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4

The Toxicity of Fenitrothion and Permethrin

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1. Introduction

Fenitrothion: An organophosphorus insecticide, fenitrothion (*O*,*O*-dimethyl *O*-4-nitro-*m*-tolyl phosphorothioate; CAS No. 122-14-5), which is a yellow-brown liquid with an unpleasant odor at room temperature, was introduced in 1959 by both Sumitomo Chemical Company and Bayer Leverkusen, and later by American Cyanamid Company (Hayes, 1982; Hayes and Laws, 1990; Worthing and Walker, 1987).

Organophosphorus insecticides began with the massive development of agriculture and agribusiness after World War II. At that time, parathion, one of the famous organophosphorus insecticides, was used in large quantities for preventing rice-stem borer worldwide. However, because of the high acute toxicity, parathion was thought to be an extremely hazardous substance. In man, an oral dose of 3-5 mg/kg is usually fatal. The following case report additionally came across the high toxicity and persistence in humans (Clifford and Nies, 1989). A 25-year-old worker in a pesticide-formulating plant was contaminated after accidentally spilling a 76% parathion solution on his groin and scrotal areas. Although he showered and changed clothes immediately, the resulting nausea and diarrhea made him consult a doctor two days later. The worker placed the parathion-saturated uniform in a plastic bag to be burned. But the contaminated clothing was laundered, and then was used in succession by a second worker, who wore it until he had complaints similar to the first worker. The coveralls were again laundered and used by still a third intoxicated worker. Totally, three workers suffered from toxic reaction to parathion. This case shows the toxic nature of parathion and its persistence on clothing even after successive laundering. Moreover, Etzel et al. (1987) reported that 49 persons in Sierra Leone were acutely poisoned by parathion in May and June 1986, 14 of whom later died. The case-control study of the employed 21 cases and 22 household controls was undertaken to explore which factors were associated with the development of the symptoms such as excess salivation, excess tearing, increased urination, diarrhea, convulsions, and loss of consciousness. Each case and control were questioned about foods and beverages that had been consumed during the 4 hours before becoming ill (for cases) or on the day of a case's illness (for controls). The odds ratio of cases (12.7; 95% confidence interval (CI), 2.4-83.8) for taking bread was significantly increased, suggesting that cases were more likely than controls to have eaten bread within the 4 hours before becoming ill. In addition, when stratified by age, the odds ratio was far higher in children under 18 years (odds ratio, 21.7; 95% CI, 2.4-264.6) than adults (odds ratio, 2.3; 95% CI, 0.02-195.9). This may be due to the higher consumption of parathion based on body weight or higher susceptibility to the

insecticide in the former than the latter. Parathion was detected from residue floor on the truck that had brought the wheat flour from the milling factory to the general store where the baker purchased it, suggesting that the flour had been contaminated during transport. The authors estimated that 10-15 ml of parathion may have spilled onto a 22.5 kg bag of flour in the truck. Besides these, many cases of parathion intoxication have been reported to date (Aardema et al., 2008; Eyer et al., 2003; Hoffmann and Papendorf, 2006; Laynez et al., 1997).

In light of this background, fenitrothion was developed in place of parathion for its highly selective toxicity to insects over humans and animals. While the structure of fenitrothion is similar to that of parathion, its residual effects and acute toxicity are lower than parathion (Miyamoto, 1969). An oral LD50 of parathion is approximately 6 mg/kg for rats, against 330 mg/kg for fenitrothion, which is more rapidly broken down and does not persist in areas where they are used. Fenitrothion is effective against a wide range of pests on rice, cereals, fruits, vegetables, stored grains, cotton and forests, and also in public health programs for control of flies, mosquitoes and cockroaches. Fenitrothion is produced at the rate of 15,000 to 20,000 tons per year worldwide, and is available in emulsifiable concentrates, ultra-low-volume concentrates, powders, granules, dustable powders, oil-based sprays and in combination with other pesticides.

Permethrin: Permethrin (3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; CAS No. 52645-53-1) was first synthesized in 1973 and marketed in 1977 as a photostable pyrethroid (Elliott et al., 1973). Approximately 600 tons per year is at present used worldwide not only in agriculture but also in forestry, household settings, and public health programs.

Pyrethroids represented a major advancement as a high insecticide potential, but showed relatively low potential for mammals. Their development was especially timely with the identification of problems with DDT use. Pyrethroids consist first of identifying components of pyrethrum, which were extracted from East African chrysanthemum flowers, long known to have insecticidal properties. Pyrethrum rapidly knocks down flying insects, but has low mammalian toxicity and negligible persistence, which are good for the environment but yield poor efficacy when applied in the field. In the 1960s, 1st-generation pyrethroids, including bioallethrin, tetramethrin, resmethrin and bioresmethrin, were developed. They are more active than natural pyrethrum, but are unstable in sunlight. Then, permethrin, cypermethrin and deltamethrin were discovered as a 2nd generation of more persistent compounds. They are substantially more resistant to degradation by light and air, thus making them suitable for use in agriculture.

Permethrin is highly effective for protection of stored grains, cotton and other crops, and the control of body lice and household noxious insects. Technical products, which are a brown or yellowish-brown liquid, are a mixture of *cis* and *trans* isomers in the ratio of 40:60 or 25:75, and are available in emulsifiable concentrates, ultra-low-volume concentrates, wettable powders, and dustable powders.

2. Absorption, metabolism and excretion in laboratory animals and humans

In mammals, fenitrothion and permethrin are absorbed via gastrointestinal or respiratory tract and skin, and are rapidly metabolized and excreted.

