on a dose-weighted chi-square trend test.
[e]Significantly different from the control group ($p < 0.05$) based on the Fisher's exact test.
[f]Significantly different from the control group ($p < 0.01$) based on the Fisher's exact test.
[g]Significantly different from the control group ($p < 0.001$) based on the Fisher's exact test.
[h]Significant trend at $p < 0.01$ based on a dose-weighted chi-square trend test.

TABLE 11-4 Mice with One or More Adenomatous Tumors in the Lungs in the Burroughs Wellcome Mouse Study

Dose, mg/kg/day	Males		Females	
	Incidence	Percent	Incidence	Percent
0	26/99	26.3	3/96	3.1
10	14/75	18.7	5/71	7.0
50	17/73	23.3	7/74	9.5
250	16/74	21.6	15/74[a]	20.3
Historical control[b]			20.4 (7.5-30.0%)	

[a]Statistically significantly different from control group, $p < 0.05$.
[b]Historical control data (mean and percentage range) derived from nine studies containing 807 female CFLP control mice and mice affected with lung adenomas and carcinomas.
Source: EPA, 1989a.

CARCINOGENICITY STUDIES IN RATS

Permethrin has also been tested for its carcinogenicity in rats. Two of these studies were considered negative for permethrin's carcinogenicity and the third study was considered equivocal by EPA (EPA, 1989a).

ICI Rat Study

In the ICI rat study, Wistar rats (60 of each sex per group) were fed permethrin (purity 93.1-98.9%; cis/trans ratio, 40:60) at 0, 500, 1,000, or 2,500 ppm (0, 25, 50, or 125 mg/kg per day) for 2 years. No carcinogenic effects were noted at any concentration (Richards et al., 1977; Ishmael and Litchfield, 1988).

Signs of poisoning, such as tremors and hyperexcitability, were noted during the first 2 weeks of dosing in the animals that received the highest dose. There was no mortality attributable to permethrin, and growth and food consumption were unaffected. There were no effects on hematological, ophthalmological, urological, or other clinical chemistry measurements. Liver aminopyrine *N*-demethylase activity was increased in all permethrin-treated animals. Bone-marrow smears of the animals

showed no unusual findings. Gross and microscopic examination of tissues and organs was performed after 1 and 2 years, and all animals that died with neoplastic changes were examined. Kidney weight was also increased, predominantly in males, at all doses. Examination of the sciatic nerve showed no effects attributable to permethrin. Liver weights were higher in male and female rats that received permethrin for 1 year at 2,500 ppm (25 mg/kg) than in the control animals. After 2 years, the liver weight and liver-to-body-weight ratios were higher in all permethrin-treated males than in the corresponding controls. In the females, higher values of absolute and relative liver weights, compared with the controls, were recorded only in the group of animals given 1,000 mg/kg. Hepatocyte vacuolation was seen at 1 year in males fed at only the highest dose and in females at all doses. The smooth endoplasmic reticulum showed significant increases at 52 weeks in males and females at all doses. At the end of the study, notable endoplasmic reticulum increases were detected only at the highest doses, although insignificant increases were noted at all doses in males and females. The NOEL for liver effects was 500 ppm (25 mg/kg per day) and the LOEL was 1,000 ppm (50 mg/kg per day) (EPA, 1989a; CEPA, 1992).

FMC Rat Study

Long-Evans rats (60 males and 60 females per group) were fed permethrin (purity unknown; cis/trans ratio, 40:60) at 0, 20, 100, or 500 ppm (0, 1, 5, 25 mg/kg per day) for 2 years (Braun and Rinehart, 1977). Two independent evaluations of the histopathological data from this study concluded that there was no carcinogenic potential for permethrin. Although there was a dose-dependent increase in gross liver weight in both males and females, those values were small and not statistically significant.

The initial examination of lung tissue from males suggested that there was a dose-related increase in lung tumors (Table 11-5), although the difference was not statistically significant at any dose, nor was there a significant dose-related trend. The lung tissue from all males was reexamined after step-sectioning at 250 μm intervals. The incidence from the second reading (8 of 60, 5 of 55, 9 of 60, and 9 of 59 at 0, 20, 100,

TABLE 11-5 Incidence of Pulmonary Tumors in FMC Rat Study After Administering Permethrin in the Diet for 2 Years[a]

	Dose, ppm			
Sex and Tumor	0	20	100	500
Males				
Adenoma	1/59 (2%)[b]	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.
[b]The number in parentheses represents the incidence in percentage.

and 500 ppm, respectively) was not statistically significant either. In their analysis of the data, EPA adjusted the incidence by the amount of lung tissue examined. The adjusted incidence at mid and high doses was marginally significant ($p = 0.10$) by pair-wise comparison with concurrent controls. EPA (1989a) concluded that the evidence for lung tumors in these male rats was equivocal, and considering a maximum tolerated dose (MTD) was not reached, this finding was significant.

