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2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PYRETHRINS AND PYRETHROIDS IN THE UNITED STATES

Pyrethrum is the natural extract that occurs in the flowers of *Chrysanthemum cinerariaefolium* and *Chrysanthemum cinereum*. Pyrethrum has long been recognized as possessing insecticidal properties; over the years, first the chemical extracts of pyrethrum, and then more recently, the specific synthetic chemical analogs have been produced. The six active insecticidal compounds of pyrethrum are called pyrethrins. The six individual pyrethrins are pyrethrin I, pyrethrin II, cinerin I, cinerin II, jasmolin I, and jasmolin II. The pyrethroids are synthetic analogs and derivatives of the original pyrethrins and represent a diverse group of over 1,000 powerful insecticides. Although they are based on the chemical structure and biological activity of the pyrethrins, the development of synthetic pyrethroids has involved extensive chemical modifications that make these compounds more toxic and less degradable in the environment. A list of the pyrethrins and some of the more common pyrethroids is presented in Table 2-1. While many pyrethroids have been developed, only about a dozen or so are frequently used in the United States. The individual pyrethroids are typically grouped into two general classes, called Type I and Type II, based on a combination of toxicological and physical properties, which is further described in Chapters 3 and 4. Also, the individual pyrethroid substances, due to a complex chemical structure, are often composed of two, four, or eight isomers, and their commercially manufactured products routinely contain a mixture of these various isomers. Thus, the production of individual pyrethroids with slightly varying isomeric ratios can often be the reason for the differences in the reported toxicities of the same compound. See Chapter 4 for the structures and explanation of the isomerism, as well as more information on the chemical and physical properties of the pyrethrins and pyrethroids.

Both groups, the pyrethrins and the pyrethroids, are very important insecticides because of their rapid paralysis of flying insects, relatively low mammalian toxicity, and rapid rate of degradation in the environment. They are typically used as insecticides for both home and commercial use. Also, the pyrethrins and pyrethroids are often formulated with compounds such as piperonyl butoxide, piperonyl sulfoxide, and sesamex, which act as synergists to increase the effectiveness of the insecticide. Currently, the products containing small amounts of pyrethroids for uses around the home are still classified as general use pesticides; however, emulsified or granular concentrate formulations that are applied to fields were classified as restricted use pesticides by EPA in 1995. Formulated commercial pyrethroid products

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Table 2-1. Pyrethrins and Pyrethroids Discussed in the Profile^a

Pyrethrins	Type I pyrethroids	Type II pyrethroid
Constituents of natural pyrethrum extract	Derivatives of pyrethrins that do not include a cyano group and may elicit tremors	Derivatives of pyrethrins that include a cyano group and may elicit sinuous writhing (choreoathetosis) and salivation
Pyrethrin I	Allethrin	Cyfluthrin
Pyrethrin II	Bifenthrin	Cyhalothrin
Cinerin I	Permethrin	Cypermethrin
Cinerin II	Phenothrin(Bio)	Deltamethrin
Jasmolin I	Resmethrin	Fenvalerate
Jasmolin II	Tefluthrin	Fenpropathrin
	Tetramethrin	Flucythrinate
		Flumethrin
		Fluvalinate
		Tralomethrin

^aType I and Type II pyrethroids are described in more detail in Section 3.5.2, Mechanisms of Toxicity.

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(like most pesticides), also contain a high percentage of other (sometimes referred to as “inert”) ingredients, many of which may be potentially toxic. Federal law only requires that the percentage of “inert” ingredients be defined and does not require the actual chemicals that make up the “inert” ingredients to be identified on a pesticide label.

Pyrethrins and pyrethroids are released to the environment due to their use as insecticides. They can be applied to crops from aerial and ground-based sprayers or applied indoors from commercially available sprays or aerosol bombs. These compounds are readily degraded in the atmosphere by natural sunlight and usually do not persist for more than several days to a few weeks. Certain pyrethroids such as permethrin and cyhalothrin, where the isobutenyl group attached to the cyclopropane moiety has been altered, are slightly more stable to sunlight than other pyrethroids. Air concentrations are usually in the $\mu\text{g}/\text{m}^3$ range (both indoors and outdoors) after spraying, but diminish over time as these compounds are degraded or removed by wet and dry deposition. In soils, pyrethrins and pyrethroids are not very mobile and usually do not leach into groundwater, unless a large spill has occurred. These compounds are biodegraded in soil and water and can also undergo hydrolysis under alkaline conditions. Since these compounds adsorb strongly to soils, they are not taken up substantially by the roots of vascular plants. These compounds bioconcentrate in aquatic organisms and are extremely toxic to fish.