Fenitrothion: After uptake into the body, fenitrothion is metabolized by hepatic cytochrome P450 (CYP) to form fenitrooxon, which is thought to have a higher potential acute neurotoxicity than the parent compound. Fenitrooxon is further metabolized to

dimethylphosphate and 3-methyl-4-nitrophenol (MNP) by paraoxonase 1 (PON1). MNP and methylphosphate are also produced by glutathione-S-aryltransferase (GST) and PON1. In another pathway, fenitrothion is directly metabolized to MNP and dimethylthiophosphate by PON1 or MNP and methylthiophosphate by GST and PON1 (Figure 1). Interestingly, its major metabolic route differs between mammals and birds as mentioned later. Most of the metabolites are excreted in urine within 24 hours in humans (Nosal and Hladka, 1968), and within 2-4 days in the rat, guinea-pig, mouse, and dog (Miyamoto et al., 1963; Miyamoto, 1964). Species and sexes differences are observed in the composition of the metabolites. MNP, which is also contained in diesel exhaust emissions, has potential adverse effects on the reproductive systems in mammals and birds. Fenitrothion at doses of 0.18 and 0.36 mg/kg per day was administered to 12 human volunteers for 4 days (Meaklim et al., 2003). Pharmacokinetic parameters could only be determined at the high dosage, because the blood levels of fenitrothion at the low dosage were below the detectable level. Fenitrothion concentrations showed a wide range of interindividual variability, with peak blood levels achieved 1-4 hours after dosing, and the half-life ranged from 0.8 to 4.5 hours. Serum concentrations of fenitrothion were measured in 15 patients after acute fenitrothion intoxication, who admitted to the hospital 0.5-12 hours after the ingestion of 5-50 g fenitrothion (Koyama et al., 2006). The serum fenitrothion concentrations ranged from undetectable (< 0.01 μg/ml) to 9.73 μg/ml. Serum fenitrothion concentrations were less than 7 μg/ml in the patients with mild intoxication, while in the severe cases, the levels were more than 7 μg/ml. The elimination half-lives in the mild cases were 9.9 ± 7.7 hours (mean ± SD), and the serum fenitrothion concentrations declined below the detectable level in 48 hours. The elimination half-lives relating to two severe cases were 5.3 and 6.7 hours in the alpha phase (under direct hemoperfusion), and 35 and 52 hours in the beta phase, respectively. The serum fenitrothion concentrations fell below the detectable level in 300 hours.

Permethrin: Regarding its metabolism, permethrin is converted to 2,2-dichlorovinyl-2,2-dimethylcyclopropane-1-carboxylic acid and 3-phenoxybenzyl alcohol (3PBAlc) by carboxyl-esterase. The latter metabolite is followed by oxidation to form 3-phenoxybenzaldehyde, and finally 3-phenoxybenzoic acid (3PBA) (Figure 2). The metabolites are reported to be endocrine-disrupting agents, but most studies mention permethrin toxicity is derived from itself (Yuan et al., 2010). In general, *trans* isomer is more rapidly metabolized than *cis* isomer, which is related to the lower susceptibility of *cis* isomer to enzymatic hydrolysis of the ester linkage (Soderlund and Casida, 1977; Zhang et al., 2008). Besides hydrolytic pathway by carboxylesterase, oxidative metabolic pathway of both *cis*-and *trans*-permethrin in rat and human hepatic microsomes was recently reported (Scollon et al., 2009). The toxicokinetics of permethrin (with a *cis*:*trans* ratio of 25:75) was investigated after single oral doses to rats (Anadon et al., 1991). The plasma level of permethrin was maximal within 4 hours after dosing, and then was slowly eliminated from plasma with a half-life of 12.4 hours. The bioavailability of permethrin was found to be 60.7%. The maximum permethrin concentrations in the central and peripheral nervous system were higher than plasma concentrations, and declined with half-life similar to those of plasma. Clearance of *trans*- and *cis*-permethrin from the blood was also investigated in a man who drank an emulsifiable concentrate formulation of permethrin (consisting of 43.5% *cis* and 56.5% *trans*) (Gotoh et al., 1998). The serum concentrations of *cis*- and *trans*-permethrin peaked 3-4 hours after ingestion and then declined, with *trans*-permethrin cleared from the blood more quickly than *cis*-permethrin. Levels of the *trans* isomer were below the detectability threshold within 25 hours after exposure, whereas *cis* isomer was still detectable 10 days after exposure. The present study indicated that the differential persistence of *cis* and

trans isomers in human is consistent with a difference in the metabolic rate of *cis*- and *trans*-permethrin in animal studies (Anadon et al., 1991).

