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LITERATURE REVIEW

Permethrine

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Background

Pyrethroids, a group of synthetic insecticides, started to be manufactured in the 1970s at the same time as the removal of organochlorine insecticides, such as DDT, from the consumer market. The synthetic pyrethroids not only inherit biologic activity (ability to kill insects) from their natural counterpart, pyrethrin, which is found in Chrysanthemums, but also show improvements in their environmental stability. Pyrethroids are widely used in agriculture, forestry, the textile industry, and public health programs worldwide. With the phaseout of organophosphorus pesticide (OP) use in residential environments in the United States, the consumer uses of pyrethroids have increased since the late 1990s[1]. In Indonesia, permethrin have been used widely as insectiside to fight agains *aedes aegepty* since 1980s. Almost 80% of insectiside use permethrin based on Indonesia Ministry of Agricultural data in 2008. a. To complicate the matter, data released by the Ministry of Agriculture of Indonesia in 2022 showed that approximately 82% of insecticides registered to control Ae. aegypti in Indonesia are pyrethroid-based products including permethrin[2].

In recent studies, pyrethoids including permethrin have been identified inducing neurotoxicity in human. In addition, permethrin, the most widely used pyrethroid insecticide, is suspected of being an endocrine-disrupting. chemical, and has been classified as a potential carcinogen at high exposure level. Although existing research is still limited to animal experiments and only case reports of human intoxication, existing research shows consistent results. Based on this

result, routine biomonitoring of permethrin exposure in workers become essential for monitoring further health adverse effects in workers[3].

General Characteristic of Permethrin

Physical and Chemical Properties of Permethrin

Pyrethrum is a naturally occurring mixture of chemicals found in certain chrysanthemum flowers. Pyrethrum was first recognized as having insecticidal properties around 1800 in Asia and was used to kill ticks and various insects such as fleas and mosquitos. Six individual chemicals have active insecticidal properties in the pyrethrum extract, and these compounds are called pyrethrins. The six individual pyrethrins are pyrethrin I, pyrethrin II, cinerin I, cinerin II, jasmolin I, and jasmolin II. Pyrethrum looks like a tan-colored dust as ground flowers or a syrupy liquid as the crude extract. Pyrethrins are only slightly soluble in water, but they dissolve in organic solvents like alcohol, chlorinated hydrocarbons, and kerosene. Pyrethrins are often used in household insecticides and products to control insects on pets or livestock. Pyrethrins break down quickly in the environment, especially when exposed to natural sunlight. Pyrethroids are manufactured chemicals that are very similar in structure to the pyrethrins[3]. 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[4].

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. Permethrin is used extensively by agriculture for control of foodcrop pests. Permethrin is 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). 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. All of U.S Army clothes has the treatment with permethrin especially in their combat practice to reduce tick-borne diseases[4].

The physical and chemical properties of permethrin are shown in **Figure 2.1** the following listbelow :

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)

Figure 2.1. The physical and chemical properties of Permethrin

Toxicokinetics of Permethrin

Workers may be exposed to permethrin by different routes during spraying or work in treated fields. Direct exposure may occur through the respiratory tract and the skin, and inadvertent ingestion is possible. In the general population, the main route of exposure is the diet.

Absorption

Numerous studies have illustrated the absorption of Type I and Type II pyrethroids through occupational exposure by detecting pyrethroid metabolites in urine. In certain instances, plasma levels of pyrethroids were undetectable (below 5 µg/L). The rapid absorption of pyrethroids following inhalation is evident from the presence of urinary metabolites within 30 minutes of exposure. Leng et al.'s 1997 study revealed an increase in urinary metabolites correlating with higher exposure levels, suggesting that absorption via inhalation is not capacity-limited within the studied exposure range (10–160 mg/m3). However, occupational exposure to pyrethroids in humans may involve inhalation, oral, and/or dermal routes. Studies providing comprehensive estimates of total pyrethroid absorption following inhalation or occupational exposure were not identified[4].

Rats administered permethrin in dimethyl sulfoxide at 1.6-4.8 mg/kg of

body weight showed oral absorption estimates of approximately 70% for the cis/trans (35:65) isomer mix . Only 3-6% of the dose appeared in feces as unmetabolized and presumably unabsorbed permethrin, suggesting that actual absorption might exceed 70%. Anadon et al. (1991) estimated a 60% bioavailability of permethrin by comparing the "area under the curve" (AUC) for permethrin in blood after gavage with the AUC after intravenous injection. This low estimate may be attributed to first-pass biotransformation of permethrin by the liver following absorption. Thus, while the exact gastrointestinal absorption of permethrin remains unknown, these studies propose 70% as a conservative estimate for rat absorption[4].