The major deficiency in the study was that there was no clear evidence of toxicity even at the highest dose tested. CEPA (1992) assigned a NOEL of greater than 500 ppm (25 mg/kg per day), whereas EPA assigned a LOEL of 100 ppm (5 mg/kg per day) based on increased liver weights. There was no mortality, and the animals did not reveal adverse effects on growth, food consumption, or behavior attributable to the administration. Hematological, clinical chemistry, and urinalysis measurements were performed at either 6 months or 1 year and at the end of the study. There were no compound-related effects on a wide variety of parameters examined, and ophthalmological examination indicated no abnormalities.

Burroughs Wellcome Rat Study

Seventy-five Wistar rats of each sex per group were given permethrin (purity unknown; cis/trans ratio, 25:75) in the diet at 0, 10, 50, or 250 mg/kg per day for 103 weeks in a Burroughs Wellcome study. No evidence of carcinogenicity of permethrin was reported in the study (McSheehy et al., 1980). Hepatocytic hypertrophy was observed histopathologically in both sexes at mid and high doses. The NOEL and LOEL were 10 and 50 mg/kg per day, respectively, based on liver hypertrophy (CEPA, 1992). The major deficiencies were the lack of information regarding the diet analysis and purity of the test article.

TUMOR PROMOTION STUDIES: SHIMKIN MOUSE LUNG BIOASSAY

Groups of 16 male and 16 female strain A/J mice were given permethrin at 0, 285, 475 (females only), 713.5, or 1,425 mg/kg (cis/trans ratio, 40:60) for 3 days a week for 8 weeks. Animals in the positive control group were given urethane (1,000 mg/kg). Animals were sacrificed after 24 weeks and examined for lung tumors (Cunnick, 1985). The frequency of lung tumors in the permethrin-treated mice was equivalent to the corn oil and untreated control groups. Urethane produced the expected tumor-promoting response. No evidence that permethrin promoted lung tumors was seen in this study.

CONCLUSIONS

Evidence of permethrin's possible carcinogenicity in humans is derived from bioassays in rodents. Permethrin has been tested in seven chronic toxicity studies, three studies in rats and four in mice.

The three rat studies were negative for carcinogenicity; however, the studies were not conducted at doses high enough to adequately assess the oncogenic potential of permethrin. In spite of some deficiencies in some of the mouse studies, two of the four showed evidence of carcinogenicity.

In the second FMC mouse study, the primary findings were as follows: in males, statistically significant ($p < 0.01$) increases in liver adenomas at all doses were observed, along with a statistically significant ($p < 0.01$) dose-related trend. (Tumor frequencies were above the historical control range at all nonzero doses.) In females, statistically significant ($p < 0.01$) increases in lung adenomas and carcinomas combined were observed at the mid and high doses, along with a statistically significant ($p < 0.01$) dose-related trend. In addition, lung adenomas and carcinomas separately showed statistically significant ($p < 0.01$) dose-related trends. In the Burroughs Wellcome mouse study, there was a statistically significant ($p < 0.01$) increase in lung tumors in females at the highest dose as well as a statistically significant ($p < 0.01$) dose-related trend.

Permethrin was also tested in Shimkin mouse lung bioassay to determine if permethrin is a tumor promoter. This assay did not show any evidence that permethrin promoted lung tumors, however the Shimkin assay is not a definitive mouse oncogenicity assay.

Based on the weight of evidence from animal studies, the subcommittee concluded that permethrin is a possible human carcinogen.