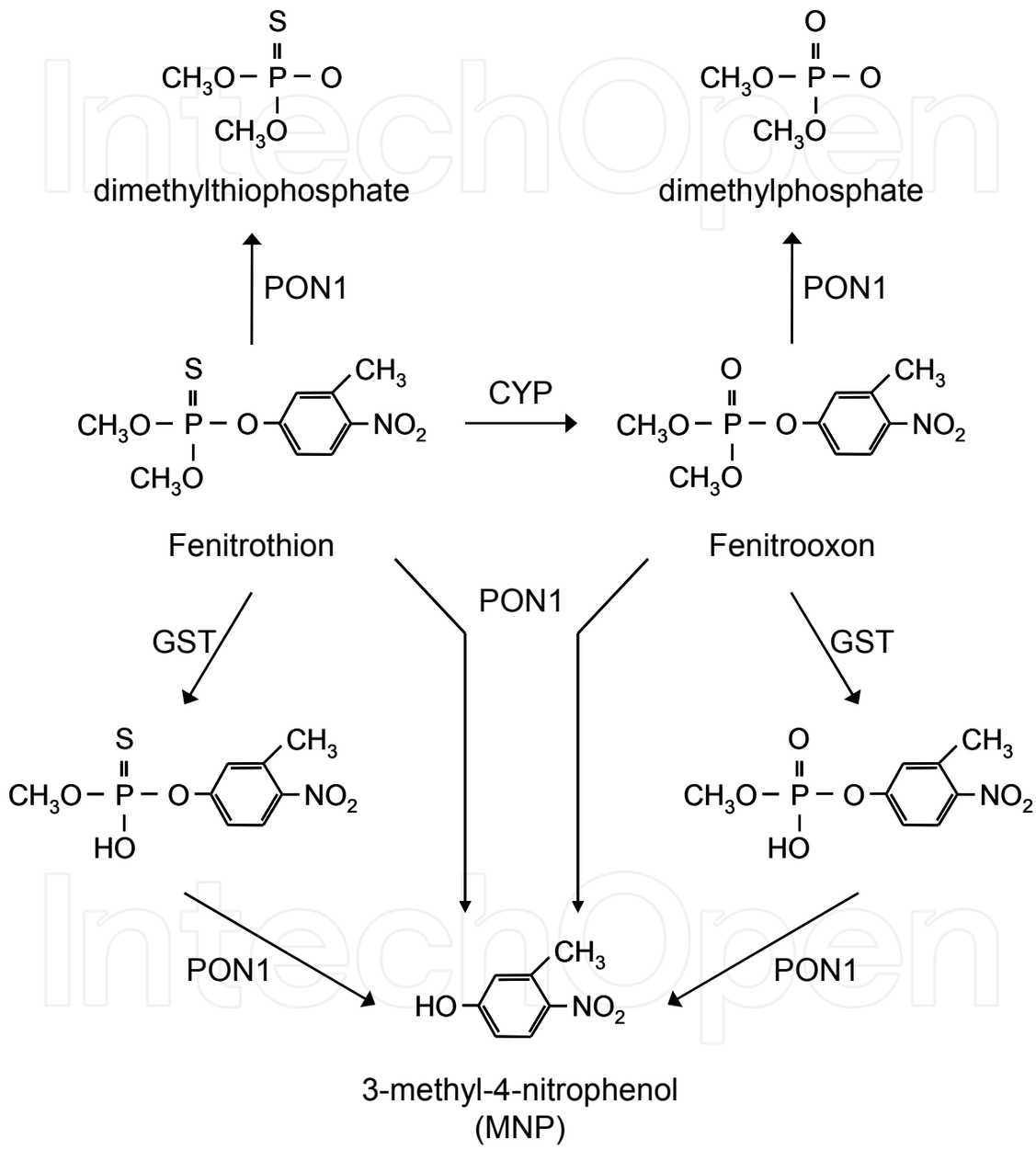

Fig. 1. Metabolic pathway of fenitrothion in mammals or birds. This figure was adopted from WHO (1992) with slight modifications. In mammals, dimethylthiophosphate, dimethylphosphate and MNP were the major urinary metabolites of fenitrothion and fenitrooxon. In birds, MNP was the major urinary metabolite of fenitrothion and fenitrooxon. GST activity was found to be lower than in mammals.

