# 3. HEALTH EFFECTS

## 3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of pyrethrins and pyrethroids. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

## 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between

"less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of pyrethrins and pyrethroids are indicated in Table 3-2 and Figure 3-2.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for pyrethrins and pyrethroids. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Pyrethrum, the natural extract of the flowers of *Chrysanthemum cinerariaefolium* and *Chrysanthemum cocineum*, contains six active insecticidal compounds called pyrethrins. Pyrethroids are synthetic analogs and derivatives of pyrethrins and represent a diverse group of over 1,000 powerful insecticides (Mueller-Beilschmidt 1990). 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. The pyrethrins and some of the more common pyrethroids are listed in Table 2-1. Pyrethrins and pyrethroids pose relatively little hazard to mammals (including humans) by common routes of exposure at levels likely to be encountered in the environment or resulting from the normal use of pyrethrin- or pyrethroid-containing substances.

Two different types of pyrethroids are recognized, based on differences in basic structure (the presence or absence of a cyano group) and the symptoms of poisoning in laboratory rodents (Coats 1990; Verschoyle and Aldridge 1980). In general, Type I pyrethroids do not include a cyano group, and clinical signs of Type I pyrethroid-induced toxicity include whole body tremors. Type II pyrethroids include a cyano group and are characterized by their elicitation of salivation and sinuous writhing (choreoathetosis).

Toxicity among the various pyrethroids varies greatly, as is evidenced by the wide range in $LD_{50}$ values (concentrations or doses that result in 50% mortality in exposed laboratory animals). These differences are dependent on a number of factors including specific pyrethroid, ratios of stereo and optical isomers within a given pyrethroid formulation, and vehicle. Acute oral $LD_{50}$ values are generally lower in Type II than Type I pyrethroids, indicating a greater degree of toxicity for Type II pyrethroids. In the case of tetramethrin, like all other Type I pyrethroids, isomers of the 1R conformation are considerably more toxic than those of the 1S conformation. The 1S isomer can also inhibit toxicity by competitive inhibition at a number of stereospecific pyrethroid binding sites, thus preventing binding of the more toxic 1R isomer (Narahashi 1986). Furthermore, it has been observed that the cis isomers possess greater mammalian toxicity than the trans isomers. For Type II pyrethroids, the S conformation at the alpha carbon adjacent to the cyano group is considerably more toxic than the R conformation. Consult Chapter 4 for additional information regarding the structural properties of Type I and Type II pyrethroids.

Neurological signs are typically the result of acute toxicity and do not appear to be significantly amplified following repeated low-level exposures. This may be a result of rapid metabolism and elimination of

pyrethrins and pyrethroids by mammals. Available animal data indicate that the nervous system is the primary target of pyrethrin- or pyrethroid-induced toxicity. However, changes in liver weight and liver metabolism of chemicals have sometimes been used as an index of adverse effect levels for pyrethroids. In addition, a few recent studies indicate the potential for adverse neurodevelopmental, reproductive, and immunological effects at exposure levels below those expected to result in overt signs of neurotoxicity. Available data indicate that pyrethrins may be a carcinogenic concern to humans.

Based on the wide range of differences in levels of animal toxicity to pyrethrins and various pyrethroids, factors related to chemical properties and exposure scenarios of a given pyrethroid must be taken into account when assessing health risk. Human exposure to pesticides such as pyrethrins and pyrethroids often involves simultaneous exposure to other chemicals, which may range from impurities in a technical grade of a particular pyrethrin- or pyrethroid-containing product to dispersal agents, wetting agents, solubility agents, and additional pesticides in a given end-formulated product.

### 3.2.1 Inhalation Exposure

#### 3.2.1.1 Death

Two case reports were located in which death was associated with allergic reactions to dog shampoo products containing pyrethrins (Wax and Hoffman 1994). An 11-year-old girl, who had been diagnosed with asthma at 6 years of age, was asymptomatic when she began to wash her dog with a shampoo containing 0.2% pyrethrin. Within 10 minutes, the subject suffered a severe acute asthmatic attack and died <3 hours later, despite medical treatment (Wagner 2000). This girl had experienced a mild increase in asthmatic symptoms when she had used the same shampoo 2 years earlier. A 37-year-old female, who had a 10-year history of mild asthma that did not require chronic medication, developed severe shortness of breath 5 minutes after beginning to wash her dog with a shampoo containing 0.06% pyrethrin (Wax and Hoffman 1994). The subject quickly went into cardiopulmonary arrest and died a short time later, despite efforts to revive her. Postmortem examination revealed pulmonary findings consistent with reactive airway responses. The relative contributions of inhalation and dermal exposure routes were not addressed in these reports. No other reports were located regarding death in humans following inhalation exposure to pyrethrins or pyrethroids.

Information regarding death in animals following inhalation exposure to pyrethrins or pyrethroids is mainly derived from studies designed to assess lethal toxicity in animals following airborne exposure to

pyrethrins or pyrethroids for durations of 2–4 hours. In rats exposed to pyrethrum extract, an estimated airborne concentration in which death could be expected in 50% of the exposed animals ($LC_{50}$) was 3,400 mg/m$^3$ (Schoenig 1995). Most synthetic pyrethroids are more toxic than natural pyrethrins (the active neurotoxic components of pyrethrum extract). Results from studies of rats exposed to synthetic pyrethroids indicate $LC_{50}$ values ranging from approximately 23 to 1,000 mg/m$^3$ (Curry and Bennett 1985; Flucke and Thyssen 1980; Hext 1987; Kavlock et al. 1979; Pauluhn and Thyssen 1982). No specific patterns could be discerned regarding the relatively wide range of $LC_{50}$ values among the various pyrethroids for which inhalation data were available. One series of studies assessed acute inhalation lethality of several Type I pyrethroids (Miyamoto 1976). In most cases, lethality was not observed following exposure to airborne pyrethroid concentrations ranging from 685 to 2,500 mg/m$^3$. In some cases, higher concentrations could not be attained. The only report of death was in rats and mice exposed to a mixture of (+)-allethronyl (+)-trans allethrin for 3 hours. $LC_{50}$ values were 1,600 and 2,720 mg/m$^3$ for rats and mice, respectively, but minimum concentrations in which death was noted were not presented in the report. Miyamoto (1976) also assessed the toxicity of several Type I pyrethroids in rats and mice repeatedly exposed (2–4 hours/day, 5 days/week for 4 weeks) to atmospheres containing pyrethroid concentrations ranging from 6.1 to 210 mg/m$^3$. Although clinical signs of toxicity were noted at concentrations of 61.3 mg/m$^3$ (allethrin) and 200 mg/m$^3$ (furamethrin), no exposure-related deaths occurred during the study period.

#### 3.2.1.2 Systemic Effects

No reports were located in which cardiovascular, gastrointestinal, musculoskeletal, renal, endocrine, dermal, or ocular effects were associated with inhalation exposure of humans or animals to pyrethrins or pyrethroids. Systemic effects related to occupational exposure are generally associated with dermal exposure to pyrethrins or pyrethroids, and are therefore presented in Section 3.2.3.2.

**Respiratory Effects.** Limited information was available regarding respiratory effects in humans following inhalation exposure to pyrethrins or pyrethroids. Hypersensitivity pneumonitis, characterized by pleuritic chest pain, nonproductive cough, and shortness of breath, was diagnosed in a 24-year-old woman following repeated indoor use of a pyrethrum-based insecticide (Carlson and Villaveces 1977). A pulmonary challenge test to the insecticide resulted in an itchy and runny nose within 2 minutes following initiation of exposure, but no cough or shortness of breath. Subsequent skin tests resulted in immediate skin reactions and allergic pulmonary responses to pyrethrum, but not to other ingredients in the

insecticide. Signs of respiratory irritation, such as shortness of breath, cough, and congestion, were reported among five office workers, commencing upon entry into a building that had been treated for termites 2 days previously with a cypermethrin formulation that contained xylene-based aromatic petroleum solvents, trimethylbenzene, and paraffinic oils (Lessenger 1992). Symptoms worsened after the air-conditioning system was activated in an attempt to clear the air. It was determined that a portion of the insecticide had been injected into ventilation ducts. The possible influence of inert ingredients was not evaluated. Among 12 workers who sprayed lambda-cyhalothrin indoors, daily interviews following spraying on each of 6 consecutive days revealed 11 complaints of nasal irritation and 6 complaints of throat irritation (Moretto 1991). Coughing, dyspnea, increased nasal secretions, and sneezing were reported by plant nursery workers who used pyrethroids for treating conifer seedlings (Kolmodin-Hedman et al. 1982). Sniffles and sneezes were noted in subjects exposed to deltamethrin and fenvalerate while packaging the insecticides (He et al. 1988).

Signs of respiratory irritation were reported in laboratory animals acutely exposed to aerosols of pyrethroids at lethal or near-lethal airborne concentrations (Curry and Bennett 1985; Flucke and Thyssen 1980; Hext 1987; Pauluhn and Thyssen 1982). Intermediate-duration (90-day) repeated exposures of rats to mean analytical pyrethrin concentrations $\geq$30 mg/m$^3$ resulted in clinical and microscopic evidence of respiratory irritation; a no-effect level was 11 mg/m$^3$ (Schoenig 1995). More detailed information regarding respiratory effects was not available in the report.

**Hematological Effects.** In studies available for review, no information was located regarding hematological effects in humans following inhalation exposure to pyrethrins or pyrethroids. Available information regarding adverse hematological effects in animals is limited to a single account in which anemia was indicated in rats repeatedly exposed to pyrethrins at mean analytical airborne concentrations $\geq$30 mg/m$^3$ for 90 days (Schoenig 1995). More detailed information regarding hematological effects was not available in the report.

**Hepatic Effects.** In studies available for review, no information was located regarding hepatic effects in humans following inhalation exposure to pyrethrins or pyrethroids. Available information regarding hepatic effects in animals is limited to a single account in which increased liver weights were reported in rats repeatedly exposed to pyrethrins at a mean analytical airborne concentration of 356 mg/m$^3$ for 90 days (Schoenig 1995).

**Body Weight Effects.** No information was located regarding body weight effects in humans following inhalation exposure to pyrethrins or pyrethroids. Available information regarding body weight effects in animals is limited. Decreased body weight gains were reported in rats repeatedly exposed to pyrethrins at mean analytical airborne concentrations $\geq$100 mg/m$^3$ for 90 days (Schoenig 1995).

### 3.2.1.3 Immunological and Lymphoreticular Effects

Hypersensitivity pneumonitis, characterized by pleuritic chest pain, nonproductive cough, and shortness of breath, was diagnosed in a 24-year-old woman who was hospitalized for 2 weeks following repeated indoor use of a pyrethrum-based insecticide (Carlson and Villaveces 1977). In this patient, levels of antibodies IgG, IgM, and IgE were all elevated. Symptomatic treatment was employed, and a week after discharge, a pulmonary challenge test to the insecticide resulted in an itchy and runny nose within 2 minutes following initiation of exposure, but no cough or shortness of breath. Subsequent skin tests resulted in immediate skin reactions and allergic pulmonary response to pyrethrum, but not to other ingredients in the insecticide. In a review of literature pertaining to pyrethrum (Moore 1975), it was noted that many individuals who were sensitive to ragweed were also sensitive to pyrethrum, but that the sensitization effect arose mainly from a volatile oil contained in the pyrethrum extract, not from the pyrethrins. On the other hand, pyrethrins were implicated in two cases of severe asthmatic reactions to exposure to dog shampoo products containing pyrethrins (Wagner 2000; Wax and Hoffman 1994). A 45-year-old female animal keeper, who was suspected to be suffering from pesticide intoxication, indicated that she had been exposed to pyrethroid insecticides over a period of 13 years (Mitsche et al. 2000). Upon skin (scratch) testing, dose-dependent allergic responses (wheals and flares) were elicited from the Type I pyrethroids, S-bioallethrin and permethrin.