Dermal absorption of permethrin, more pertinent to human exposure, has been explored in various laboratory animals, including rats[8] and mice[9]. Limited studies on dermal absorption of permethrin in humans have also been conducted. The percutaneous absorption of permethrintends to be lower in humans compared to other mammalian species. Human absorption rates were determined when permethrin was applied to the scalp in a cream-rinse shampoo or to theentire body in a dermal cream. Reported absorption rates in three studies ranged from 0.3% to 2%. Although not a precise estimate due to potential binding to macromolecules or storage in body tissues, a dermal absorption rate of 2% was assumed for humans[4,5].

Distribution

Pyrethroids are lipophilic molecules that generally undergo rapid absorption and distribution following ingestion by mammals. Unless isolated in lipid depots, they

are quickly metabolized and eliminated from the body. Permethrin persists longer in fat than in other tissues. Cis permethrin is retained longer trans isomer. 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, 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[6]. 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[6]. There have been no studies conducted on the distribution of permethrin in the tissues of primates, including humans. From the results of studies in laboratory animals, it is concluded that permethrin is rapidly and widely distributed and concentrated in central and peripheral nerve tissues [4].

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. 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 mechanism.[4].

Additional investigations on distribution would provide a further understanding of the extent of distribution of pyrethroids to nervous system tissues (a principal target of pyrethroid toxicity) and to define the time-course for distribution and tissue retention, particularly in tissues that are targets for toxicity. Extremely limited information is available regarding distribution of pyrethroids to the fetus and into breast milk. Additional studies are needed to assess the potential risks of exposure in utero and via breast milk. Additional studies also may be warranted to identify factors that may alter distribution of pyrethroids and to define potential differences in distribution with respect to age and sex[3,4].

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[4].

The two major pathways for metabolism of permethrin are oxidation and hydrolysis. Figure 2-2 and Figure 2-3 show the metabolic pathways and sites of metabolic attack. The relative contributions of the esterase and oxidase in the in vitro hepatic metabolism ofpermethrin 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[4].

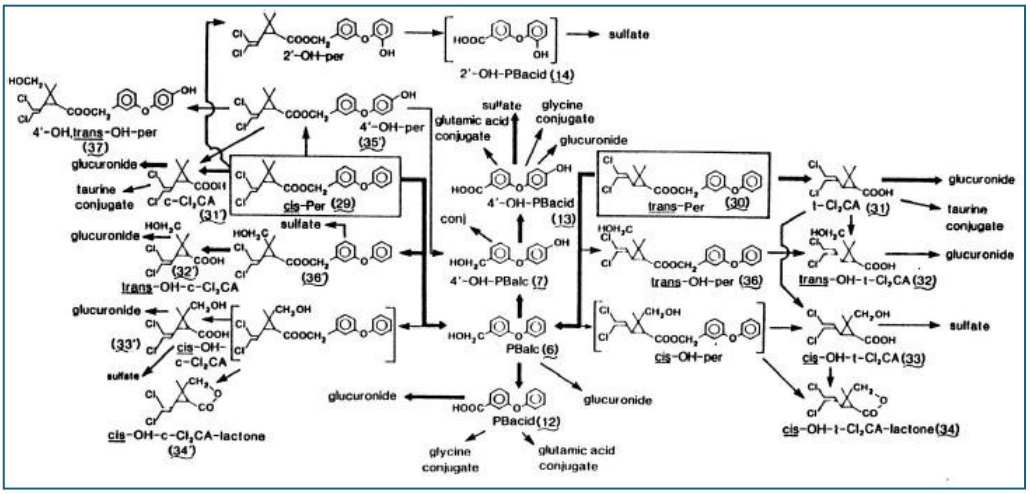

Figure 2.2. Metabolic pathway of permethrin[7]