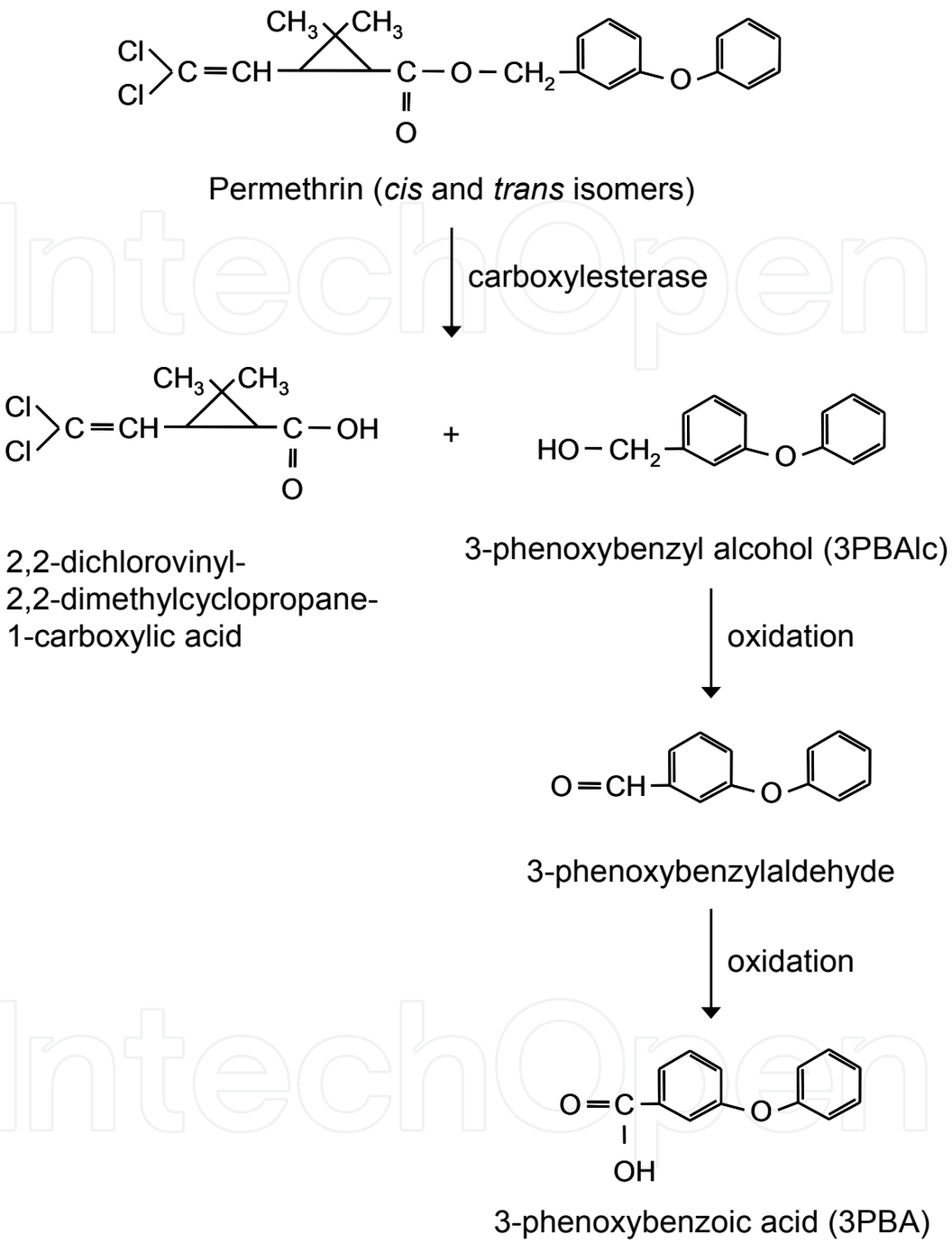

Fig. 2. Metabolic pathway of permethrin in mammals. This figure was adopted from WHO (1990) with slight modifications. Carboxylesterase plays an important role in the hydrolytic biotransformation of permethrin. The expression of carboxylesterase is ubiquitous with high levels in various tissues. Amon various animal tissues, the highest hydrolase activity is typically found in the liver and other tissues, such as testis, kidney and plasma. Unlike mouse, rat, rabbit, horse and cat, human plasma contains no carboxylesterase.

3. Toxicity for experimental animals and humans

Fenitrothion

Since it is a cholinesterase (ChE) inhibitor, exposure to fenitrothion causes ChE activity depression in plasma, red blood cells, brain, and liver tissues. The acute toxicity of fenitrothion is considered to be low in mammals, because of the high metabolic rate (Hayes, 1982; Spencer, 1981).

Animal: The no-observed-adverse-effect levels (NOAEL), based on brain-ChE activity, were 10 mg/kg diet in both short- and long-term studies on rats, in long-term studies on mice, and were 50 mg/kg diet in short-term studies on dogs, respectively (WHO, 1992). Fenitrothion was given to female rats by gavage every other day from gestational day 6-15 at doses 3, 15, 30 and 45 mg/kg (Berlińska and Sitarek 1997). The maternal death rates were 39% and 88% at doses of 30 and 45 mg/kg, respectively. At 30 mg/kg, fenitrothion caused a significant decrease in maternal body weight gain, food consumption, hemoglobin and hematocrit values, and absolute weights of liver and kidney, but an increase in relative weights of adrenal and ovary. At 15 mg/kg, fenitrothion significantly decreased maternal relative liver weight. Although fenitrothion at doses of 3-30 mg/kg did not induced teratogenic effects, at 30 mg/kg it showed embryotoxicity, such as a significant increase in the frequency of early resorption per litter, postimplantation loss, and fetuses and litters with dilation of the cerebral ventricles. Furthermore, fenitrothion produced delayed ossification of sternum and cranium, and decreased fetal body weight and length. The frequency of fetuses and litters with dilation of the cerebral ventricles was increased at a dose of 15 mg/kg. Thus, Berlińska and Sitarek concluded that the NOAEL for developmental toxicity in rats was 3 mg/kg per day, and the lowest-observed-adverse-effect level was 15 mg/kg per day.

Recent studies showed the endocrine-disrupting effect of fenitrothion. Berger and Sultatos (1997) demonstrated that fenitrothion treatment caused a dose-dependent decrease in 2-hydroxyestradiol and 4-hydroxyestradiol production in mouse hepatic microsomes even at a dosage as low as 7 mg/kg, and an increase in 16 alpha-hydroxyestrone and estriol production. In another study, 7-week-old castrated Sprague-Dawley rats were subcutaneously treated with testosterone propionate (50 μg/day in 0.2 ml corn oil) and orally with corn oil vehicle or fenitrothion (15 or 30 mg/kg per day) once a day for 7 days (Tamura et al. 2001). Both fenitrothion doses caused significant decreases in the weights of ventral prostate, seminal vesicle, and levator ani plus bulbocavernosus muscles. In contrast, blood acetylcholinesterase activity was only inhibited at the higher dose (30 mg/kg). Tamura et al. also demonstrated in an *in vitro* experiment that fenitrothion blocked dihydrotestosterone-dependent androgen receptor (AR) activity in a concentration-dependent and competitive manner in HepG2 human hepatoma liver cells, which were transiently transfected with human AR and an AR-dependent luciferase reporter gene, suggesting that fenitrothion may be a competitive androgen receptor antagonist.