No animal studies were located in which inhalation exposure to pyrethrins or pyrethroids could be associated with immunological or lymphoreticular effects.

### 3.2.1.4 Neurological Effects

Shortness of breath, nausea, headache, and irritability were experienced by five office workers upon entering their work area 2 days after it had been sprayed with cypermethrin in an effort to eliminate termites (Lessenger 1992). The symptoms were exacerbated when the air-conditioning system was

activated to ventilate the area, but levels of cypermethrin in the air were not measured. Signs of neurotoxicity have been associated with acute occupational (inhalation and dermal) exposure to various pyrethroids during outdoor or indoor spraying (Chen et al. 1991; He et al. 1991; Moretto 1991; Shujie et al. 1988; Zhang et al. 1991). In a cross-sectional survey on the prevalence of acute pyrethroid poisoning of cotton workers conducted in China in 1987 and 1988 (Chen et al. 1991), approximately 27% (696 of 2,588) of the workers who sprayed pure pyrethroids reported having experienced symptoms such as abnormal facial sensations (paresthesia), dizziness, headache, nausea, loss of appetite, blurred vision, and tightness of the chest. Eight of these workers were diagnosed with mild acute pyrethroid poisoning, characterized in part by listlessness and muscular fasciculations. He et al. (1991) reported increased peripheral nerve excitability in cotton workers following 3 days of exposure to deltamethrin during spraying. Nerve excitability was assessed by presenting two sequential electrical stimuli of equal intensity and duration to the median nerve area of the wrist and recording the median nerve activity at the lateral side of the elbow. Following deltamethrin exposure, median nerve conduction measurements revealed a significant increase in the supernormal period, defined as a period after recovery of normal excitability (from a given action potential) during which an action potential induced by a second stimulus is higher in amplitude than the first action potential. In some of these studies, air concentrations of pyrethroids in the breathing zone of the sprayers were measured and ranged from approximately 0.005 to 2.0 $\mu g/m^3$. However, one study reported air concentrations as high as 24 $\mu g/m^3$ (Shujie et al. 1988). Among sprayers, dermal contact was considered to be the major source of exposure, although some of the sprayers also reported symptoms of nasal and laryngeal irritation (Moretto 1991). Facial paresthesia, dizziness, fatigue, miliary red facial papules, and sniffles and sneezes were noted in subjects exposed to deltamethrin and fenvalerate while packaging the insecticides (He et al. 1988). Air sampling indicated pyrethroid levels in the range of 0.005–0.055 $mg/m^3$, but dermal contact was also evident, and may have been the basis for increased signs of toxicity during summer months.

In studies of acute lethality associated with inhalation exposure to pyrethrins or pyrethroids, neurological effects were observed at or near lethal exposure levels. However, most studies do not include dose-response data for exposure levels much lower than those resulting in death. Tremors were observed in rats acutely exposed to pyrethrins at mean analytical airborne concentrations $\geq$2,100 $mg/m^3$, but not at a concentration of 690 $mg/m^3$ (Schoenig 1995). Acute exposure of rats to aerosols of a 13% formulation of cyhalothrin, at analytical concentrations ranging from 3.6 to 68 $mg/m^3$, resulted in dose-related increasing severity of neurological signs, ranging from temporary lethargy, abnormal posture, and salivation at the lowest concentration, to convulsions and death within 15 minutes postexposure at the highest concentration (Curry and Bennett 1985). Disturbed posture and abnormal motor activity were observed

in rats exposed to aerosols of cyfluthrin for 4 hours at an analytical concentration of 17 mg/m$^3$, the lowest level presented. A concentration of 735 mg/m$^3$, which was lethal to many of the rats, caused severe behavioral disturbances in surviving rats that continued for 3 days postexposure (Pauluhn and Thyssen 1982). A group of female rats exhibited no signs of toxicity in response to acute exposure to cyfluthrin at an analytical concentration of 44 mg/m$^3$ (Flucke and Thyssen 1980). Both male and female rats, similarly exposed to a concentration of 57 mg cyfluthrin/m$^3$, showed signs of restlessness and altered gait. Labored breathing, hyperactivity, and tremors were reported in rats repeatedly exposed (6 hours/day, 5 days/week for 90 days) to pyrethrins at a mean airborne concentration of 356 mg/m$^3$ (Schoenig 1995). Repeated 6-hour inhalation exposures to atmospheres containing cyfluthrin concentrations of 10.5 mg/m$^3$ or higher resulted in dose-related unspecified clinical signs of behavioral disorders (Flucke and Thyssen 1980; Thyssen 1980). Occasional salivation was observed in rats repeatedly exposed to atmospheres of cypermethrin at a concentration of 50 mg/m$^3$; a concentration of 250 mg/m$^3$ resulted in additional signs of neurotoxicity that included decreased activity, lacrymation, head and paw flicking, and tip toe gait (EPA 1996).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

No reports were located regarding the following health effects in humans or animals following inhalation exposure to pyrethrins or pyrethroids:

#### 3.2.1.5 Reproductive Effects

#### 3.2.1.6 Developmental Effects

#### 3.2.1.7 Cancer

### 3.2.2 Oral Exposure

#### 3.2.2.1 Death

Among 573 cases of acute pyrethroid poisoning reported in China between 1983 and 1988, 344 cases with accidental poisoning were considered to have been largely due to ingestion of pyrethroids (He et al. 1989). Four deaths were reported; two of these were related to occupational exposure. Peter et al. (1996)

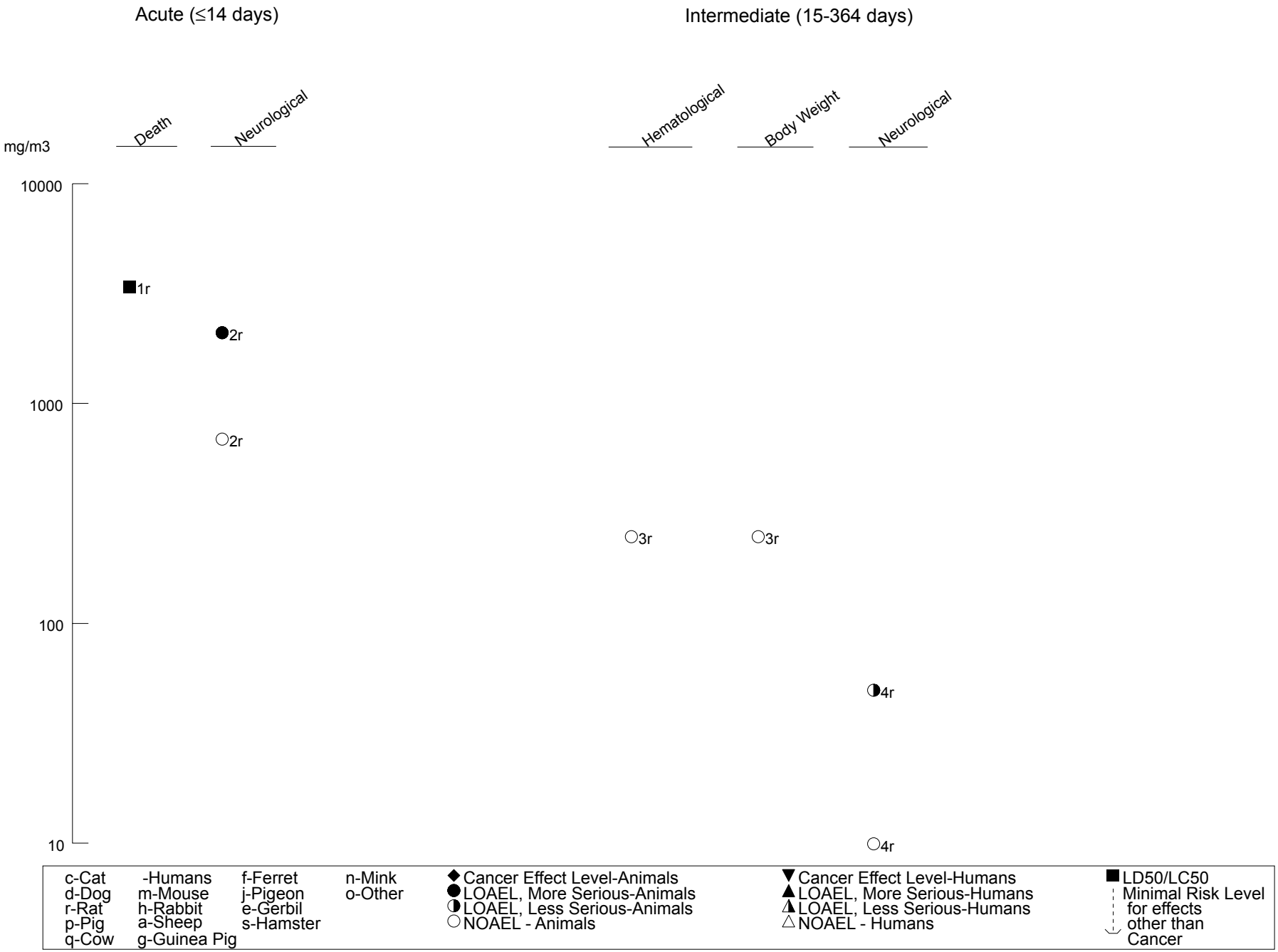
**Table 3-1 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Inhalation**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/m³) | LOAEL Less Serious (mg/m³) | LOAEL Serious (mg/m³) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **ACUTE EXPOSURE** | | | | | | |
| | **Death** | | | | | | |
| 1 | Rat (CD) | 1x 4 hr | | | | 3400 (LC50) | Schoenig 1995 Pyrethrum extract |
| | **Neurological** | | | | | | |
| 2 | Rat (CD) | 1x 4 hr | | | | 2100 (tremors) | Schoenig 1995 Pyrethrum extract |
| | | | | 690 | | | |
| | **INTERMEDIATE EXPOSURE** | | | | | | |
| | **Systemic** | | | | | | |
| 3 | Rat (Wistar) | 21 d 6 hr/d, 5 d/wk (nose-only) | Hemato | 250 | | | EPA 1996 Cypermethrin 1:1 cis:trans |
| | | | Bd Wt | 250 | | | |
| | **Neurological** | | | | | | |
| 4 | Rat (Wistar) | 21 d 6 hr/d, 5 d/wk (nose-only) | | 10 | 50 (salivation) | | EPA 1996 Cypermethrin 1:1 cis:trans |

a The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; d = day(s); Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; x = time(s); wk = week(s)

Figure 3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - inhalation



reported the death of a 30-year-old male approximately 2 days after he had consumed about 30 mL of deltamethrin. In another case, an adult male rapidly developed convulsions, became comatose, and died shortly after having accidentally ingested an unknown amount of 10% cypermethrin (Poulos et al. 1982). No other information was located regarding death in humans following oral exposure to pyrethrins or pyrethroids.