CARCINOGENICITY RISK ASSESSMENT

Hazard Identification

The U.S. Army (1989) based its quantitative risk assessment for permethrin on the 24-month chronic feeding study in CD-1 mice that was described above in the second FMC study. This study was selected for carcinogenic risk assessment because it showed the most significant increase in tumors. The oral carcinogenic potency factor (upper 95% confidence limit) was calculated on the basis of the combined adenomas and carcinomas of the lung in females. That is the same set of data that EPA used to calculate its carcinogenic potency factor (unit risk) for permethrin (EPA, 1988), and which it subsequently confirmed as an appropriate basis for quantitative risk assessment (EPA, 1989b). CEPA (1992) likewise identified the combined lung tumors in female mice observed in the second FMC mouse study as the most relevant for assessing carcinogenic risk to humans from exposure to permethrin.

TABLE 11-6 Combined Lung Adenoma and Carcinoma in Female CD-1 Mice

Concentration, ppm (mg/kg/day)	Tumor Incidence
0 (0)	15/74
20 (2.7)	24/74
2,500 (333)	35/75
5,000 (667)	44/75

The tumor incidence data used by the Army for dose-response modeling are shown in Table 11-6.

Dose-Response Assessment

The U.S. Army (1989) calculated a human-equivalent carcinogenic potency factor of 0.016 $(mg/kg/day)^{-1}$ and EPA calculated a value of 0.018, even though both used the linearized multistage model for dose extrapolation (EPA, 1986) on the same data and both extrapolated to humans on the basis of body surface area $(body\ weight)^{2/3}$ (EPA, 1986). That slight difference in estimated potency is the result of modest differences in procedure. Whereas the Army used all the animals that were examined at each dose to fit the dose-response model, EPA included only those animals that were still at risk at the time of observation of the first tumor in any group. Also, the Army used 70 kg and 0.03 kg as representative human and mouse weights, respectively, and EPA used 60 kg and 0.025 kg.

CEPA calculated a human oncogenic potency factor of only 0.011 $(mg/kg/day)^{-1}$. The data modeled by CEPA were the same as those used by EPA, except for the denominator of the lowest-dose group. However, CEPA's dose scaling differed from that of the Army and EPA in several respects, including extrapolation to humans on the basis of $(body\ weight)^{3/4}$. CEPA's report did not appear to give sufficient details to permit reproducing the calculations on dose scaling.

Based on the available information, there is no compelling reason to use a carcinogenic potency factor other than the U.S. Army's (1989) calculated value of 0.016 $(mg/kg/day)^{-1}$.

Risk Characterization

An upper bound on the lifetime carcinogenic risk is estimated by multiplying the carcinogenic potency factor by the estimated average daily lifetime dose. The same carcinogenic potency factor applies for each exposure group; only the lifetime daily exposure value differs from group to group, depending on the particular exposure scenario (see Chapter 2 for details on exposure assessment).

No adjustment has yet been made to account for the fact that the carcinogenic potency factor, 0.016 $(mg/kg/day)^{-1}$, is based on the oral administered dose rather than the internal absorbed dose. To use this potency factor in conjunction with the calculated human internal dose resulting from dermal exposure, it should be adjusted upward by an oral absorption factor for the experimental animals. Following CEPA (1992), a 70% oral absorption rate for the experimental animals is assumed. (The absorption rate of 70% for permethrin was estimated from rat pharmaco-kinetic studies.) Dividing 0.016 $(mg/kg/day)^{-1}$ by 0.7 gives a revised potency factor of 0.023 $(mg/kg/day)^{-1}$.

Military Nonfield Personnel

The upper bound on lifetime carcinogenic risk is estimated to be

$$2.3 \times 10^{-2} (mg/kg/day)^{-1} \times 6.8 \times 10^{-5}\ mg/kg/day = 1.6 \times 10^{-6}\ .$$

The calculated risk is 2.7 times higher than the Army's value of 6×10^{-7} (U.S. Army, 1989) (see Appendix A) because of the upward adjustment in dose that resulted from the Army's revised exposure factors (18 hr/day for 10 years vs. 16 hr/day for 6 years) and the upward adjustment in carcinogenic potency that resulted from the inclusion of an oral absorption factor (70% vs. 100%). That value is somewhat lower than the values calculated by CEPA for both the general public and park and forestry workers. However, CEPA's exposure scenarios were completely different from the Army's—inhalation being the primary route of exposure for CEPA.

Military Field Personnel

Unless topically applied DEET is shown to enhance appreciably the absorption of permethrin from impregnated uniforms, the upper-bound lifetime carcinogenic risk for field personnel will be estimated to be the same as the risk for nonfield personnel, i.e., 1.6×10^{-6}.