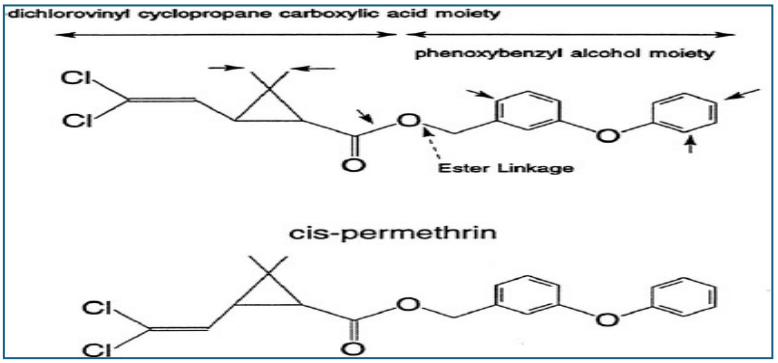

Figure 2.3. Chemical structure of permethrin[7]

The major pyrethroid hydrolyzing esterase is located in mammalian liver microsomes and is probably a carboxyl esterase. The cis and trans pyrethroid isomers show dramatic substrate specificity—the trans form being hydrolyzed up to 50 times faster than the cis form. Pyrethroid hydrolysis is inhibited by dialkylphosphorylating agents, such as organophosphoruspesticides, in vitro and in vivo. 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[4].

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. Oxidative reactions occur at the cyclopropane carboxylic acid moiety, at the alcoholmoiety, 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 ofthe esters. The various c-hydroxylations are probably catalyzed by cytochrome P-450[4].

Although the metabolism of pyrethroids has been extensively studied in laboratory animals, the specific enzymes responsible for the biotransformation of pyrethroids have not been identified. Further research identifying these enzymes would allow the evaluation of many potential factors, such as age, sex, and other chemicals and drugs, that could alter the metabolism of pyrethroids. This is of particular importance since metabolism of pyrethroids is generally accepted as the primary detoxifying mechanism in mammals[4].

Elimination

The metabolites of pyrethrin are commonly eliminated in forms such as alcohols, phenols, or carboxylic acids and their glycine, sulfate, or glucuronide conjugates. Various species and systems have identified at least 80 metabolites from both cis and trans permethrin (IUPAC, 1981). Gaughan et al. (1977) conducted a study in which the 1R trans, 1RS trans, 1R cis, and 1RS cis isomers, individually labeled in the acid and alcohol moieties, were orally administered to rats, and the metabolites in urine and feces were determined. The findings indicated no significant metabolic difference between 1R and 1RS isomers, although, as mentioned earlier, cis permethrin isomers were more prone to oxidative metabolism than the trans counterparts. After 12 days, 97-100% of the radioactivity was found in urine and feces, with unchanged permethrin detected solely in the feces. The cis isomers retained radioactivity longer than the trans isomers, and the alcohol label retained it longer than the acid label. Notably, only 45-54% of the radiocarbon from the cis isomer appeared in the urine, while 81-90% from the trans isomer did. The more hydrolytically stable cis isomer resulted

in metabolites with the ester bond intact, excreted in the feces, likely via bile. Permethrin's large molecular weight suggests its potential for biliary excretion. Major metabolites from both isomers included sulfate and glucuronide conjugates of the phenoxybenzoic acid portion and the glucuronide conjugate of the cyclopropane carboxylic acid portion. Similar results were observed in studies with rhesusmonkeys (Sidon et al., 1988), where the position of the 14C radiolabel influenced urine radioactivity recovery. The specific excretion mechanisms of permethrin compounds remain unknown. However, the water solubility of pyrethroid metabolites, resulting from metabolism, suggests renal and biliary excretion pathways. Although pyrethroids and their metabolites may be eliminated, at least in part, through glomerular filtration due to their molecular size, information on their binding to plasma proteins and potential restriction of glomerular filtration is lacking. No details were found on excretion mechanisms for biliary or salivary routes. Additionally, the passage of pyrethroids into milk lacks information, but it is likely to occur through lipid diffusion across membranes, with retention in milk fat.