Animal studies associate mortality with relatively high oral exposure to pyrethrins and pyrethroids. Acute oral $LD_{50}$ values for total pyrethrins from undiluted pyrethrum extract were 2,370 and 1,030 mg/kg in male and female rats, respectively (Schoenig 1995). Acute oral $LD_{50}$ values for pyrethroids in rats range from approximately 18 to >5,000 mg/kg (Casida et al. 1983; Metcalf 1995; Valentine 1990). The wide range in $LD_{50}$ values is dependent on a number of factors including specific pyrethroid, ratios of stereo and optical isomers within a given pyrethroid formulation, and vehicle. For example, an acute oral $LD_{50}$ value of 3,801 mg/kg was reported for rats receiving a gavage dose of permethrin (45/55 cis/trans) neat, whereas the $LD_{50}$ value was 584 mg/kg when the dose was administered in corn oil vehicle (DOD 1977). Acute oral $LD_{50}$ values are generally lower in Type II than Type I pyrethroids, indicating a greater degree of toxicity for Type II pyrethroids. Pyrethroid-induced mortality appears to be influenced by ambient temperature. Acute oral $LD_{50}$ values for cismethrin in female rats increased from 157 mg/kg at 4°C to 197 mg/kg at 20°C and >1,000 mg/kg at 30°C (White et al. 1976). In a 4-week oral study, mortality was observed in rats after 3–5 days of daily oral administration of cyfluthrin at a dose level of 80 mg/kg/day (Flucke and Schilde 1980). In mice, repeated administration of fenvalerate, at a dose level of 80 mg/kg/day, also resulted in mortality that was considered to be compound related (Cabral and Galendo 1990). In 90-day oral studies, compound-related death was noted in rats and mice given diets containing pyrethrins at concentrations ≥10,000 ppm (800 and 1,900 mg/kg/day for rats and mice, respectively) (Schoenig 1995). Compound-related mortality was also reported in pregnant rats and rabbits repeatedly administered oral doses of pyrethrins (in 0.5% methyl cellulose) ≥150 and 600 mg/kg/day, respectively (Schoenig 1995). Three of four dogs died during an 8-week oral study in which pyrethrins were administered in the diet at a concentration of 6,000 ppm (approximate dose of 100 mg/kg/day) (Schoenig 1995). One of six dogs, administered 1,000 ppm of fenvalerate in the diet (approximate dose of 80 mg/kg/day), was euthanized *in extremis* during week 24 after exhibiting signs of extreme neurotoxicity (Parker et al. 1984b). One of six dogs, given daily oral doses of cyhalothrin at 3.5 mg/kg, was killed during week 46 of a 52-week oral dosing study, due to persistent pyrethroid-induced convulsions (Hext et al. 1986). Mortality was also observed during a 90-day oral exposure to permethrin in the diets of rats (DOD 1977). All 10 male and female rats in the projected 850 mg/kg/day exposure groups died during the study; actual doses were 505 and 870 mg/kg/day in males and females, respectively. Mortality was

not significantly increased in rats or mice administered permethrin in the diet at concentrations resulting in estimated daily doses of up to 104 mg/kg/day for 2 years in rats or 350 mg/kg/day for 98 weeks in mice (Ishmael and Litchfield 1988).

Selected oral $LD_{50}$ values for some pyrethroids are recorded in Table 3-2 and plotted in Figure 3-2.

#### 3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

No reports were located regarding respiratory, cardiovascular, musculoskeletal, dermal, or ocular effects following oral exposure of humans or animals to pyrethrins or pyrethroids.

**Gastrointestinal Effects.** Information regarding gastrointestinal effects following oral exposure is mainly limited to clinical signs following exposure to pyrethroids. Symptoms such as epigastric pain, nausea, vomiting, and diarrhea have been reported in human subjects who consumed relatively large quantities of pyrethroids (Gotoh et al. 1998; He et al. 1989). Diarrhea was reported in dogs ingesting pyrethroids in the diet at dose levels as low as 1–6 mg/kg/day for treatment periods ranging from 13 weeks to 1 year (EPA 1981; IRIS 2003a, 2003b, 2003c). Gastritis and mucosal erosion and ulceration were observed in male mice fed esfenvalerate in the diet for 90 days at a concentration resulting in a mean dose of 106 mg/kg/day (EPA 1991a).

**Hematological Effects.** Information regarding hematological effects following oral exposure is limited. Leukocytosis was observed in 15% of 235 human cases of pyrethroid poisoning in which blood tests were performed (He et al. 1989). In most animal studies that examined hematological end points, no significant alterations were observed. However, Shakoori et al. (1992a) reported significantly decreased red blood cell count, hemoglobin content, and mean corpuscular hemoglobin, as well as increased white blood cell count in rabbits following daily oral administration of fenvalerate at a dose level of 10 mg/kg for 7 days. Schoenig (1995) reported evidence of anemia in surviving dogs that were fed pyrethrins in the diet for 8 weeks at a concentration resulting in a dose level of approximately 100 mg/kg/day. Decreases in red blood cell counts, hemoglobin, and hematocrit were observed in male and female mice fed esfenvalerate in the diet for 90 days at a concentration resulting in mean doses of 106 and 113 mg/kg/day,

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **ACUTE EXPOSURE** | | | | | | |
| | **Death** | | | | | | |
| 1 | Rat (NS) | once (GO) | | | | 413 F (LD50) | DOD 1977 Permethrin (45/55 cis/trans) |
| 2 | Rat (Sprague-Dawley) | once (G) | | | | 3801 F (LD50) | DOD 1977 Permethrin (45/55 cis/trans) |
| 3 | Rat (Sprague-Dawley) | once (GO) | | | | 383 M (LD50) | DOD 1977 Permethrin (45/55 cis/trans) |
| 4 | Rat (Long-Evans) | once (G) | | | | 4892 M (LD50)<br>2712[b] F (LD50) | DOD 1977 Permethrin (45/55 cis/trans) |
| 5 | Rat (Sprague-Dawley) | once (GO) | | | | 584 M (LD50) | DOD 1977 Permethrin (45/55 cis/trans) |
| 6 | Rat (Sprague-Dawley) | 14 d (F) | | | | 699[b] M (death in 6/6)<br>769 F (death in 5/6) | DOD 1977 Permethrin (45/55 cis/trans) |
| 7 | Rat (Long-Evans) | 14 d (F) | | | | 515 F (death in 3/6 in first 5 days) | DOD 1977 Permethrin (45/55 cis/trans) |
| 8 | Rat (CD) | once 4 hr (NS) | | | | 2370 M (LD50)<br>1030[b] F (LD50) | Schoenig 1995 Pyrethrum extract |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **Systemic** | | | | | | |
| **9** | Rat (Long-Evans) | 14 d (F) | Hepatic | | 218 F (increased liver-to-body weight ratio) | | DOD 1977 Permethrin (45/55 cis/trans) |
| **10** | Rat (Sprague-Dawley) | 14 d (F) | Hepatic | 186[b] M<br>210 F | 379 M (increased liver-to-body weight ratio) | 369[b] F (increased liver-to-body weight ratio) | DOD 1977 Permethrin (45/55 cis/trans) |
| **11** | Rat (Sprague-Dawley) | Gd 6-15 1x/d (GO) | Bd Wt | 40 F | 80 F (suppressed maternal body weight gain, 33% lower than controls) | | EPA 1994a Resmethrin |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **Neurological** | | | | | | |
| **12** | Rat (Sprague-Dawley) | 14 d (F) | | 186[b] M<br>210 F | | 379 M (muscle tremors)<br>369[b] F (muscle tremors) | DOD 1977<br>Permethrin (45/55 cis/trans) |
| **13** | Rat (Long-Evans) | 14 d (F) | | 92[b] M<br>114 F | | 185[b] M (muscle tremors)<br>218 F (muscle tremors) | DOD 1977<br>Permethrin (45/55 cis/trans) |
| **14** | Rat (CD) | Gd 6-15 1x/d (G) | | 75 F | | | EPA 1988c<br>Pyrethrum extract |
| **15** | Rat (CD) | Gd 6-15 1x/d (G) | | 37.5 F | | 75 F (transient tremors 2/5 dams) | EPA 1988c<br>Pyrethrum extract |
| **16** | Rat (Wistar) | Gd 7-16 1X/d (GO) | | 150 | | | EPA 1991b<br>Permethrin (40/60 cis/trans) |
| **17** | Rat (Wistar) | Gd 7-16 1X/d (GO) | | 50 F | | 150 F (tremors, head flicking, piloerection) | EPA 1991b<br>Permethrin (40/60 cis/trans) |
| **18** | Rat (Sprague-Dawley) | once (GO) | | 5 | | 20 (tremors, salivation, ataxia) | EPA 1992b<br>Esfenvalerate |
| **19** | Rat (Sprague-Dawley) | Gd 6-15 1x/d (GO) | | 80 F | | | EPA 1994a<br>Resmethrin |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **20** | Rat (Long-Evans) | once (GO) | | 25[c] | | 75 (abnormal motor movements, decreased grip strength) | McDaniel and Moser 1993 Permethrin 50:50 cis:trans |
| **21** | Rat (Long-Evans) | once (GO) | | | 20[d] (altered gait, decreased activity) | | McDaniel and Moser 1993 Cypermethrin 50:50 cis:trans |
| **22** | Rat (CD) | once (NS) | | 710 M[b] 320 F | | | Schoenig 1995 Pyrethrum extract |
| **23** | Rabbit (New Zealand) | Gd 7-19 1x/d (G) | | 25 F | 100 F (salivation, head arching, labored breathing in 1/16 does) | | EPA 1988c Pyrethrum extract |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **Neurological** | | | | | | |
| **24** | Rabbit (New Zealand) | Gd 7-19 1x/d (G) | | 150 F | | 300 F (tremors in 1/5 does, 11% weight loss) | EPA 1988c Pyrethrum extract |
| | **Developmental** | | | | | | |
| **25** | Rat (CD) | Gd 6-15 1x/d (G) | | 75 | | | EPA 1988c Pyrethrum extract |
| **26** | Rat (CD) | Gd 6-15 1x/d (G) | | 150 | | | EPA 1988c Pyrethrum extract |
| **27** | Rat (Wistar) | Gd 7-16 1X/d (GO) | | 150 | | | EPA 1991b Permethrin (40/60 cis/trans) |
| **28** | Rat (Beagle) | Gd 6-15 1x/d (GO) | | 40 | 80 (slightly increased incidences of skeletal variations, delayed ossification) | | EPA 1994a Resmethrin |
| **29** | Rabbit (New Zealand) | Gd 7-19 1x/d (G) | | 150 | | | EPA 1988c Pyrethrum extract |
| | **INTERMEDIATE EXPOSURE** | | | | | | |
| | **Death** | | | | | | |
| **30** | Rat (Sprague-Dawley) | 90 d (F) | | | | 505[b] M (death in 10/10)<br>870 F (death in 10/10) | DOD 1977 Permethrin (45/55 cis/trans) |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **Systemic** | | | | | | |
| **31** | Rat (Sprague-Dawley) | 90 d (F) | Hepatic | 73.6[b] M<br>76.3 F | 243.5[b] M (increased liver-to-body weight ratio)<br>250.7 F (increased liver-to-body weight ratio) | | DOD 1977<br>Permethrin (45/55 cis/trans) |
| **32** | Rat (Wistar) | 28 d (F) | Bd Wt | 1 F | | | EPA 1985a<br>Cyhalothrin |
| **33** | Rat (Wistar) | 90 d (F) | Ocular | 21.2 M | | | EPA 1985b<br>Cyhalothrin |
| | | | Bd Wt | 5.4 M | 21.2 M (depressed body weight, 10-16%) | | |
| **34** | Rat (CD) | Gd 6-15 1x/d (GO) | Bd Wt | 15 F | | | EPA 1986a<br>Cyhalothrin |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **Systemic** | | | | | | |
| **35** | Rat (Wistar) | continuous | Bd Wt | 9.2 M[b]<br>10.3 F | | | EPA 1986b<br>Cyhalothrin |
| **36** | Rat (Sprague-Dawley) | 13 wk (F) | Bd Wt | 150.35 M[b]<br>189.66 F | | | EPA 1994b<br>Permethrin 50:50 cis:trans |
| **37** | Mouse (B6C3F1) | 90 d (F) | Gastro | 30.5 M[b]<br>113 F | 106 M (mucosal erosion and ulceration, gastritis) | | EPA 1991a<br>Esfenvalerate |
| | | | Hemato | 30.5 M[b]<br>36.8 F | 106 M[b] (decreased RBCs, hemoglobin, hematocrit)<br>113 F (decreased RBCs, hemoglobin, hematocrit) | | |
| | | | Dermal | 30.5 M[b]<br>36.8 F | 106 M[b] (dermatitis, hyperkeratosis, ulceration)<br>113 F (dermatitis, hyperkeratosis, ulceration) | | |
| | | | Bd Wt | 30.5 M[b]<br>36.8 F | 106 M[b] (50% suppressed body weight gain)<br>113 F (35% suppressed body weight gain) | | |
| **38** | Dog (Beagle) | 26 wk 1x/d (C) | Gastro | 1[e] | 2.5 (diarrhea) | | EPA 1981<br>Cyhalothrin |
| | | | Ocular | 10 | | | |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | | | Bd Wt | 10 | | | |
| | **Neurological** | | | | | | |
| **39** | Rat (CD) | >120 d continuous (F) | | | 27 (hypersensitivity to sound) | | EPA 1992c Cypermethrin |
| **40** | Rat (CD) | 2 gen continuous (F) | | 70.8 | | | EPA 1994a Resmethrin |
| **41** | Rat (Sprague-Dawley) | 13 wk (F) | | 15.49[f] M<br>18.66 F | | 91.51[b] M (tremors, staggered gait, hindlimb splay)<br>111.37 F (tremors, staggered gait, hindlimb splay) | EPA 1994b Permethrin 50:50 cis:trans |
| **42** | Mouse (B6C3F1) | 90 d (F) | | 30.5[b] M<br>36.8 F | | 106[b] M (tremors, staggered gait, hindlimb splay)<br>113 F (multiple signs including tremors, convulsions, abnormal gait) | EPA 1991a Esfenvalerate |
| **43** | Dog (Beagle) | 26 wk 1x/d (C) | | 2.5 | | 10 (muscle tremors, incoordination) | EPA 1981 Cyhalothrin |