On the other hand, Okahashi et al. (2005) suggested that lower-dose fenitrothion did not cause disruption of endocrine systems in animals. They administered fenitrothion to Crj:CD(SD)IGS parental rats at concentrations of 10, 20, and 60 (3.81 mg/kg per day) ppm in the diet for 10 weeks prior to mating, and throughout mating, gestation and lactation. Their offspring were exposed from weaning until maturation at the age of 10 weeks. In the parental animals, brain cholinesterase activity was remarkably reduced in males exposed to 60 ppm fenitrothion and in females exposed to 20 and 60 ppm fenitrothion. Reproductive

performance, organ weights, histopathology, and sperm analytical parameters were not influenced. In the offspring, no effects on anogenital distance, retention of areolae/nipples, onset of puberty, organ weights, histopathological findings, and sperm parameters were observed. In conclusion, fenitrothion had no effects on the reproductive or endocrine systems of the parental animals and their offspring, even at a toxic dose suppressing brain cholinesterase activity in parental animals. The concentration of 60 ppm (3.81 mg/kg per day) is 750 times higher than the acceptable daily intake (ADI) of fenitrothion (0.005 mg/kg body weight). Therefore, any potential risk of exposure may be negligible, and fenitrothion at in-use levels in the environment may be unlikely to cause disruption of human endocrine systems.

Human: WHO (1990) classified technical grade fenitrothion as "moderately hazardous" (Class II). ADI of fenitrothion was established as 0.005 mg/kg body weight by the Joint FAO/WHO Expert Committee on Pesticide Residues in 2000. Nosal and Hladka (1968) reported that administration of fenitrothion at a single oral dose of 0.042-0.33 mg/kg body weight and repeated administration of 0.04-0.08 mg/kg body weight to human volunteers did not cause inhibition in plasma and erythrocyte ChE, and the urinary MNP was completely excreted within 24 hours. Chronic symptoms of exposure to fenitrothion in humans include general malaise, fatigue, headache, loss of memory and ability to concentrate, anorexia, nausea, thirst, loss of weight, cramps, muscular weakness and tremors.

Permethrin

Permethrin acts on the axons in the peripheral and central nervous systems, causing prolonged opening of sodium channels. The acute toxicity of permethrin in mammalians is relatively low, though the LD50 value varies considerably according to the vehicle used and the *cis*:*trans* isomeric ratio (FAO, 1999; U.S. EPA, 2007).

Animal: NOAEL is assigned at 5 mg/kg body weight per day for permethrin with an isomer ratio of *cis*:*trans* 40:60 from the viewpoint of the effects on liver weight in 2-year and 26-week studies in rats, and a 3-month study in dogs. NOAEL is not available for respective *cis* and *trans* isomers (WHO, 1990). The rat appeared to be the most sensitive species with an oral LD50 of 400 mg/kg body weight for *cis*:*trans* 40:60 permethrin administered in corn oil, against 650 mg/kg body weight in mice. The neurotoxicity of intravenous- or orally-administered *cis*-permethrin is over 10-fold greater than that of *trans* isomer. Neonatal rats are more sensitive than adult rats to the acute toxic effects of permethrin, which are thought to be related to differences in permethrin metabolism.

In their acute neurotoxicity study, Freeman (1993a) performed a functional observational battery (FOB) approximately 12 hours following administration of 10, 150 or 300 mg/kg of technical grade permethrin (mixture of *cis* and *trans*) in corn oil to male and female Sprague-Dawley rats. At doses of 150 and 300 mg/kg, permethrin caused salivation, tremor, splayed hindlimbs, abnormal posture, staggered gait, decreased grip strength, exaggerated reaction to sound, exaggerated hindlimb flexion, convulsions, and mortality. No treatment-related effects were observed at the lowest dose of 10 mg/kg. In a behavioral neurotoxicity study (McDaniel and Moser, 1993), technical grade permethrin was administered by gavage in corn oil to Long-Evans hooded rats, at doses of 25, 75 and 150 mg/kg, and the FOB were evaluated at 2 and 4 hours following treatment. Results of the present study are consistent with the acute regulatory study (Freeman, 1993a) including tremor, chromodacryorrhea, decreased grip strength and an exaggerated startle response. However, the absence of salivation, splayed hindlimbs and convulsions and the presence of aggressive sparring in

the latter study (McDaniel and Moser, 1993) were inconsistent with the findings of the regulatory acute neurotoxicity study (Freeman, 1993a).

In a subchronic neurotoxicity study (Freeman, 1993b), technical grade permethrin was administered through the diet to male and female Sprague-Dawley rats, at concentrations of 250, 1500 and 2500 ppm (18, 101 and 170 mg/kg per day, respectively). At the 1500 and 2500 ppm dietary levels, permethrin produced tremor, splayed hindlimbs, abnormal posture, a staggered gait, and decreased grip strength. No such effects were observed at the lowest dose of 250 ppm.