Garment Workers

The upper bound on lifetime carcinogenic risk due to dermal exposure associated with handling impregnated fabric is estimated to be

2.3×10^{-2} (mg/kg/day)$^{-1}$ $\times$ 3.0×10^{-5} mg/kg/day = 6.9×10^{-7} .

That calculated upper bound is less than half the value estimated for military personnel. It characterizes the carcinogenic risk to garment workers, provided that dermal contact of hands and forearms with treated fabric is the only relevant source of exposure to permethrin. It does not account for the possibility that workers might be exposed to permethrin via airborne particles of treated fabric.

Conclusions

An upper bound on the lifetime carcinogenic risk to military personnel wearing permethrin-impregnated uniforms is estimated to be 1.6×10^{-6}. That value applies to non-field and field personnel, assuming that topically applied DEET does not enhance dermal absorption of permethrin.

As stated earlier, somewhat less than 5% of the skin would be exposed to have overlapping exposure to DEET and permethrin. If the recommended pharmacokinetics studies are done and the results of those studies indicate an enhanced absorption of permethrin from simultaneous exposure to DEET, that would mean higher exposure of permethrin in soldiers wearing permethrin-impregnated BDUs and applying DEET to skin areas not covered by BDUs. In that case, carcinogenic risk should

be reevaluated to determine if the revised carcinogenic risk is acceptable.

Thus, based on current data, permethrin impregnation of uniforms is not considered to pose a serious carcinogenic hazard to either field or non-field military personnel. However, if it is possible to have two sets of uniforms, treated and untreated, then it is recommended that only uniforms worn by field personnel be made from permethrin-impregnated fabric.

The estimated upper-bound lifetime carcinogenic risk to garment workers, 6.9×10^{-7}, is less than half the calculated upper-bound risk to military personnel. However, that value does not reflect any possibility that workers might be exposed to permethrin via airborne particles of fabric, and, therefore, it might not represent a true upper bound on the overall carcinogenic risk to garment workers.

12

Summary of Recommendations

The Subcommittee to Review Permethrin Toxicity from Military Uniforms conducted a health assessment of wearing BDUs impregnated with permethrin. This assessment was performed by evaluating the toxicity of permethrin in humans and animals and by evaluating the potential exposure of soldiers to permethrin from wearing permethrin-impregnated BDUs. The toxic end points evaluated were acute and subchronic toxicity, dermal and ocular toxicity, neurotoxicity, liver and other organ toxicity, immunotoxicity, reproductive and developmental toxicity, genotoxicity, and carcinogenicity. In addition, the report includes discussion on pharmacokinetics, exposure assessment, and carcinogenic risk assessment of permethrin.

The subcommittee's conclusions and recommendations are listed below. The recommendations are intended to provide additional toxicity data and related data on permethrin that will enable risk assessors to evaluate the risk of wearing permethrin-treated BDUs with more confidence. The subcommittee recommends further research in exposure assessment, pharmacokinetics, dermal toxicity, neurotoxicity, immunotoxicity, and genotoxicity. The subcommittee, however, does not recommend further research for other toxicity end points, because it believes that information available on those end points is adequate to address the question of safety of wearing or sewing permethrin-impregnated BDUs.

EXPOSURE ASSESSMENT

The subcommittee considered the dermal route to be the only relevant route of exposure to permethrin from wearing permethrin-impregnated BDUs. At present, there is no information to indicate that significant exposure will occur by any route other than dermal absorption. The average lifetime dermal dose for military personnel from wearing permethrin-impregnated BDUs (permethrin impregnation at a concentration of 0.125 mg/cm^2) was calculated to be 6.8×10^{-5} mg/kg per day. The average daily lifetime internal dose for garment workers was calculated to be 3.0×10^{-5} mg/kg per day, less than half the daily dose calculated for military personnel. That dose is only for dermal exposure from direct contact with permethrin-treated cloth and does not include possible exposure to permethrin by inhalation or ingestion of permethrin-impregnated airborne particles. Thus, the above estimated internal dose of 3.0×10^{-5} mg/kg per day possibly represents a lower bound on the overall exposure of garment workers to permethrin.

- The subcommittee recommends that studies be conducted to collect data on representative permethrin-exposure factors to produce a more complete and accurate risk characterization for garment workers.