[a] Key to figure

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **Reproductive** | | | | | | |
| **44** | Rat (albino) | 65 d 1x/d (GW) | | | | 1 M (50% reduction in successful impregnation) | Abd El-Aziz et al. 1994 Deltamethrin |
| **45** | Rat (Wistar) | continuous | | 9.2 M[b] 10.3 F | | | EPA 1986b Cyhalothrin |
| **46** | Rat (CD) | continuous (F) | | 45 | | | EPA 1992c Cypermethrin |
| **47** | Rat (CD) | 2 gen continuous (F) | | 70.8 | | | EPA 1994a Resmethrin |
| | **Developmental** | | | | | | |
| **48** | Rat (CD) | Gd 6-15 1x/d (GO) | | 15 | | | EPA 1986a Cyhalothrin |
| **49** | Rat (CD) | 2 gen continuous (F) | | 34.8 | | 70.8 (decreased pup survival) | EPA 1994a Resmethrin |
| **50** | Rat (Wistar) | Gd 4-21 Ld 1-21 1x/day (GO) | | | 10 (increased levels of dopamine and muscarinic receptors in striatal membrane) | | Malaviya et al. 1993 Fenvalerate |
| **51** | Rat (Wistar) | Gd 4-21 Ld 1-21 1x/day (GO) | | | 15 (increased levels of dopamine and muscarinic receptors in striatal membrane) | | Malaviya et al. 1993 Cypermethrin |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| **52** | Rat (Wistar) | Gd 4-21 1x/day (GO) | | | 15 (increased levels of muscarinic receptors in striatal membrane) | | Malaviya et al. 1993 Cypermethrin |
| **53** | Rat (Wistar) | Gd 4-21 1x/day (GO) | | | 10 (decreased levels of dopamine receptors in striatal membrane) | | Malaviya et al. 1993 Fenvalerate |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **CHRONIC EXPOSURE** | | | | | | |
| | **Systemic** | | | | | | |
| 54 | Rat (Alpk/AP) | 2 yr (F) | Hemato | 21.5[b] M<br>23.1 F | | | EPA 1985c<br>Cyhalothrin |
| | | | Ocular | 21.5[b] M<br>23.1 F | | | |
| | | | Bd Wt | 21.5 M<br>4.6[b] F | 23.1 F (decreased body weight, 12.5%) | | |
| 55 | Rat (CD) | 2 yr (F) | Hemato | 130[b] M<br>173 F | | | EPA 1994c<br>Pyrethrum extract |
| | | | Hepatic | 130[b] M<br>173 F | | | |
| | | | Ocular | 130[b] M<br>173 F | | | |
| 56 | Mouse (CD-1) | 2 yr (F) | Bd Wt | 51 F | | | EPA 1985d<br>Cyhalothrin |
| 57 | Mouse (CD-1) | 18 mo (F) | Hepatic | 13.8[b] M<br>16.6 F | 346[b] M (hepatic effects including increased liver weight, discoloration, vacuolar fatty changes)<br>413 F (liver effects including increased liver weight, discoloration) | | EPA 1994c<br>Pyrethrum extract |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | | | Bd Wt | 686[b] M | | | |
| | | | | 834 F | | | |
| **58** | Mouse (CD-1) | 85 wk (F) | Cardio | 137.9[b] M | | | EPA 1994d Resmethrin |
| | | | | 165.8 F | | | |
| | | | Gastro | 137.9[b] M | | | |
| | | | | 165.8 F | | | |
| | | | Hepatic | 137.9[b] M | | | |
| | | | | 165.8 F | | | |
| | | | Renal | 137.9[b] M | | | |
| | | | | 165.8 F | | | |
| | | | Bd Wt | 137.9[b] M | | | |
| | | | | 165.8 F | | | |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **Neurological** | | | | | | |
| **59** | Rat (CD) | 2 yr (F) | | [b]130 M<br>173 F | | | EPA 1994c<br>Pyrethrum extract |
| **60** | Rat (Wistar) | 2 yr (F) | | [b]37.5 M<br>40.2 F | | [b]187.2 M (slight whole body tremors during first 2 weeks)<br>200.1 F (slight whole body tremors during first 2 weeks) | Ishmael and Litchfield 1988<br>Permethrin (40/60 cis/trans) |
| **61** | Rat (Sprague-Dawley) | 104 wk (F) | | [b]17 M<br>20 F | | 70 M (abnormal gait, muscular incoordination) | Parker et al. 1984a<br>Fenvalerate |
| **62** | Mouse (CD-1) | 2 yr (F) | | 57.6 M<br>[b]51 F | | | EPA 1985d<br>Cyhalothrin |
| **63** | Mouse (CD-1) | 18 mo (F) | | [b]686 M<br>834 F | | | EPA 1994c<br>Pyrethrum extract |
| **64** | Mouse (CD-1) | 85 wk (F) | | [b]137.9 M<br>165.8 F | | | EPA 1994d<br>Resmethrin |
| **65** | Mouse (Swiss) | 2 yr (F) | | [b]295.1 M<br>348.1 F | | | Ishmael and Litchfield 1988<br>Permethrin (40/60 cis/trans) |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | | Reference Chemical Form |
|---|---|---|---|---|---|---|---|---|
| **66** | Dog (Beagle) | 1 yr (C) | | 100 | | 1000 | (tremors, incoordinated gait, convulsions, excessive salivation) | EPA 1983 Permethrin (40/60 cis/trans) |
| **67** | Dog (Beagle) | 1 yr (F) | | 5 | | | | EPA 1987 Esfenvalerate |
| **68** | Dog (Beagle) | 52 wk 1x/d (GO) | | 0.5 | | 3.5 | (muscle tremors, ataxia) | Hext et al. 1986 Cyhalothrin |
| **69** | Dog (Beagle) | 52 wk | | 5 | | 15 | (tremors, gait abnormalities, incoordination, disorientation, hypersensitivity to sound) | IRIS 2003a Cypermethrin |

**Table 3-2 Levels of Significant Exposure to Pyrethrins And Pyrethroids - Oral (continued)**

| Key to figure[a] | Species (Strain) | Exposure/ Duration/ Frequency (Specific Route) | System | NOAEL (mg/kg/day) | LOAEL Less Serious (mg/kg/day) | LOAEL Serious (mg/kg/day) | Reference Chemical Form |
|---|---|---|---|---|---|---|---|
| | **Cancer** | | | | | | |
| **70** | Rat (CD) | 2 yr (F) | | | | 42.9[b] M (CEL: thyroid follicular cell adenomas)<br>173 F (thyroid and liver tumors) | EPA 1994c<br>Pyrethrum extract |

a The number corresponds to entries in Figure 3-2.

b Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effects for the most sensitive gender are presented.

c Used to derive an acute-duration oral minimal risk level (MRL) of 0.3 mg/kg/day for permethrin (95% purity; 50/50 cis/trans). The MRL was derived by dividing the NOAEL of 25 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intrahuman variation).

d Used to derive an acute-duration oral minimal risk level (MRL) of 0.02 mg/kg/day for cypermethrin (97% purity, 50/50 cis/trans, in corn oil vehicle). The MRL was derived by dividing the LOAEL of 20 mg/kg/day by an uncertainty factor of 1000 (10 for the use of a LOAEL, 10 for animal to human extrapolation and 10 for intrahuman variation).

e Used to derive both an acute- and intermediate-duration oral minimal risk level (MRL) of 0.01 mg/kg/day for cyhalothrin. The MRL was derived by dividing the NOAEL of 1 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intrahuman variation).

f Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.2 mg/kg/day for permethrin. The MRL was derived by dividing the NOAEL of 15.5 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for intrahuman variation).