Effects of permethrin on endocrine or reproductive function are investigated, but the report is very limited. Castrated rats (5-week-old) were pretreated with testosterone propionate and orally given permethrin (mixture of *cis* and *trans*, 24.8% and 71.8%) at doses of 10, 50 and 100 mg/kg per day for 10 days. A mixture of *cis*- and *trans*-permethrin showed anti-androgen-like effects on male rats such as significant reductions in androgen-dependent sex accessory tissue (ventral prostate, seminal vesicles, levator ani and bulbocavernosus muscles, Cowper's gland and glans penis) weights (Kim et al., 2005). *cis*-Permethrin at 0, 35 and 70 mg/kg was orally administered to IRC mice for 6 weeks, and male reproductive toxicity was investigated. This chemical dose-dependently decreased testicular and plasma testosterone levels, along with a dose-dependent increase in circulating LH and declines in epididymal sperm count and sperm motility (Zhang et al., 2007). Testicular residue concentrations of *cis*-permethrin from the individual animals were also strongly inversely correlated with testicular testosterone levels. The exposure-related reductions in mRNA and protein expression levels of peripheral benzodiazepine receptor, steroidogenic acute regulatory protein and cytochrome P450 side-chain cleavage, which are involved in testosterone synthesis in testis, were observed, as well as structural changes in Leydig cell mitochondria, suggesting that the mitochondrial damage caused by permethrin exposure may result in a reduction of testosterone synthesizing elements and thereby decrease testosterone levels. In a follow-up study in mice, *cis*-permethrin induces reproductive toxicity whereas at the same dose *trans*-permethrin does not because of a faster metabolic rate than *cis* isomer (Zhang et al., 2008). Zhang et al. also reported that *cis*-permethrin caused structural abnormalities in the seminiferous tubules. However, it must be noted that these studies to date have used dose levels much higher than encountered by non-occupationally exposed humans.

Human: Permethrin is a moderately to practically non-toxic pesticide in EPA toxicity class II or III, depending on the formulation. Formulations in the case of possible eye and skin irritation are grouped into class II. Permethrin belongs to the type I group of pyrethroids because it lacks a cyano group, and typically causes tremor (T-syndrome), incoordination, hyperactivity, prostration, and paralysis. An ADI of 0.05 mg/kg body weight for *cis*:*trans* 40:60 or 25:75 permethrin was established in 1987. Rishikesh et al. (1978) evaluated staff involved with bagging, mixing, or spraying a 5% preparation of permethrin (cis/trans ratio, 25:75) in Nigeria by a questionnaire and urinalysis. Regardless of the protective equipment worn by the sprayers, only 2 mg of permethrin was absorbed after exposure to 6 kg of permethrin, which was excreted in 24 hours.

4. Toxicity for ecosystem

Fenitrothion

In the environment, fenitrothion is degraded by photolysis and hydrolysis. In the presence of ultraviolet radiation or sunlight, the half-life of fenitrothion in water is less than 24 hours.

The presence of micro-flora may accelerate degradation. Miyamoto et al. (1966) studied the degradation of fenitrothion by *B. subtilis*. The major metabolite was aminofenitrothion, and other minor metabolites detected were dimethyl thiophosphoric acid and desmethyl fenitrothion. In the bacteria, aminofenitrothion is further degraded to desmethyl aminofenitrothion, but the rate is slower than the parent compound. No reduction of desmethyl fenitrothion to desmethyl aminofenitrothion was detected, and dimethyl phosphoric acid was not formed from aminofenitrothion (Figure 3). Thus, the degradation of fenitrothine in *B. subtilis*, may be quite different from the metabolic route of experimental animals and humans. In the absence of sunlight or microbial contamination, fenitrothion is stable in water. In soil, biodegradation is the primary route, though photolysis may also play a role. Airborne concentrations of fenitrothion and its levels in water may decrease rapidly by photolysis and hydrolysis. The concentrations of fenitrothion that are likely to be found in the environment do not have any effects on microorganisms in soil or water. In laboratory studies, fenitrothion is highly toxic for aquatic invertebrates in both freshwater and seawater, while fish are less sensitive to fenitrothion than invertebrates, and the most sensitive life stage is early larva. Fenitrothion is highly toxic to bees (LD50, 0.03-0.04 μg/bee) when bees are exposed to direct treatment or to dried residues on foliage (U.S. EPA, 1987).

Furthermore, fenitrothion was found to be highly toxic to upland game birds, but not so toxic to waterfowl. Indeed, the acute oral LD50 values were determined to be 23.6 and 1190 mg/kg body weight for bobwhite quail and mallards, respectively. Even in reproduction studies, NOEL was 10 mg/kg body weight for the quail and 100 mg/kg body weight for the mallard, respectively. There are quantitative differences in the composition of metabolites of fenitrothion between mammalian and avian species. For example, in rats, mice and dogs, demethylated products at the *P*-*O*-methyl linkage by GST accounted for 30 to 60% of the total urinary metabolites (Hollingworth et al., 1967; Miyamoto et al., 1976), whereas in the birds only 10 to 15%. This may be due to lower GST activity in avian species compared with that in mammalians. Mihara et al. (1979) also revealed that oxidative activities of the *m*-methyl group of fenitrothion and fenitrooxon in livers from hen, quail, pheasant and duck were higher than those of mammalian liver, while *O*-demethylate activity for fenitrothion or fenitrooxon was lower in these birds. In birds, MNP is the major metabolite of fenitrothion by hydrolysis, though a pathway exists with oxidation of the *m*-methyl group of fenitrothion or fenitrooxon. The metabolite MNP is then conjugated with uridine diphosphate glucuronic acid or 3'-phosphoadenosine-5'-phosphosulfate by catalytic action of uridine diphosphate glucuronosyltranferase (UGT) and sulfotransferase (SULT), respectively (Mackenzie et al., 1997). Hepatic UGT and SULT activities investigated in vitro for MNP in Japanese quail, mice and rats revealed lower UGT activity for MNP in quail than rats and mice, but no significant difference in SULT activity (Lee et al., 2007). In addition, the SULT activity was only one-tenth of the UGT activity, suggesting that the latter enzyme plays an important role in MNP elimination in vivo. Li et al. (2008) reported that the birds treated with 100 mg/kg of MNP induced acute toxicological responses such as dyspnea and tremor, and finally death. MNP may cause acute toxicity and death, possibly by a rapid decrease in blood pressure followed by ischemic shock, because the potential vasodilatory action of MNP had been reported in rats (Mori et al., 2003; Taneda et al., 2004). However, none of the rats died after treatment with 100 mg/kg of MNP (Li et al., 2007), suggesting that the sensitivity to MNP is higher in quail than in rats. For these reasons, fenitrothion causes higher toxicity in birds than in mammals.