PHARMACOKINETICS

Wearing permethrin-impregnated BDUs and applying DEET to exposed skin provide nearly 100% protection against bites of insects and other arthropods. DEET's enhancement of the dermal penetration of a variety of chemicals suggests that the use of DEET in conjunction with permethrin might facilitate the dermal absorption of permethrin. Research specifically on the interaction of DEET and permethrin has not been conducted and represents an area of uncertainty regarding the dermal absorption of permethrin. Facilitated absorption of permethrin by DEET is a possible concern for military personnel who apply DEET to the exposed skin and wear permethrin-treated BDUs. Although the area of skin with potentially overlapping coverage is small and is assumed to be of minor importance, the magnitude of the effect is not known with certainty.

- The subcommittee recommends that the Army conduct a human pharmacokinetic study with combined exposure to permethrin and DEET. Specifically, this study would involve three groups of volunteers: a group wearing untreated uniforms (control); a group wearing uniforms treated with permethrin; and a group wearing uniforms treated with permethrin and using DEET for skin protection. Urine samples would be collected from these individuals over a specified time, and the appearance of the permethrin metabolite 3-(2,2-dichlorovinyl)-2,-2-dimethylcyclopropane carboxylic acid (CVA), could be quantitated by mass spectrometry. An increase in CVA in the urine of the DEET-permethrin group would suggest a potential interactive effect.
- The subcommittee also recommends that military personnel apply DEET only to areas of the skin not covered by BDUs to reduce potential interactive effects of DEET on permethrin absorption. The interactive effects can probably be minimized if the areas of the body covered by permethrin-impregnated BDUs are not also covered by DEET.

DERMAL TOXICITY

Review of the available information on dermal toxicity of permethrin indicates that permethrin might be a skin sensitizer at high doses in guinea pigs, although the Draize repeat insult patch test in 184 human subjects did not cause any dermal sensitization. However, several subjects described a transient burning, stinging, or itching sensation. The results of the photochemical irritation studies showed that permethrin does not cause phototoxicity (photo irritation). Therefore, the weight of evidence indicates that exposure to permethrin from wearing permethrin-impregnated BDUs at the recommended concentrations (0.125 mg/cm^2 of fabric) is unlikely to cause skin sensitization or other skin effects in humans.

- A few persons might be hypersensitive to permethrin-treated BDUs and thus develop skin sensitization. The subcommittee recommends that the Army monitor soldiers for hypersensitivity when they begin to wear permethrin-treated BDUs on a regular basis.

NEUROTOXICITY

Permethrin is neurotoxic at high doses in animals. It produces a variety of neurotoxic effects, some of which are tremors, salivation, paresthesia, splayed gait, depressed reflexes, and tiptoe gait; reversible axonal injury occurs at very high doses. Although animal data clearly demonstrate the neurotoxic properties of high doses of permethrin, human data are needed to substantiate that finding.

- The subcommittee recommends that data be collected on neurotoxicity of permethrin in humans from epidemiological studies of workers or from accidental human exposures.

IMMUNOTOXICITY

No human data or in vivo animal data are available to evaluate the immunotoxic potential of permethrin in humans. The only two laboratory studies reported in the literature that were conducted in in vitro systems are inconclusive about the immunotoxological effects of permethrin.

- The subcommittee recommends that immunotoxicological studies be performed in laboratory animals to ascertain the immunotoxic properties, if any, of permethrin in the mammalian species. These studies should follow the recommendations for conducting additional research as presented in the 1992 National Research Council report entitled *Biologic Markers in Immunotoxicology*.

GENOTOXICITY

Studies conducted to determine the potential of permethrin to produce gene mutations in microbial and mammalian systems were all negative.

Studies conducted to determine the potential of permethrin to produce chromosomal damage provided an array of results. Of the two in vivo studies conducted in the micronucleus assay, one was negative and the other was inadequate. Three in vitro studies in which clastogenicity of

permethrin was investigated provided evidence of potential clastogenicity of permethrin. Small statistically significant elevations in sister chomatid exchanges, micronuclei, and chromosomal aberrations in human lymphocyte cultures were reported. Chromosomal aberrations were also reported in Chinese hamster ovary cells. All three in vitro studies were performed in one laboratory by the same investigators.

Other genotoxicity tests of permethrin (dominant lethal test and tests for DNA damage in microbial and mammalian cells) were negative.