B = both; Bd Wt = body weight; (C) = capsule; cardio = cardiovascular; d = day(s); (F) = feed; F = female; (G) = gavage; gastro = gastrointestinal; gen = generation; Gd = gestation day; (GO) = gavage in oil; (GW) = gavage in water; hemato = hematological; hr = hour(s); Ld = lactation day; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mg/kg/day = milligram per kilogram per day; mo = month(s); NOAEL = no-observed-adverse-effect level; (NS) = not specified; ppd = post-parturition day; wk = week(s); x = time; yr = year(s)

Figure 3-2. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral

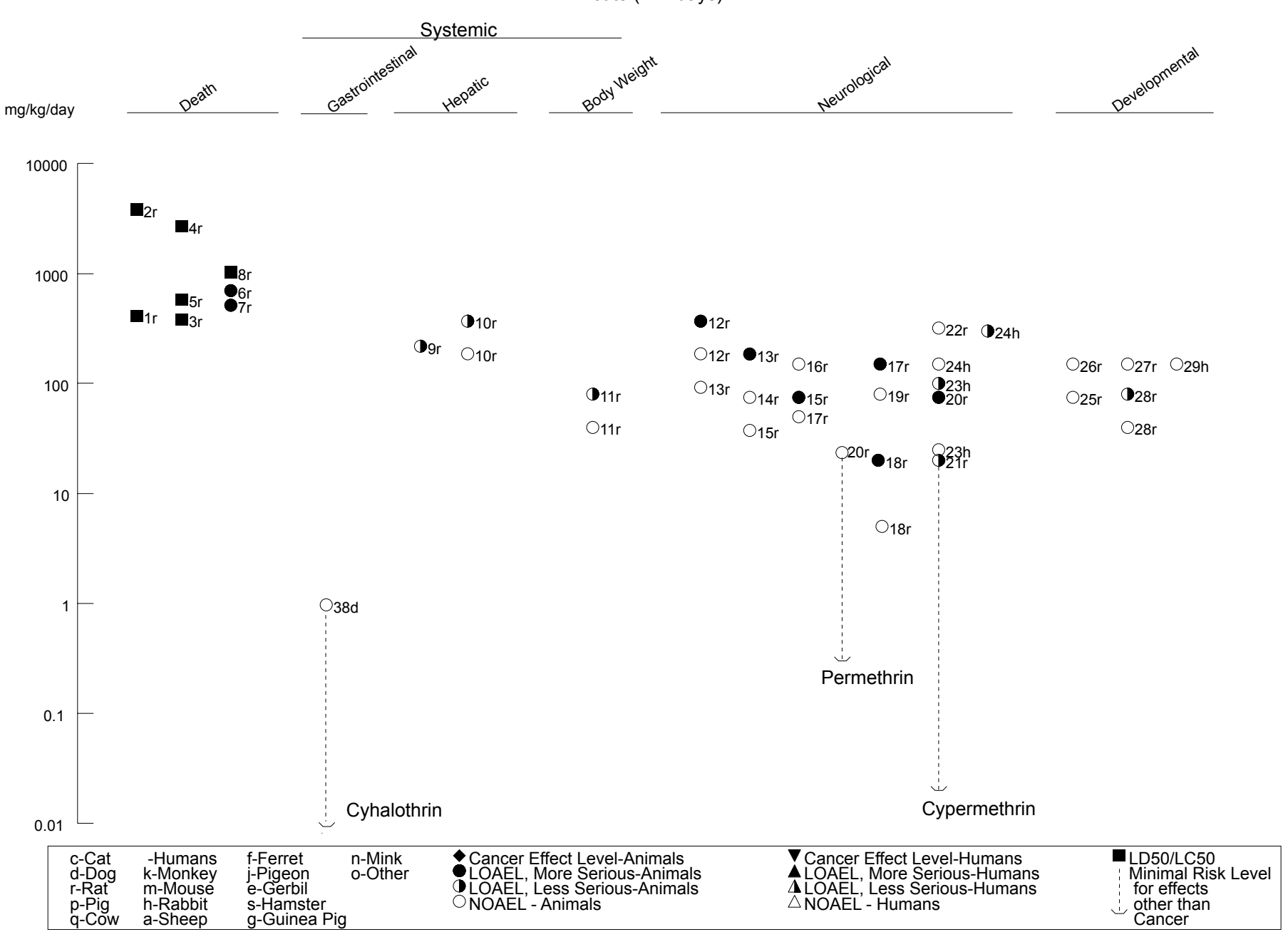


Figure 3-2. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral (*Continued*)

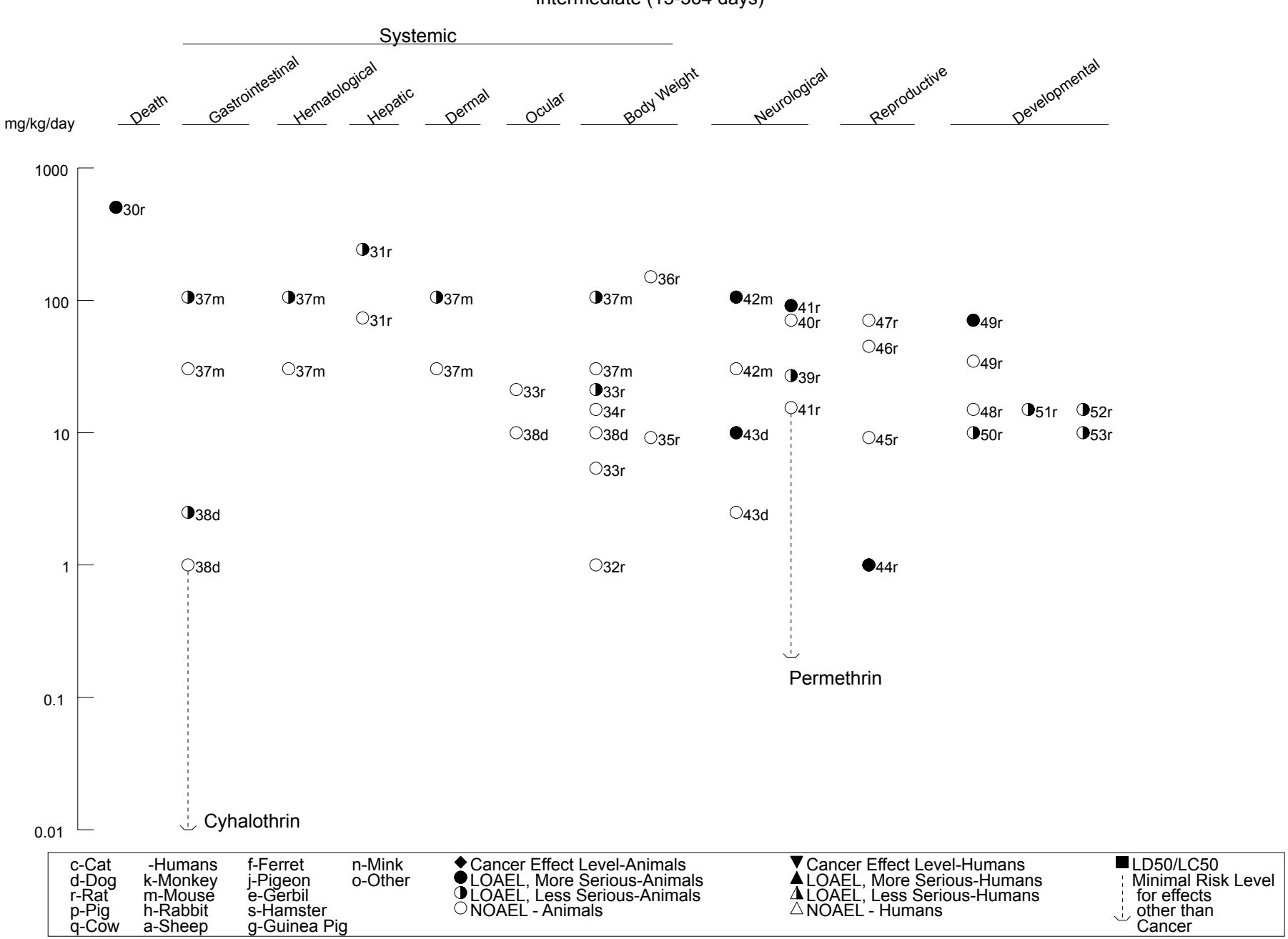
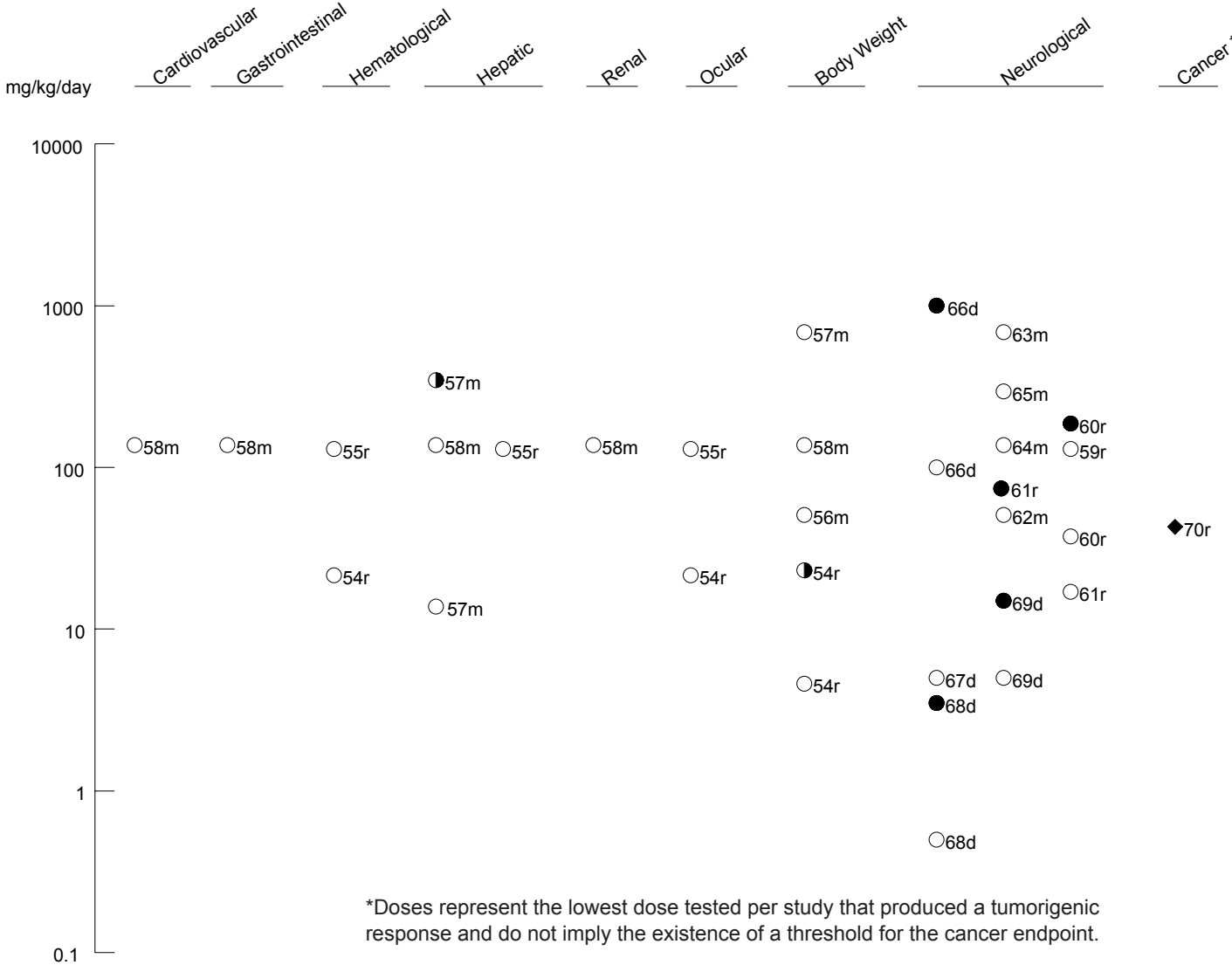


Figure 3-2. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral (*Continued*)

Chronic (≥365 days)



respectively (EPA 1991a). In a 6-month feeding study in dogs, decreased red blood cell counts and decreased hematocrit and hemoglobin were observed at a dietary concentration of fenpropathrin that resulted in a dose level of approximately 20 mg/kg/day (Parker et al. 1984b). Hematology and blood chemistry data from rats and mice, administered permethrin in the diet at concentrations resulting in estimated doses of up to 104 mg/kg/day for 2 years (rats) or 350 mg/kg/day for 98 weeks (mice), did not indicate significant treatment-related hematological effects (Ishmael and Litchfield 1988). Hematological effects were not seen in male or female rats fed cyhalothrin or pyrethrum extract in the diet for 2 years at concentrations resulting in cyhalothrin doses of 21.5 and 23.1 mg/kg/day (males and females, respectively) or total pyrethrin doses of 130 and 173 mg/kg/day (males and females, respectively) (EPA 1985c, 1994c).