The general population is primarily exposed to pyrethrins and pyrethroids from the ingestion of foods, particularly vegetables and fruits. Exposure due to inhalation of ambient air is also possible after these compounds have been used. Pyrethrins and pyrethroids are also employed in a variety of pet shampoos, lice treatments, household insecticide sprays, and aerosol bombs that can be used in or around the home, and the use of these products can lead to both dermal and inhalation exposure. Occupational exposure to agricultural workers who apply these compounds onto crops can be substantial, with dermal exposure considered the most important pathway (see Section 6.5).

The average daily intake (AVDI) of permethrin for eight different age/sex groups has been estimated from market basket surveys conducted by the Food and Drug Administration (FDA). Based upon market basket surveys conducted from 1986 to 1991, the AVDI of permethrin ranges from about 36 to 71 $\text{ng}/\text{kg}/\text{day}$ (see Table 6-4). Since permethrin is the most frequently used pyrethroid in the United States, the data from these surveys may represent a reasonable first approximation for the average total intake of all the pyrethroids.

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2.2 SUMMARY OF HEALTH EFFECTS

Pyrethrins and pyrethroids are used extensively as effective insecticides, but pose relatively little hazard to mammals (including humans) by natural routes of exposure at levels likely to be encountered in the environment or resulting from the normal use of pyrethrin- or pyrethroid-containing substances. Signs and symptoms of acute toxicity vary according to the type of pyrethroid to which one may be exposed. However, almost all systemic effects are related to the action of pyrethrins and pyrethroids on the nervous system. These chemicals exert their profound effect by prolonging the open phase of the sodium channel gates when a nerve cell is excited. In rodents, effects such as tremors are induced if the open state is prolonged for brief periods; effects such as sinuous writhing (choreoathetosis) and salivation occur if the open state is prolonged for longer periods. Neurological signs typically result from acute toxicity. Low-level chronic exposures to pyrethrins and pyrethroids usually do not cause neurological signs in mammals, largely due to rapid metabolism and elimination. However, direct skin contact may cause temporary paresthesia (abnormal cutaneous sensations such as tingling, burning, stinging, numbness, and itching) that is limited to the area of contact. Available animal data do not indicate that pyrethrins or pyrethroids significantly affect end points other than the nervous system, although changes in liver weight and metabolism of chemicals have sometimes been used as an index of adverse effect levels for pyrethroids. Results of a few recent animal studies suggest that neurodevelopmental, reproductive, and immunological effects may result following exposure to some pyrethroids at levels below those that induce overt signs of neurotoxicity. Available data indicate that pyrethrins may be a carcinogenic concern to humans. No human data are available regarding the potential for pyrethroids to cross the placental barrier and enter a developing fetus. Limited animal data indicate that transfer of pyrethroids across the placenta to the fetus may occur. Although pyrethroids have not been identified in human breast milk, very low levels of pyrethroids (<1% of an orally administered dose) are excreted into milk of lactating animals.

Neurological Effects. Pyrethrins and pyrethroids act principally on the sodium channels of nerve cells in exerting their toxic effects. Two different types of pyrethroids are recognized, based on differences in basic structure (the presence or absence of a cyano group in the alpha position) and the symptoms of poisoning in laboratory rodents. Type I pyrethroids do not include a cyano group; their effects typically include rapid onset of aggressive behavior and increased sensitivity to external stimuli, followed by fine tremor, prostration with coarse whole body tremor, elevated body temperature, coma, and death. The term T-syndrome (from tremor) has been applied to Type I responses. Clinical signs of neurotoxicity in animals exposed to pyrethrins are similar to those of Type I pyrethroids. Type II

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pyrethroids include a cyano group; their effects are usually characterized by pawing and burrowing behavior, followed by profuse salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremors that progress to sinuous writhing (choreoathetosis). Clonic seizures may be observed prior to death. Body temperature usually is not increased, but may decrease. The term CS-syndrome (from choreoathetosis and salivation) has been applied to Type II responses. In general, the distinction between Type I and Type II pyrethroids is clear. However, two of the cyano-pyrethroids, fenpropathrin and cyphenothrin, have been shown to trigger responses intermediate to those of T- and CS-syndrome, characterized by both tremors and salivation. These neurological responses to pyrethroid poisoning are typically of acute duration. There is no evidence to indicate that long-term, low-level exposure of adults to pyrethroids might result in more severe neurological effects.

Whereas distinctive signs of these neurotoxic symptoms (T- and CS-syndrome) occur in humans diagnosed with mild to severe pyrethroid poisoning, levels high enough to trigger these symptoms are not likely to occur under most exposure scenarios. Pyrethroids (particularly Type II pyrethroids containing the cyano group) frequently induce paresthesia among individuals occupationally exposed via unprotected areas of the skin. This effect is often observed at exposure levels far below those in which other clinical signs of neurotoxicity might be expected to occur. Pyrethroid-induced parasthesia typically peaks within 3–6 hours following dermal exposure and resolves within 12–24 hours. Some animal studies indicate that exposure to pyrethroids may result in other less overt signs of neurotoxicity, such as changes in startle and avoidance responses, altered levels of spontaneous motor activity, and changes in operant conditioned responses, which may occur at levels below those eliciting typical T- or CS-syndrome.