The subcommittee believes that the weight of evidence suggests that permethrin does not produce gene mutations but is a potential clastogen in certain in vitro systems.

- Three in vitro studies from one laboratory showed small statistically significant increases in the clastogenic effects of permethrin. These results have not been independently confirmed by other investigators. The subcommittee recommends that these studies be repeated by other investigators to determine if the positive findings of permethrin's clastogenicity can be confirmed. If these findings are confirmed, the clastogenicity of permethrin should also be studied in vivo with an adequate number of animals and dosages of permethrin.

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Appendix A

QUANTITATIVE RISK ASSESSMENT PERMETHRIN-IMPREGNATED BATTLE DRESS UNIFORM OCTOBER 1989

1. REFERENCES. See . . . list of references cited in this assessment.
2. BACKGROUND AND INTRODUCTION. The following describes the procedures used to quantify the potential carcinogenic risks from wearing the permethrin-impregnated Battle Dress Uniform (BDU). A risk assessment is an attempt to describe potential health risks resulting from specific exposure scenario to a given contaminant. For the present assessment, we proceeded in stages as recommended in reference 1.

a. Hazard Evaluation. This is the process of gathering and evaluating all data that may reveal the type of adverse effects produced by a substance. This can include animal as well as human toxicity data.
b. Dose Response Evaluation. In this step, the dose response relationships are described for each biological response. This step also includes extrapolation of animal data to humans, if required.
c. Human Exposure Evaluation. Qualitative and quantitative descriptions of each potential exposure route are detailed. Populations at risk and sensitive subgroups should also be identified.
d. Risk Characterization. This involves combining the analyses in the above steps to provide a measure of the potential risks.

3. PERMETHRIN RISK ASSESSMENT.

a. Hazard Evaluation. Several recent reviews have summarized the toxicity of permethrin (references 2 and 3) and these should be consulted

for more complete information. In this assessment, we will focus on potential carcinogenic risks. Seven long term carcinogen bioassays have been performed with permethrin. Of these, only one (FMC Mouse II) showed a statistically significant dose-related increase in cancer. In this study, female mice exhibited an increased incidence of alveolar cell adenomas and carcinomas. These animals also tended to have a dose-related increase in liver adenomas and carcinomas. This study was used by the Environmental Protection Agency (EPA) as the basis for classifying permethrin as a Category C compound (possible human carcinogen).

b. Dose Response Extrapolation. A key toxicity value in quantifying potential carcinogenic risk is the carcinogen potency factor. This value represents the slope of the upper 95% confidence interval of the extrapolated dose response curve. A published potency factor was not available for permethrin, so we derived a value based on the positive female mouse data. This process involved extrapolation of the bioassay data from high doses to low doses and then to humans. We used the Linearized Multistage Model for dose extrapolation. This model is relatively conservative and results in a plausible upper bound estimate of risk (reference 4). This is also the model used by the EPA for most of their published potency factors. As recommended in reference 5, alveolar cell adenomas were combined with carcinomas for use in the dose response extrapolation. Animal doses were converted to human dose levels using a surface area correction as described in reference 4. Table 1 summarizes the data and results of the dose response extrapolation.

c. Exposure Assessment. The current exposure assessment addresses potential human exposures resulting from wearing a permethrin-impregnated BDU. It is anticipated that this treatment process will be utilized by military personnel, deployed to areas posing a recognized threat from insect-borne diseases. Two potential exposure routes should be addressed: inhalation of vapor volatilizing from the fabric and dermal exposures.

(1) Inhalation. Since permethrin is a solid at room temperature and has a relatively low vapor pressure (10 torr at 50° C), the inhalation route is probably insignificant and will not be considered further.

TABLE 1. Data Summary and Dose Response Extrapolation

Concentration in Food (ppm)	Daily Dose* (mg/kg/day)	Human Equivalent** Dose (mg/kg/day)	Tumor Incidence
0	0	0	15/74
20	2.7	0.2	24/74
2500	333	25	35/75
5000	667	50	44/65
Oral Potency Factor: 0.016 $(mg/kg/day)^{-1}$			

* Based on animal weight of 30 grams and 4 grams food per day.
** Human equivalent Dose = Animal Dose / $(70\ kg / 0/03\ kg)^{1/3}$