In a number of oral animal studies that were performed for the pesticide industry and evaluated by the EPA, statistically significant hematological effects were attributed to adaptive responses rather than pyrethroid-induced hematotoxicity *per se*. However, treatment-related anemia was reported in mice treated for 90 days with esfenvalerate in the food, which resulted in doses of approximately 106–113 mg/kg/day (EPA 1991a).

**Hepatic Effects.** No studies were located regarding hepatic effects in humans following oral exposure to pyrethrins or pyrethroids. Some animal studies indicated increased liver weights, congestion, hepatocellular hypertrophy, and other microscopic signs of liver changes in laboratory animals during intermediate- and chronic-duration oral exposure to pyrethrins or pyrethroids, particularly at dose levels also resulting in clinical signs of neurotoxicity (Hext et al. 1986; IRIS 2003d, 2003e; Ishmael and Litchfield 1988; Parker et al. 1984a, 1984b; Schoenig 1995). Increased liver enzyme activity has also been observed in some animal studies (EPA 1985a, 1985b, 1994c; Schoenig 1995). These hepatic effects may reflect, at least in part, an adaptive response similar to that seen following exposure to many other xenobiotics (Ishmael and Litchfield 1988; Okuno et al. 1986a). Increased liver weight and liver discoloration were noted in mice fed pyrethrum extract in the diet for 18 months at concentrations resulting in doses of total pyrethrins of approximately 346 and 413 mg/kg/day in males and females, respectively. The male mice also exhibited vacuolar fatty liver changes (EPA 1994c).

**Renal Effects.** No studies were located regarding renal effects in humans following oral exposure to pyrethrins or pyrethroids. Available information regarding renal effects in animals is limited to a report of decreased kidney weights and tubular degeneration in rats consuming pyrethrins (from pyrethrum extract) in the diet at concentrations resulting in dose levels ≥320 mg/kg/day for 90 days (Schoenig

1995), and a report of a small decrease in kidney weight in male rats receiving permethrin in the diet at concentrations resulting in estimated daily doses of 19.4–91.5 mg/kg for 2 years (Ishmael and Litchfield 1988). However, the magnitude and statistical significance of these renal changes were not presented in these reports. In a 2-year feeding study reported by Sumitomo Chemical America, Inc., and summarized in IRIS (2003c), increased absolute and relative kidney weights were observed in male (but not female) rats fed fenpropathrin (in corn oil) at a dietary concentration of 600 ppm (calculated daily doses of 22.8 and 23.98 mg/kg for males and females, respectively).

**Endocrine Effects.** No studies were located regarding endocrine effects in humans following oral exposure to pyrethrins or pyrethroids. Limited data were available regarding endocrine effects in animals following oral exposure to pyrethroids. Serum levels of the thyroid hormones $T_3$ and $T_4$ were significantly decreased in mice administered fenvalerate at a dose level of 120 mg/kg/day for 15 days (Maiti and Kar 1998). Akhtar et al. (1996) reported similar effects in rats administered bifenthrin or lambda-cyhalothrin at daily oral dose levels of 0.5 mg/rat (approximately 0.75 mg/kg/day) and 0.2 mg/rat (approximately 2 mg/kg/day), respectively, for 21 days. Lambda-cyhalothrin treated rats also exhibited a significantly decreased serum $T_3/T_4$ ratio, relative to controls. In addition, both bifenthrin and lambda-cyhalothrin treatment resulted in significantly increased serum TSH levels, compared with control rats. The studies of Maiti and Kar (1998) and Akhtar et al. (1996) did not include dose-response information, nor were thyroid tissues examined. However, these studies indicate that pyrethroids may exert a direct or indirect influence on the thyroid. Pyrethroid-induced decreased plasma testosterone may also serve as an indication of potential for pyrethroid-mediated endocrine effects. Significantly reduced plasma testosterone levels were noted as early as day 14 in groups of male rats administered deltamethrin in oral doses of 1 or 2 mg/kg for 65 days, and remained lower than controls throughout 21 days of posttreatment observation (Abd El-Aziz et al. 1994). El-Khalek et al. (1999) observed significant decreases in plasma testosterone levels in rats administered cypermethrin in oral doses of 3.8 or 7.7 mg/kg/day for 65 days, also demonstrating that this effect lasted throughout 30 days of posttreatment observation. In a 2-year feeding study reported by Sumitomo Chemical America, Inc., and summarized in IRIS (2003c), absolute and relative pituitary weights were nearly doubled in male rats fed fenpropathrin (in corn oil) at a dietary concentration of 600 ppm (calculated daily dose of 22.8 mg/kg). Female rats of the 600 ppm group (calculated daily dose of 23.98 mg/kg) exhibited decreased absolute and relative ovary weights.

**Body Weight Effects.** No studies were located regarding body weight effects in humans following oral exposure to pyrethrins or pyrethroids. Reduced body weights or body weight gains were reported in some studies of laboratory animals administered pyrethrins (from pyrethrum extract) for intermediate or

chronic durations. For instance, decreased body weight gain and food consumption were observed in rats administered 3,000–20,000 ppm (total pyrethrins; approximately 320–1,600 mg/kg/day) in the diet for 90 days. Decreased body weight and food consumption were noted in dogs administered total pyrethrins at 6,000 ppm (approximately 100 mg/kg/day) in the diet for 8 weeks. Decreased body weight was also reported in rats administered total pyrethrins at 3,000 ppm (approximately 250 mg/kg/day) in the diet for 104 weeks. Weight loss was observed in rabbit does administered 600 mg total pyrethrins/kg/day on gestation days 7–19. In a 2-generation reproductive toxicity study involving dietary exposure, decreased body weights and food consumption were observed in $F_1$ parental rats that had been exposed to pyrethrins during fetal and neonatal development, as well as premating, mating, and gestation. The reports of Schoenig (1995) did not include more detailed descriptions of body weight effects at dose levels that also resulted in clinical signs of neurotoxicity (Ishmael and Litchfield 1988; Parker et al. 1984a; Schoenig 1995).

The EPA (IRIS 2003c) reviewed a report by Sumitomo Chemical America, Inc. in which slightly reduced weight gain was noted in dogs administered fenpropathrin in the diet at dose levels ≥500 ppm (12.5 mg/kg/day) for 3 months. Ishmael and Litchfield (1988) reported initial decreases in body weight gain in rats and mice administered permethrin at 2,500 ppm in the diet for 2 years (rats) or a lifetime (mice), in the absence of apparent changes in food consumption. Estimated daily doses of permethrin were 91.5 and 103.8 mg/kg/day for male and female rats, respectively, and 295.1 and 348.1 mg/kg/day for male and female mice, respectively, based on body weight and food consumption values presented. The decreased body weight gain was seen only during the first 6 weeks of treatment in rats and sporadically during the first 52 weeks of treatment in mice. Parker et al. (1984a) observed significant decreases in mean body weight gain among rats fed fenvalerate at 1,000 ppm in the diet (approximate doses of 70 and 80 mg/kg/day for males and females, respectively) from week 16 (males) and week 44 (females) through week 104. No treatment-related changes in food consumption were observed, and no treatment-related significant changes in body weight were seen in groups receiving ≤250 ppm of fenvalerate in the diet, relative to controls. Suppressed body weight gain was seen in male and female mice ingesting daily doses of esfenvalerate of 106 and 113 mg/kg, respectively, for 90 days (EPA 1991a). Female rats, administered cyhalothrin in the diet at a concentration resulting in a dose level of 23.1 mg/kg/day for 2 years, exhibited body weights that were 12.5% lower than controls (EPA 1985c).

### 3.2.2.3 Immunological and Lymphoreticular Effects

No reports were located in which immunological or lymphoreticular effects in humans could be specifically associated with oral exposure to pyrethrins or pyrethroids. See Section 3.2.1.3 for information regarding immunological effects in humans following exposures to pyrethrins or pyrethroids that were likely mixed (inhalation, dermal, and possibly oral).

Information on immunotoxicity of selected pyrethroids is available from oral studies in rats, mice, and rabbits repeatedly administered pyrethroids at doses low enough that clinical signs of neurotoxicity were not observed (Blaylock et al. 1995; Demian 1998; Demian and El-Sayed 1993; Dési et al. 1986; Lukowicz-Ratajczak and Krechniak 1992). Dési et al. (1986) conducted a series of studies in rats and rabbits. In rats, a single oral dose of cypermethrin at 125 mg/kg resulted in statistically significant changes, which included suppression of the humoral immune response, decreases in rosette-forming lymphocytes and ratio of lymphocytes to leukocytes, and decreased relative spleen weight. Although doses of cypermethrin at 6.25, 12.5, or 25 mg/kg/day for 6 or 12 weeks did not result in significant changes in relative spleen weight, a significantly reduced humoral immune response was observed at the 25 mg/kg/day dose level, and both the 12.5 and 25 mg/kg/day levels resulted in significant decreases in rosette-forming lymphocytes. Dose-dependent significant suppression of the humoral immune response in rabbits was observed by the end of week 1 of a study in which cypermethrin was administered orally to rabbits 5 days/week for 6 weeks at levels of 75, 150, or 300 mg/kg/day.

Lukowicz-Ratajczak and Krechniak (1992) administered deltamethrin to female mice in oral doses of 6 mg/kg/day for 84 days or 15 mg/kg/day for 14 days. Treatment at both dose levels resulted in significant immunosuppression of the humoral immune response and a significant decrease in enzyme activity in lymphocytes isolated from the lymph nodes and spleen. These effects occurred earlier in the treatment period in high-dose mice. Other signs of immunotoxicity included decreased numbers of splenic plaque-forming cells, decreased percentages of rosette-forming lymphocytes in lymph nodes and spleen, depressed cell-mediated immune response that was expressed as decreased swelling of the foot pad in response to deltramethrin exposure of mice previously immunized with sheep red blood cells, and decreased interleukin-1 activity.

Demian and coworkers (Demian 1998; Demian and El-Sayed 1993) demonstrated dose-related deltamethrin-induced suppression of the humoral immune response, decreased numbers of splenic plaque-forming cells and rosette-forming lymphocytes, decreased total serum protein (as well as alpha-1-,

alpha-2-, and gamma-globulins), and increased serum albumin content in male mice. Doses used by Demian and coworkers were described as being 0.1 and 0.2 of the oral $LD_{50}$ value, but this value was not identified in the reports.

Blaylock et al. (1995) assessed the immunotoxic potential of permethrin by examining immune responses of splenocytes from female mice that had been administered permethrin at 0–0.4 mg/kg/day (0–1% of the oral $LD_{50}$ value) for 10 days. At the highest dose tested (0.4 mg/kg/day), significantly reduced mixed lymphocyte responses, T-lymphocyte cytotoxic activity, and natural killer cell activity were observed in the absence of significant treatment-related changes in spleen weights. The toxicological significance of these findings is uncertain because the mice were not assessed for compromised immune function.

Severe leukopenia was observed in male rats orally administered cypermethrin at 40 mg/kg/day for 90 days (Varshneya et al. 1992). A delayed type skin hypersensitivity test, performed on day 61 (following intradermal injection of tuberculin on day 60), revealed 24 and 27% decreases in reactivity in the 20 and 40 mg/kg/day dose groups, respectively. Examination of organ weights revealed a significant decrease in relative spleen weight within the high-dose group. However, no definite treatment-induced effect was noticed in the humoral immune response. Madsen et al. (1996) reported increased numbers of antibody forming cells in the spleen and enhanced natural killer cell activity in rats administered deltamethrin at oral dose levels of 5 or 10 mg/kg/day for 28 days. See Section 3.2.2.6 for information regarding immunological effects in rats exposed via their mothers during gestation.