Cancer. Increased incidences of thyroid follicular cell tumors were reported in male and female rats administered pyrethrins (57.57% pyrethrum extract) in the diet for 2 years. The female rats also exhibited increased incidences of hepatocellular adenomas and combined adenomas and/or carcinomas. In a review of this rat carcinogenicity study, the Cancer Assessment Review Committee for pyrethrins attributed the increased incidences of thyroid and liver tumors to pyrethrum treatment and classified pyrethrins as “likely to be a human carcinogen by the oral route.”

Developmental Effects. Standard developmental studies have not elucidated typical signs of developmental toxicity in animals exposed to pyrethrins or pyrethroids.

Eriksson and coworkers reported alterations in brain muscarinic receptor density and increased spontaneous activity in mice that had received oral (gavage) doses of pyrethroids during critical stages of

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neonatal neurological development; however, limitations in study design and lack of success in duplicating the results render the studies of questionable value for the purpose of risk assessment. *In utero* exposure of rats resulted in cellular changes indicative of compromised immunological function.

Reproductive Effects. Standard reproductive toxicity studies, including some that were performed for three successive generations, did not indicate that pyrethrins or pyrethroids might be of particular concern to reproductive success. However, a few recent studies have indicated that relatively low-level, intermediate-duration oral exposure of adult male laboratory animals to some Type II pyrethroids may result in damage to reproductive organs, abnormal sperm characteristics, reduced plasma testosterone levels, and reduced fertility.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

No inhalation MRLs were derived for pyrethrins or pyrethroids for inhalation exposure since adequate data were not available for this route of exposure.

Oral MRLs

No oral MRLs were derived for pyrethrins since adequate data were not available. Oral MRLs were derived for selected pyrethroids, based on cleared reviews (Data Evaluation Records, DERs) of studies submitted to EPA by the pesticide industry and a study published in the open literature (McDaniel and Moser 1993). The DERs were used because the associated primary studies were not available to ATSDR for independent assessment. The MRLs were developed for specific technical-grade pyrethroids and may not be applied to a different composition of that pyrethroid or for a different pyrethroid. For example, the intermediate-duration oral MRL of 0.2 mg/kg/day that was derived for permethrin accounts for oral exposure to technical-grade permethrin (95.3% purity; isomeric ratio 50/50 cis/trans; corn oil vehicle). Isomeric ratio, administration vehicle, purity of the compound, and formulation of a pyrethroid-containing pesticide must all be taken into account when assessing the risk of exposure.

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Acute-duration Oral MRLs

- An MRL of 0.3 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to permethrin (95% purity; 50/50 cis/trans).

This MRL is based on a no-observed-adverse-effect level (NOAEL) of 25 mg/kg for neurological impairment in rats (McDaniel and Moser 1993). An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 to account for intrahuman variation). Groups of Long-Evans rats (8/sex/dose) were administered permethrin (95% purity; 50/50 cis/trans; in corn oil vehicle) in single gavage doses of 0, 25, 75, or 150 mg/kg. Selected rats from each dose group were subjected to functional observational battery (FOB) and motor activity assessment at 2 and 4 hours following dosing. A lowest-observed-adverse-effect level (LOAEL) of 75 mg/kg was identified for neurological impairment that included increased excitability and aggressiveness, abnormal motor movement, and decreased grip strength and motor activity.

- An MRL of 0.02 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to cypermethrin (97% purity; 50/50 cis/trans).

This MRL is based on a lowest-observed-adverse-effect level (LOAEL) of 20 mg/kg for neurological impairment in rats (McDaniel and Moser 1993). An uncertainty factor of 1,000 was used (10 for lack of a NOAEL, 10 for animal to human extrapolation, and 10 to account for intrahuman variation). Groups of Long-Evans rats (8/sex/dose) were administered cypermethrin (97% purity; 50/50 cis/trans; in corn oil vehicle) in single gavage doses of 0, 20, 60, or 120 mg/kg. Selected rats from each dose group were subjected to functional observational battery (FOB) and motor activity assessment at 2 and 4 hours following dosing. LOAEL of 20 mg/kg was identified for neurological impairment that statistically significantly altered gait and decreased motor activity. A NOAEL was not established.

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to cyhalothrin.