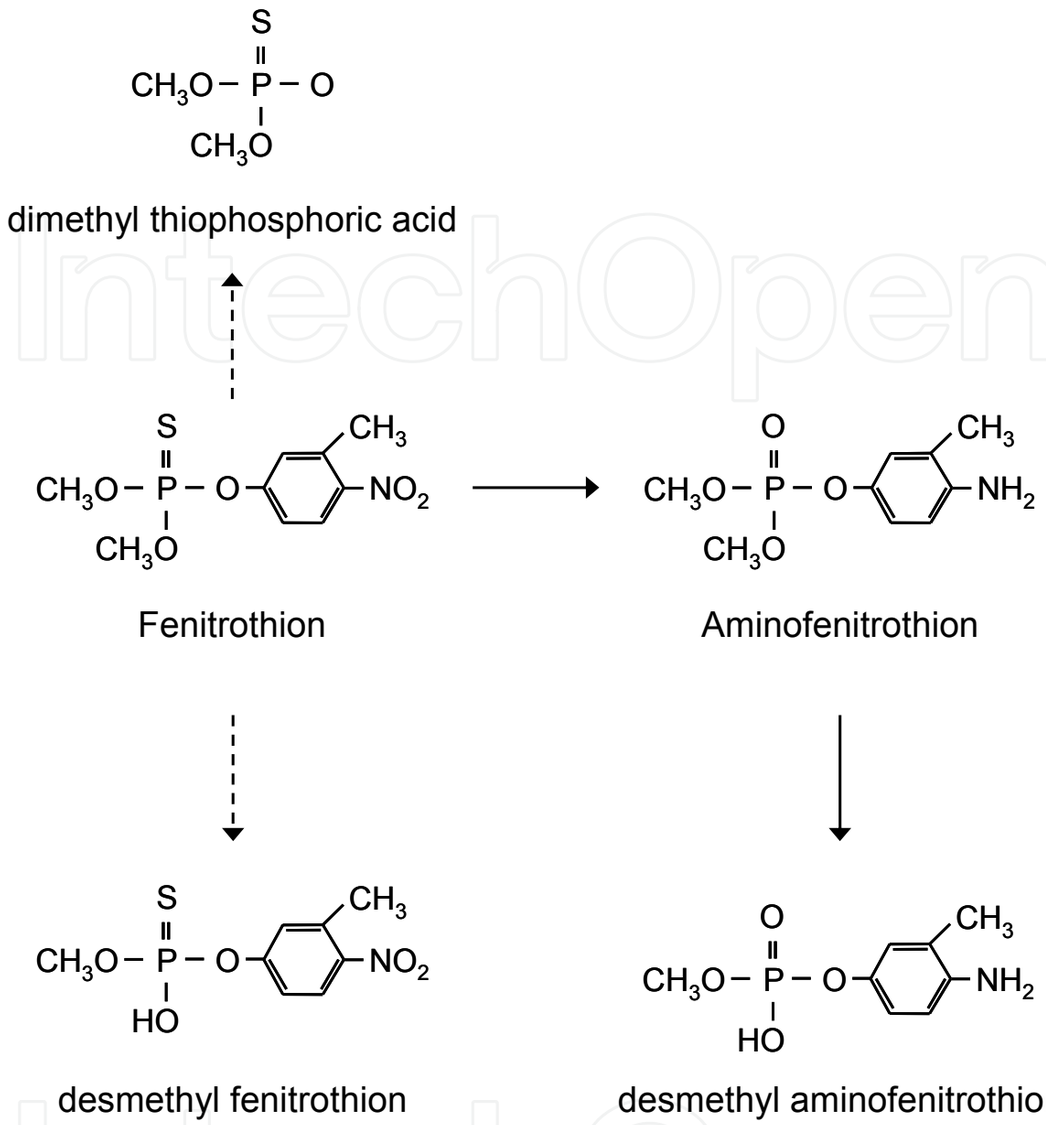

Fig. 3. Pathway of degradation of fenitrothion by *B. subtilis* in environment. This figure was adopted from Miyamoto et al. (1966) with slight modifications. Aminofenitrothion was the major metabolite of fenitrothion in *B. subtilis.*

Permethrin

Permethrin is photodegraded by sunlight in water and on soil surfaces. Under aerobic conditions in soil, permethrin degrades with a half-life of 28 days. Permethrin deposited on plants degrades with a half-life of approximately 10 days. Thus, in the environment, permethrin is hydrolyzed, and the resultant acid and alcohol are conjugated. However, permethrin itself evidences very little movement within the environment, because it binds very strongly to soil particles and is nearly insoluble in water and not expected to leach or contaminate groundwater. Permethrin has been shown to be highly toxic for aquatic arthropods and fish, because they have lower levels of carboxylesterase activity than

mammals. However, the extreme susceptibility to permethrin may be ascribed to its high sensitivity to sodium channels rather than low carboxylesterase activity. Permethrin is also highly toxic to honey bees (LD50, 0.11 μg/bee), yet exhibits very low toxicity to birds when given orally or fed in the diet. LD50 is >3000 mg/kg body weight for a single oral dosage and >5000 mg/kg diet for dietary exposure, respectively. One of the reasons for the different toxicity of permethrin among species is negatively correlated its toxic action to their body temperature, thus generally showing more acute effects on cold-blooded animals (insects, fish, etc) than warm-blooded animals (mammals and birds).