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

#### 3.2.2.4 Neurological Effects

In cases of accidental or intentional ingestion of relatively large quantities of solutions containing pyrethroids, neurotoxic signs such as headache, muscular fasciculations, convulsions, and coma have been reported (Gotoh et al. 1998; He et al. 1989; Peter et al. 1996).

Numerous investigators have reported signs of neurotoxicity in laboratory animals administered lethal and sublethal oral doses of pyrethrins and pyrethroids. Two different types of pyrethroids are recognized,

based on symptoms of poisoning and chemical structure (Coats 1990; Verschoyle and Aldridge 1980). Chapter 4 contains information regarding chemical properties of Type I and Type II pyrethroids. Type I pyrethroids induce neurological signs that include aggressive behavior and increased sensitivity to external stimuli, fine tremor, prostration with coarse whole body tremor, elevated body temperature, and coma. Pyrethrins induce neurological effects similar to those induced by Type I pyrethroids (Mbaria et al. 1993; Schoenig 1995). Effects induced by Type II pyrethroids include pawing and burrowing behavior, profuse salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremor that progresses to sinuous writhing (choreoathetosis). The presence of a cyano group within Type II pyrethroids also distinguishes this group from Type I pyrethroids. However, fenpropathrin and cyphenothrin, which are considered to be Type II pyrethroids by the presence of a cyano group, induce intermediate neurological responses characterized by both tremors (typical of Type I pyrethroids) and salivation (typical of Type II pyrethroids) (Miyamoto et al. 1995; Wright et al. 1988).

Acute oral dosing with Type I or Type II pyrethroids results in typical clinical signs of neurotoxicity within minutes to hours, with symptoms subsiding within several hours to a few days (EPA 1992b; Eriksson and Nordberg 1990; Hudson et al. 1986; Parker et al. 1983, 1984a, 1984b, 1985; Ray and Cremer 1979; Southwood 1984). Refer to Section 3.5.2 for a detailed discussion of mechanisms of toxicity associated with exposure to Type I and Type II pyrethroids. Several investigators reported typical signs of Type I or Type II pyrethroid poisoning in laboratory animals during repeated oral administration of pyrethrins or pyrethroids (from 2 days to 2 years), but there were few indications that repeated or continuous exposure might result in cumulative neurological effects (Cabral and Galendo 1990; DOD 1977; EPA 1983, 1988c, 1991a, 1991b, 1994b; Flucke and Schilde 1980; Hext et al. 1986; IRIS 2003a, 2003b, 2003c; Ishmael and Litchfield 1988; Mohan et al. 1998; Parker et al. 1984a, 1984b; Schoenig 1995). For example, Ishmael and Litchfield (1988) administered permethrin in the diet of rats and mice for 2 years and a lifetime (up to 98 weeks), respectively. Male and female rats were administered permethrin at concentrations that resulted in daily doses of 19.4, 37.5, and 91.5 mg/kg/day and 19.1, 40.2, and 103.8 mg/kg/day, respectively. Estimated doses to male and female mice were 28.7, 124.2, and 295.1 mg/kg/day and 42.8, 135.8, and 348.1 mg/kg/day, respectively. During the first 2 weeks of treatment, high-dose male and female rats exhibited slight whole body tremors, hypersensitivity to noise and other disturbances, and piloerection. These findings were not seen at lower dose levels. None of the groups of mice exhibited clinical signs of treatment-related neurotoxicity. Histological and ultrastructural examination of sciatic nerves at interim (52 weeks in rats, 26 and 52 weeks in mice) and terminal kills revealed no signs of permethrin-induced abnormalities. In a cancer bioassay, Cabral and Galendo (1990) administered fenvalerate (in arachis oil vehicle) to mice via gavage at 0, 40, or

80 mg/kg/day for 2 years. Reported noncancer effects were limited, but included observation of choreoathetosis and salivation in high-dose female mice. Parker et al. (1984a) fed fenvalerate to rats at dietary concentrations ranging from 1 to 1,000 ppm (0.07–70 mg/kg/day in males and 0.08–80 mg/kg/day in females) for 2 years. Five of 50 high-dose male rats exhibited clinical signs of neurotoxicity (abnormal gait, ataxia, muscular incoordination) during weeks 3 and 4. There was no report of clinical signs of neurotoxicity in other treatment groups.

Crofton et al. (1995) demonstrated the significance of vehicle in the expression of neurological effects in rats given single oral doses of deltamethrin. The lowest doses at which at least 50% of the exposed animals exhibited decreased motor activity ($ED_{50}$) ranged from 5.1 mg/kg for deltamethrin in corn oil to >1,000 mg/kg for deltamethrin in methyl cellulose.

Some investigators have assessed other aspects of neurotoxicity in animals administered oral doses of pyrethroids, often at doses much lower than those resulting in typical clinical signs. For example, Crofton and Reiter (1988) observed significant decreases in motor activity of rats following administration of a Type I pyrethroid (permethrin) at 200 mg/kg and Type II pyrethroids (cyfluthrin at 12.5 mg/kg, fenvalerate at 30 mg/kg, flucythrinate at 2.5 mg/kg, cypermethrin at 30 mg/kg, fluvalinate at 15 mg/kg, and a pyrethroid identified as RU26607 at 3 mg/kg). Crofton and Reiter (1988) also found that some of the pyrethroids tested affected the acoustic startle response by altering the amplitude or latency. In another rat study, a Type I pyrethroid (NAK 1901) enhanced the acoustic startle response amplitude in a dose-dependent manner, whereas a Type II pyrethroid (cypermethrin) had no effect on amplitude or latency, even at a dose level that elicited clinical signs (Hijzen et al. 1988). Hypersensitivity to sound was noted in some rats administered cypermethrin in the diet at a concentration resulting in daily intakes of 27 mg/kg for 83 days (EPA 1992c). Reduced locomotion and rearing frequency were observed in rats administered fenvalerate at single oral doses of 10 mg/kg (Spinosa et al. 1999). No treatment-related effects were seen in passive avoidance. Husain et al. (1991) observed pronounced treatment-related changes in brain levels of the neurotransmitters noradrenaline and dopamine, as well as their acid metabolites, following oral administration of fenvalerate at doses of 5–20 mg/kg/day for 21 days. The changes did not appear to be either dose-related or region specific, although the brain regions most affected appeared to be those that contribute most significantly to motor function and aggression. Significant increases were noted in grouped total activity and individual nonambulatory (but not ambulatory) activity of male mice observed for 4 hours following single oral administration of permethrin at 50 mg/kg or fenvalerate at 30 mg/kg (Mitchell et al. 1988). These effects were observed in the absence of typical clinical signs of pyrethroid-induced neurotoxicity. In another set of behavioral paradigms in

mice, fenvalerate, administered in single oral doses of 15–45 mg/kg (as little as 1/24 of the $LD_{50}$ value), resulted in significantly increased startle response latency and decreased ambulation and rearing in open field (Mandhane and Chopde 1997). Dose-related increased immobility in tail-suspension test and attenuated haloperidol-induced catalepsy were also observed. Axonal damage was observed in peripheral nerves of laboratory animals that had been administered pyrethroids in oral doses sufficient to induce clinical signs of neurotoxicity; the damage resolved upon cessation of treatment (Calore et al. 2000; Parker et al. 1985; Rose and Dewar 1983). Although the typical primary Type I and Type II clinical responses to pyrethroid poisoning can be explained by the action of Type I and Type II pyrethroids on sodium channels, the basis for these other pyrethroid-associated neurological changes is not presently known (see Section 3.5.2 for a discussion of mechanisms of toxicity).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

#### 3.2.2.5 Reproductive Effects

No reports were located regarding reproductive effects in humans following oral exposure to pyrethrins or pyrethroids.

No signs of exposure-related adverse effects on reproductive parameters, including male or female fertility indices, litter size, and numbers of viable and stillborn pups, were observed in a 2-generation reproductive study of rats administered pyrethrins (from pyrethrum extract) in the diet at concentrations up to 3,000 ppm (resulting in an average daily dose of approximately 240 mg/kg) (Schoenig 1995). No signs of reproductive toxicity were observed in a 3-generation reproductive toxicity study of fenpropathrin administered in the diet at concentrations up to 250 ppm (resulting in an average daily dose of approximately 25 mg/kg) (Hend et al. 1979). In another 3-generation reproductive toxicity study, rats were administered cyfluthrin in the diet at concentrations of 50, 150, or 450 ppm (resulting in average daily doses of 4, 11–14, or 35–40 mg/kg/day, respectively, in males and 5.5, 14–16, or 46–50 mg/kg/day, respectively, in females) (Loeser and Eiben 1983). Treatment-related reduced viability, decreased lactation, and decreased birth weight or weight gain were observed in some generations at concentrations $\geq$150 ppm.

Some investigators have reported adverse effects in male reprodutive organs following intermediate-duration oral exposure to pyrethroids at dose levels below those eliciting clinical signs of neurotoxicity. Abd El-Aziz et al. (1994) reported that male rats, administered deltamethrin in oral doses as low as 1 mg/kg/day (the lowest level tested) for 65 days, exhibited significantly lower weights of testicles, seminal vesicles, and prostate gland than vehicle controls. Sperm analysis of treated rats revealed significantly reduced sperm cell concentration, live cell percentage, and motility index, and a significantly higher percentage of total sperm abnormalities, relative to controls. Plasma testosterone levels were significantly reduced as early as 14 days following the beginning of treatment, remaining significantly lower 21 days after treatment ceased. Male fertility was tested at the end of treatment and 60 days posttreatment. At both time points, the percentage of successful matings to untreated female rats was 50% that of controls.

Similarly, oral administration of cypermethrin to male rats at 3.8 and 7.7 mg/kg/day (El-Khalek et al. 1999) and fenvalerate at 20 or 100 mg/kg/day (Hassan et al. 1993) for 65 days resulted in reduced male reproductive organ weights and significantly altered sperm characteristics. Hassan et al. (1993) also found reduced percentages of pregnancies in untreated female rats that were mated with fenvalerate-treated males, while El-Khalek et al. (1999) observed significant decreases in plasma testosterone levels in cypermethrin-treated rats.

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

#### 3.2.2.6 Developmental Effects

No reports were located regarding developmental effects in humans following oral exposure to pyrethrins or pyrethroids.

Standard tests for developmental effects in animals following oral exposure to pyrethrins or pyrethroids provide little indication that pyrethrins or pyrethroids might pose a significant developmental toxicity concern. However, more focused testing has revealed some persistent neurotoxic effects in animals exposed *in utero* and or via lactation.