This MRL is based on a NOAEL of 1 mg/kg/day for gastrointestinal effects (diarrhea) in dogs (EPA 1981). An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 to account for intrahuman variation). Groups of 4–5-month-old male and female beagle dogs (6/sex/dose) were administered cyhalothrin (in corn oil vehicle) in gelatin capsules at doses of 0, 1.0, 2.5, or 10.0 mg/kg/day for 26 weeks. The dosing volume was 0.1 mL/kg body weight. A dose-related increase in diarrhea was observed as early as the first week of treatment, and persisted throughout the study (7, 26, and 39%

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greater incidences of diarrhea in low-, mid-, and high-dose dogs, respectively, relative to controls). The 7% increased incidence of diarrhea at the 1.0 mg/kg/day dose level may not be a clear indication of an adverse treatment-related effect. However, the 26% increased incidence of diarrhea at 2.5 mg/kg/day is considered to represent a definitive adverse effect. Thus, the 2.5 mg/kg/day dose level is considered a LOAEL for gastrointestinal effects. A detailed description of the test substance was not provided in the study. The acute-duration oral MRL is based on the assumption that the test substance consisted of technical-grade cyhalothrin with a purity of approximately 90%.

Intermediate-duration Oral MRLs

- An MRL of 0.2 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to permethrin (technical grade, approximately 95% assumed purity; 50/50 cis/trans).

This MRL is based on a NOAEL of 15.5 mg/kg/day for neurological impairment in rats (EPA 1994b). An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 to account for intrahuman variation). Groups of Sprague-Dawley rats (10/sex/dose) were administered permethrin (technical grade; 50/50 cis/trans) in the diet for 13 weeks at concentrations of 0, 250, 1,500, or 2,500 ppm (respective time-weighted average doses of 0, 15.5, 91.5, or 150.4 mg/kg/day for males and 0, 18.7, 111.4, or 189.7 mg/kg/day for females). Hindlimb splay was observed as early as days 38 and 18 in some 1,500-ppm males and females, respectively. Other signs of neurotoxicity in the 1,500-ppm rats first appeared between treatment days 35 and 68. Signs of neurotoxicity appeared earlier and were more prevalent in rats of the 2,500-ppm treatment group. There were no signs of neurotoxicity in rats of the 250-ppm treatment group. This study identified a LOAEL of 1,500 ppm (91.5 and 111.4 mg/kg/day in males and females, respectively) for neurotoxicity.

- An MRL of 0.01 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to cyhalothrin.

This MRL is based on a NOAEL of 1 mg/kg/day for gastrointestinal effects (diarrhea) in dogs (EPA 1981). An uncertainty factor of 100 was used (10 for animal to human extrapolation and 10 to account for intrahuman variation). Groups of 4–5-month-old male and female beagle dogs (6/sex/dose) were administered cyhalothrin (in corn oil vehicle) in gelatin capsules at doses of 0, 1.0, 2.5, or 10.0 mg/kg/day for 26 weeks. The dosing volume was 0.1 mL/kg body weight. A dose-related increase in diarrhea was observed throughout the study (7, 26, and 39% greater incidences of diarrhea in low-, mid-, and high-dose dogs, respectively, relative to controls). The 7% increased incidence of diarrhea at the 1.0 mg/kg/day dose level may not be a clear indication of an adverse treatment-related effect. However, the 26%

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increased incidence of diarrhea at 2.5 mg/kg/day is considered to represent a definitive adverse effect. Thus, the 2.5 mg/kg/day dose level is considered a LOAEL for gastrointestinal effects. A detailed description of the test substance was not provided in the study. The intermediate-duration oral MRL is based on the assumption that the test substance consisted of technical-grade cyhalothrin with a purity of approximately 90%.

Chronic-duration Oral MRLs

No clinical signs of neurotoxicity were observed in rats administered permethrin (93.9% purity; 40/60 cis/trans ratio) in the diet for two years at concentrations up to 1,000 ppm (Ishmael and Litchfield 1994). This study was not used as the basis of a chronic-duration oral MRL because the concentrations of permethrin in the diet were not adjusted for decreased food consumption as the rats aged. However, during the second year of treatment, when the rats consumed considerably less food per kilogram of body weight, the permethrin doses were approximately 40 mg/kg/day for male and female rats. Thus, a NOAEL of at least 40 mg/kg/day was identified in this study. For this reason, the intermediate-duration oral MRL of 0.2 mg/kg/day that was based on a NOAEL of 15.5 mg/kg/day should be protective for chronic-duration oral exposure to permethrin with a purity approaching 95% and approximately equal amounts of cis and trans isomers.

An average daily intake (AVDI) of 36–71 ng/kg/day has been estimated for permethrin (see Table 6-4), the most frequently used pyrethroid in the United States (see Table 6-1). The acute- and intermediate-duration oral MRLs of 0.2 mg/kg/day should be protective of acute- and intermediate-duration oral exposure to permethrin, with the exception of accidental or intentional ingestion of permethrin in amounts several orders of magnitude greater than those experienced during the normal consumption of food or drinking water containing permethrin residues.