Health Effect of Permethrin Exposure to Human

Permethrin exhibits acute toxicity at high doses in both animals and humans, with the LD50 for animals exceeding 1g/kg. The toxicity varies based on the cis/trans ratio, with 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, ultimately, prostration, paralysis, and death. Permethrin can cause ocular irritation when directly applied to the eye, but

this is not expected from its intended use in BDUs. It can also act as a skin irritant and sensitizer after dermal exposure at high concentrations. However, at the intended concentrations in BDUs, skin irritation or sensitization is unlikely to occur. Short-term,repeated exposures up to 13 weeks do not appear highly toxic to mammals. Hematological or serum chemistry values show no effects in most studies, even at exposures with clinical signs of toxicity. Near lethal doses in rats resulted in increased liver enzymes, indicating some liver toxicity. The liver showed morphological changes, including enlargement, but these changes occurred only at clearly toxic doses and returned close to normal after exposure ceased. Dogs showed no morphological changes in the liver at doses up to 2,000 mg/kg per day for three months. Rabbits and cows exposed to permethrin for 10 or 28 days, respectively, showed no significant toxic effects.[4]

In a study involving Swedish forestry workers, exposure to airborne permethrin concentrations did not produce adverse effects. However, in another study of Swedish nursery workers, symptoms of skin and respiratory irritation were reported, with higher prevalence in those exposed to a permethrin mixture with a higher cis/trans ratio. Nigerian workers exposed to permethrin showed no adverse health effects based on a questionnaire and urinalysis. Human volunteers exposed to permethrin in an ear lobe study experienced altered skin sensation, withparesthesia developing within 30-60 minutes of application. Permetherin was found to be less irritating than pyrethroids containing an α-cyano group. Dermal toxicity studies suggest that permethrin might act as a skin sensitizer at high doses in guinea pigs, but evidence in human subjects is inconclusive. Photochemical

irritation studies showed no phototoxicity. Overall, exposure to permethrin from wearing permethrin-impregnated BDUs at recommended concentrations is unlikely to cause skin sensitization or other skin effects in humans[3,4].

The neurotoxic properties of permethrin are evident in animal data, but human data are lacking and need confirmation through epidemiological or case studies. No human or in vivo animal data are available to assess the immunotoxic potential of permethrin. In vitro studies on immunotoxic effects are inconclusive. Studies on gene mutations in microbial and mammalian systems were negative, while studies on chromosomal damage provided mixed results. Some in vitro studies indicated potential clastogenicity, but these were performed by the same investigators. Other genotoxicity tests, such as the dominant lethal test and tests for DNA damage, were negative[3].

Urine Biomonitoring

Measurement of metabolites in urine is used to assess actual exposure of workers and to provide an integrated assessment of exposure through all routes of entry. Urine sampling is more easily accessible than blood sampling and is more easily amenable to routine biomonitoring. Furthermore, given the rapid metabolism of permethrin,concentrations of permethrin in blood are more difficult to quantify than those of metabolites in urine. Three major metabolites of permethrin usually used for the biomonitoring of exposure to this pyrethroid are 3-PBA, *trans*-DCCA, and *cis*-DCCA. Their use is however limited by the fact that they are not specific to permethrin. For urine sampling, most of studies used spot urine samples or cumulative excretions over a period of either 12 or 24 hours.

However, many researchers have questioned this collection method for non-persistent exposure. Collecting urine samples is also difficult for workers if they need to collect cumulative urine for 12 or 24 hours[7].

Blood Biomonitoring

Measurement of blood for biomonitoring of permethrin exposure is using sample from venous blood. Based on research from Gabriel et.al 1997[8], 20 ml venous blood was drawn from each subject (4-12 h after exposure) for the determination of cytluthrin, cypermethrin and permethrin. Plasma was obtained by centrifugation (3 g, 25°C). The samples were analysed immediately. Plasma samples (1 ml) were subjected to precipitationof proteins, followed by liquid-liquid extraction. Detection was performed by GC-ECD (Perkin Elmer Autosystem). The pyrethroid bifenthrin served as the internal standard for quantification. The limit of detection was 5 pg/l. However there are limitation for blood biomonitoring for permethrin exposure. Permethrin especially from non persistent exposure usually have very short half-lives in blood, and the concentrations are usually lower than urinary metabolite levels. Thus, if blood is used as a matrix, the sensitivity of the analytical method and the matrix volume available for analysis may become important.Blood can also be a valuable matrix for measuring biomolecular adducts such as DNA, hemoglobin, or albumin adducts. Typically when blood is used for this type of measurement, special sample collection and/or preparation procedures, such as washing red blood cells (hemoglobin adducts) or isolation of white cells (DNA adducts), may be required. It requires high cost. If blood testing is used, the stability of both the matrix andthe target pesticide in the

blood should be considered. If testing is not performed soon aftersample collection, which is often the case, long-term storage of blood may be problematic,depending upon what form of blood is stored. Serum stores well at –70°C because it is lowin protein and stays homogeneous[8].

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