(2) Dermal. A preliminary exposure assessment was previously published (reference 6). The predicted exposure of approximately 0.005 mg/kg/day was based on continuous wear of a uniform impregnated with permethrin at a target concentration of 0.125 mg/cm^2. Skin area exposed to contaminant was assumed to be 2.2 m^2 with a dermal penetration of 2%. Although field operations may require soldiers to wear the BDU on a continual basis, this seems an unlikely scenario for more than a few days. Similarly, estimates of carcinogenic risk are typically based on a lifetime exposure; however, no one will spend an entire lifetime in the military. Finally, laundering of the BDUs removes a portion of the impregnant with each wash as does migration of the compound out of the fabric during wear. We therefore have adjusted the predicted exposure factors to account for these differences:

(a) Initial Treatment Level - 0.125 mg/cm^2
(b) Adjustment Factor - 26 %

Time-weighted average of permethrin remaining in impregnated 100% cotton and NYCO BDU fabrics through 50 washings

(reference 7).

(c) Body Contact area - 1.5 m^2

EPA has established that the average body surface area for a 70 kg man is 1.9 m^2. This value is adjusted to 1.5 m^2 when the area for hands, feet, head and neck (not contacted by the impregnated cloth) is subtracted (reference 8).

(d) Dermal Absorption - 2 % / day

Value is reported for man (reference 9).

(e) Migration - 0.49 % / day

Permethrin migrating from treated fabrics to the skin surface. Collective experimental data for 7-day exposures in animals (references 6 and 10).

(f) Body Weight - 70 kg.

The EPA uses 60 kg (132 lbs.) as the average body weight. Seventy kg (154 lbs.) is more realistic for military combat personnel.

(g) Daily Wear - 16 hrs / day

While soldiers may sleep in clothing, 16 hours per day is the maximum predicted contact time when averaged over a 6-year exposure period.

(h) Time Worn (Exposed) - 6 years

Initial assignment of 3 years is typically followed by a 3-year reenlistment.

(i) Lifetime - 75 years

From EPA guidelines (reference 8).

The Exposure Dose (ED) is derived by multiplying the values (a) through (f); the value for (f) being 1/70.

Exposure Dose = 6.8×10^{-4} mg/kg/day.

The Chronic Daily Intake (CDI) is derived by modifying the ED by the predicted exposure period:

Chronic Daily Intake = 6.8×10^{-4} mg/kg/day × (16/24) × (6/75)
= 3.6×10^{-5} mg/kg/day

d. Risk Characterization. An estimate of carcinogenic risk can be calculated using the potency factor and CDI values derived above. This calculation is shown in the following expression:

RISK = (CDI) × (Potency Factor)
= (3.6×10^{-5} mg/kg/day) × (1.6×10^{-2} mg/kg/day)
=6×10^{-7}

This value represents an upper bound estimate of carcinogenic risk under the exposure conditions outlined above. Under the assumed conditions, an individual faces a probability of *less than* 1 chance in 1,000,000 of developing cancer as a result of permethrin exposure. In terms of populations, we would expect 1 excess cancer to develop in 2,000,000 exposed individuals as a result of permethrin. These calculations are based upon very conservative assumptions, and in all likelihood, actual risks will be less than this value.

e. Uncertainties.

(1) Toxicological Assessment/Dose Extrapolation. As discussed in

reference 4, there are many uncertainties in the low dose extrapolation and animal to human extrapolation which could affect the actual risk to exposed humans. There are important species differences in contaminant uptake, distribution and metabolism as well as target organ susceptibility for which we have no information. Our potency factor derivation is also based on summaries of animal data and not the original literature. We were forced to estimate animal dose levels based on estimated body weights and food consumption rates.

(2) Human Exposure. In the exposure dose assessment, the 6.8×10^{-4} mg/kg/day estimated dose was based in part on a daily migration rate from fabric to skin of 0.49%. This value was determined experimentally in animal studies and represents the maximum rate measured over the first seven days of continuous wear. Subsequent weeks showed a much smaller transfer of contaminant (reference 11). Laundering of these garments would be expected to reduce the migration rate even further. The dermal penetration rate is a second critical value which could dramatically affect estimated risks. The 2% penetration value was taken from a literature summary (reference 9) and represents the maximum absorption seen in human volunteers. Average values were approximately half this value. Finally, the effects of weathering on the permethrin content of treated BDUs were not considered. It is likely that these factors, particularly photodynamic, may significantly accelerate degradation of the substance.

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