5. Interactive toxicity of insecticide mixture

Organophosphorus insecticides are being increasingly used in combination with pyrethroid insecticides. Fenitrothion is used in combination with other pesticides to enhance ChE inhibition by nature. However, fenitrothion inhibits not only ChE but also other esterase activity such as carboxylesterase. Trottier et al. (1980) reported that the oral administration of fenitrothion to male CD rats at a dose of 0, 2.5, 5, 10, or 20 mg/kg per day for 30 consecutive days significantly decreased liver carboxylesterase activity (by 50-80%) on days 8-30 at doses more than 2.5 mg/kg per day but had returned to control values by day 45 (15 days after termination of treatment) at all doses except 20 mg/kg per day, at which a decrease of 25% was still observed. At this dose, the values had returned to normal by day 87 (57 days after termination of treatment). A significant decrease in renal carboxylesterase activity (by 20-70%) was also observed on days 8-30 at doses over 5 mg/kg per day. Recovery of the activity was rapid, and the values were comparable to those of controls by day 38 (8 days after the end of treatment).

As described at the metabolism of permethrin, carboxylesterase plays an important role in detoxication of permethrin. Ortiz et al. (1995) examined the interactions between a commercial formulation of methyl parathion and a commercially formulated product of permethrin in male rats. When rats were treated with the mixture, 380 mg/kg of methyl parathion reduced the LD50 of permethrin by only 9.0%, whereas when rats received methyl parathion at 464 mg/kg, the LD50 of permethrin was reduced by 37% ($P < 0.001$). Results indicated that methyl parathion modified the acute toxicity of permethrin. Another study examined the effect of organophosphorus insecticide dichlorvos on excretion levels of urinary *cis*-permethrin-derived 3PBA in rats (Hirosawa et al., 2011). After *cis*-permethrin injection (20 mg/kg) via the tail vein of rats pretreated intraperitoneally with dichlorvos (low dose, 0.3 mg/kg; high dose, 1.5 mg/kg), the amounts of urinary 3PBA excretion over 48 hours were decreased to 81.1% and 70.3% of dichlorvos non-treated rats in the low- and high-dose dichlorvos groups, respectively. The plasma concentration of *cis*-permethrin-derived 3PBAlc in high-dose dichlorvos group was significantly lower than that in the dichlorvos non-treated group one hour after *cis*-permethrin injection. In contrast, no differences were observed in the excretion levels of urinary 3PBA after injection of 3PBAlc between the dichlorvos non-treated group and the high-dose dichlorvos group. These results suggested that dichlorvos may have inhibited the metabolism of the co-exposed *cis*-permethrin and thereby decreased the amount of urinary 3PBA excretion. In our recent study, we evaluated male reproductive toxicity after co-exposure to diazinon (3 mg/kg) and *cis*-permethrin (35 mg/kg) in mice. Exposure to diazinon alone and the mixture with *cis*-permethrin inhibited plasma and liver carboxylesterase activities. In the co-exposed mice,

the urinary *cis*-permethrin metabolite decreased compared to that in mice exposed to *cis*-permethrin alone. The co-exposure significantly decreased plasma testosterone levels and increased the number of degenerated germ cells within the seminiferous tubule, whereas exposure to each chemical did not. We concluded that diazinon inhibited the plasma and liver carboxylesterase activities and the metabolic rate of co-exposed *cis*-permethrin, which resulted in accentuating the reproductive toxicity of *cis*-permethrin (Wang et al., unpublished data submitted to the Journal).

Recently, since we could not find any study on the interaction between fenitrothion and permethrin, the toxicity of permethrin may be enhanced by fenitrothion via depression in carboxylesterase activity. Since fenitrothion and permethrin are used in the same place, if not purposefully in mixtures, the two insecticides could conceivably be combined. Until now, the risk assessments of combined toxicity to mammals are still insufficient and further detailed studies are warranted.

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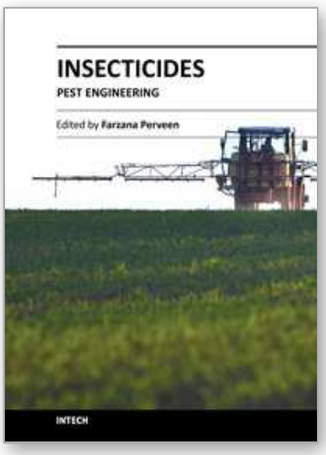

Insecticides - Pest Engineering

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This book is compiled of 24 Chapters divided into 4 Sections. Section A focuses on toxicity of organic and inorganic insecticides, organophosphorus insecticides, toxicity of fenitrothion and permethrin, and dichlorodiphenyltrichloroethane (DDT). Section B is dedicated to vector control using insecticides, biological control of mosquito larvae by Bacillus thuringiensis, metabolism of pyrethroids by mosquito cytochrome P40 susceptibility status of Aedes aegypti, etc. Section C describes bioactive natural products from sapindacea, management of potato pests, flower thrips, mango mealy bug, pear psylla, grapes pests, small fruit production, boll weevil and tsetse fly using insecticides. Section D provides information on insecticide resistance in natural population of malaria vector, role of Anopheles gambiae P450 cytochrome, genetic toxicological profile of carbofuran and pirimicarp carbamic insecticides, etc. The subject matter in this book should attract the reader's concern to support rational decisions regarding the use of pesticides.

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