Oral administration of pyrethrins (from pyrethrum extract) to female rats on gestation days 6–15 at doses in the range of 5–600 mg (total pyrethrins)/kg/day did not cause apparent developmental effects, even at doses in which maternal toxicity was observed (Schoenig 1995). However, high postimplantation loss was noted when pregnant rabbits were administered total pyrethrins at 600 mg/kg/day on gestation days 7–19 (Schoenig 1995). This dose level resulted in serious maternal toxicity (tremors, convulsions, and death). The World Health Organization (WHO 2001) reviewed the database for various pyrethroids and published a number of Environmental Health Criteria documents in which animal developmental toxicity studies (mostly unpublished or proprietary information from chemical organizations) provided little indication that pyrethroids might pose a developmental toxicity concern. The EPA evaluated a number of studies that included developmental toxicity end points, which are briefly summarized in documents in which reference doses (RfDs) were derived for selected Type I and Type II pyrethroids (IRIS 2003f). Cleared reviews (Data Evaluation Records) of some of the original studies, submitted to EPA as confidential business information, are available to the public. Most of the studies do not indicate that pyrethroids are of biologically significant developmental toxicity concern. However, decreased pup survival was noted in rats following parental exposure to resmethrin in the diet at a concentration resulting in a dose level of 70.8 mg/kg/day prior to mating and throughout gestation and lactation (EPA 1994a). Gavage administration of resmethrin (80 mg/kg/day) to other rats during gestation days 6–15 resulted in slightly increased incidences of skeletal variations and delayed ossification (EPA 1994a). No serious signs of fetotoxicity or teratogenicity were observed in fetuses of rats administered deltamethrin at doses of 1, 2.5, or 5 mg/kg/day during gestation days 6 through 15, although the highest dose level resulted in the death of 4/20 treated dams (Bhaumik and Gupta 1990). Oral administration of cypermethrin to pregnant rats at 2, 4, or 8 mg/kg/day on gestation days 6–15 resulted in neither maternal toxicity nor significant incidences of fetotoxicity or teratogenicity (Gupta 1990). Abdel-Khalik et al. (1993) reported significant dose-dependent postimplantation loss and retarded growth in fetuses of rat dams administered deltamethrin at oral dose levels of 1, 2.5, or 5 mg/kg/day on gestation days 6–15. However, since treatment-related significantly increased placental weight was noted at all dose levels, the investigators considered the developmental effects to have resulted, at least in part, from compromised placental tissues in treated dams. Kavlock et al. (1979) found no significant treatment-related signs of fetotoxicity or teratogenicity in fetuses of rat or mouse dams administered deltamethrin during major stages of organogenesis at dose levels up to and including those eliciting overt signs of maternal toxicity (up to 12 and 5 mg/kg/day in rat and mouse dams, respectively). In addition, deltamethrin administration to rat dams from gestation day 7 through lactation day 15, at daily oral doses of 2.5 or 5.0 mg/kg, resulted in no sign of adverse effects in 6-week-old female offspring that were subjected to open field

measurements of activity and exploration, although a dose-related depression in growth was observed during the period of lactation.

Eriksson and coworkers (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Eriksson and Nordberg 1990; Talts et al. 1998a) reported altered locomotory behavior and changes in muscarinic acetylcholine (MACh) receptor density in the cerebral cortex of adult mice that had been exposed to bioallethrin or deltamethrin at oral gavage dose levels in the range of 0.21 to 0.7 mg/kg/day during neonatal stages of development (post partum days 6–10). No significant differences were observed in locomotion of 17-day-old mice, relative to controls. However, when examined at 4 months of age, both bioallethrin- and deltamethrin-treated mice exhibited significantly increased spontaneous locomotor behavior (Eriksson and Fredriksson 1991). In contrast to the findings in the 0.21–0.7 mg/kg dose groups, mice administered 42 mg bioallethrin/kg daily exhibited significant decreases in locomotion and total activity counts and no significant differences in densities of MACh receptor density. Underlying mechanisms responsible for the differences observed in low-dose groups (0.21–0.7 mg/kg) and mice in the 42 mg/kg dose group, a level approaching that which would be expected to result in overt clinical signs of neurotoxicity, could not be explained. Other investigators (Ray et al. 2002; Tsuji et al. 2002) were unable to duplicate the results of Eriksson and coworkers.

Malaviya et al. (1993) observed significant increases in the levels of dopamine and muscarinic receptors of striatal membrane in rat pups that had been exposed to fenvalerate or cypermethrin *in utero*. In this study, pregnant dams were administered 10 mg fenvalerate/kg or 15 mg cypermethrin/kg on gestation days 5 through 21. These effects were more pronounced in pups that continued to be exposed via their mothers throughout 3 weeks of postpartum lactation. Other significant treatment-related effects in the brain included increased acetylcholinesterase activity and decreased activities of monoamine oxidase and $Na^+$- and $K^+$-ATPase from gestational exposure to fenvalerate, decreases in monoamine oxidase and acetylcholinesterase during lactation in fenvalerate-exposed pups, and decreases in acetylcholinesterase and $Na^+$- and $K^+$-ATPase during lactation in cypermethrin-exposed pups. The toxicological relevance of increased brain acetylcholinesterase activity is uncertain because cholinesterase levels are naturally highly variable.

Moniz et al. (1990) demonstrated pyrethroid-induced disruption of avoidance learning (significantly decreased latency in avoidance to the dark area of a maze) in 97- and 104-day-old adult rats that had nursed from mothers exposed to cyhalothrin in the drinking water throughout the entire period of lactation

at a level resulting in an estimated maternal cyhalothrin dose of 27 mg/kg/day. During the exposure period, no indication of neurotoxicity was seen in motor activity of dams or nursing pups.

Santoni and coworkers reported treatment-related increases in natural killer (NK) cell and antibody-dependent cytotoxic activity, impaired thymocyte function, and increased and decreased numbers of T cells in peripheral blood and spleen, respectively, in rats after their mothers had been orally administered cypermethrin during gestation at 50 mg/kg/day, a dose schedule that did not result in clinical signs of maternal toxicity (Santoni et al. 1997, 1998, 1999). In one phase of these studies, marked and long-lasting increases were noted in plasma adrenaline and noradrenaline concentrations of offspring (from treated dams) that were tested up to 90 days postpartum (Santoni et al. 1999). The toxicological significance of these results is uncertain.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

#### 3.2.2.7 Cancer

No reports were located regarding cancer in humans following oral exposure to pyrethrins or pyrethroids.

Results of cancer bioassays in laboratory animals are mixed. Pyrethrum extract was not oncogenic in mice following dietary administration at total pyrethrin concentrations of up to 5,000 ppm (approximately 850 mg/kg/day) for 18 months (EPA 1994c; Schoenig 1995). However, increased incidences of thyroid follicular cell tumors were reported in male rats administered pyrethrum extract in the diet at total pyrethrin concentrations of 1,000 ppm (approximately 42.9 mg/kg/day) and in both male and female rats receiving approximately 173 mg/kg/day (EPA 1994c; Schoenig 1995). The 3,000-ppm (173 mg/kg/day) group of 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 (EPA 1999) 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.”

Cancer bioassays of selected synthetic pyrethroids have also produced mixed results. Ishmael and Litchfield (1988) administered permethrin (40/60 cis/trans) in the diet to rats at concentrations of 500,

1,000, or 2,500 ppm for 2 years and to mice at concentrations of 250, 1,000, or 2,500 ppm for a lifetime. The estimated daily doses in high-dose rats were 91.5 and 103.8 mg/kg/day for males and females, respectively, based on body weight and food consumption values presented. Estimated doses to the high-dose mice were 295.1 and 348.1 mg/kg/day for males and females, respectively. There was no evidence for a carcinogenic effect in treated rats. The high-dose male (but not female) mice exhibited statistically significant elevated incidences of benign lung tumors (17/70 high-dose males versus 11/70 in controls). Cancer bioassays that employed a 25/75 (cis/trans) mixture of permethrin isomers at dietary concentrations resulting in permethrin doses of up to 250 mg/kg/day in both rats and mice revealed no evidence of carcinogenicity in rats and statistically significantly elevated incidences of benign lung tumors in female, but not male, mice (15/74 high-dose females versus 3/96 in controls).

The World Health Organization (WHO 2001) reviewed the database for various pyrethroids and published a number of Environmental Health Criteria documents in which animal cancer bioassays (mostly proprietary information from chemical organizations) provided little indication that pyrethroids should be considered carcinogens. No indications of a carcinogenic effect were observed in other cancer bioassays of fenvalerate-treated rats (Parker et al. 1984a) and mice (Cabral and Galendo 1990; Parker et al. 1983).

The Cancer Effect Levels are recorded in Table 3-2 and plotted in Figure 3-2.

### 3.2.3 Dermal Exposure

#### 3.2.3.1 Death

Two case reports were located in which death was associated with allergic reactions to dog shampoo products containing pyrethrins (Wagner 2000; Wax and Hoffman 1994). The relative contributions of inhalation and dermal exposure routes were not addressed. No other reports were located regarding death in humans following dermal exposure to pyrethrins or pyrethroids.

Several studies designed to assess the lethality of pyrethrins and pyrethroids could not establish dermal $LD_{50}$ values (exposure level resulting in death of 50% of the dosed animals), even when administered the highest concentrations possible for given pyrethrin- or pyrethroid-containing substances (see Kavlock et al. 1979; Litchfield 1985; Schoenig 1995). However, El-Elaimy (1986) observed 100% mortality within 4 days among male rats exposed by daily dermal applications of cyfluthrin that resulted in daily doses of

1,845 or 2,460 mg cyfluthrin/kg/day. Rats receiving daily doses of 615 or 1,250 mg/kg/day survived a 7-day treatment period. Death was noted in 2/10 male mice within 48 hours following dermal application of 1,800 mg fenvalerate/kg (Mitchell et al. 1988). Acute dermal $LD_{50}$ values for laboratory animals, listed by a secondary source (Metcalf 1995) for several pyrethroids, were considered to be >5,000 mg/kg, but dermal $LD_{50}$ values for tefluthrin, cyhalothrin, and cyfluthrin were in the range of 148–696 mg/kg. However, primary sources for these values were not listed and could not be verified. Deaths in domestic cats have been associated with erroneous exposure to concentrated (45–65%) permethrin products designed to be used as flea treatment for dogs (Meyer 1999). The increased sensitivity of the cat to concentrated permethrin may be the result of less efficient hepatic glucuronidation (Whittem 1995), a second step in the metabolism of pyrethroids in mammalian systems. No other information was located regarding death in animals following dermal exposure to pyrethrins or pyrethroids.

#### 3.2.3.2 Systemic Effects

No reliable reports were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, or body weight effects in humans or animals following dermal exposure to pyrethrins or pyrethroids.

**Dermal Effects.** Slight skin irritation was observed in workers in plants producing pyrethrum extract to be used as insecticide powders in an early study by McCord et al. (1921). Paresthesia (an abnormal cutaneous sensation sometimes described as tingling, burning, stinging, numbness, and/or itching) has been reported in individuals occupationally exposed to pyrethroids that contact the skin; however, paresthesia is generally considered to be a neurological effect, not a dermal effect (see Section 3.2.3.4). Reports were not located in which dermal exposure to pyrethrins or pyrethroids could be associated with other dermal effects in humans.

Animal studies indicate that dermal exposure to pyrethrins or pyrethroids may result in slight dermal irritation, but they do not elicit strongly positive responses in standard dermal sensitization tests (see, for example, DOD 1977; Litchfield 1985; Schoenig 1995).

**Ocular Effects.** No reliable reports were located regarding ocular effects in humans following dermal exposure to pyrethrins or pyrethroids. Some workers reported irritation of the eyes after dipping conifer seedlings into solutions containing fenvalerate or permethrin (Kolmodin-Hedman et al. 1982); however, control groups were not included in the survey.

Animal studies indicate that pyrethrins and pyrethroids may cause mild ocular irritation upon contact with the eye (see, for example, DOD 1977; Litchfield 1985; Schoenig 1995).

#### 3.2.3.3 Immunological and Lymphoreticular Effects

A single case report was located in which a 47-year-old farmer developed a hypersensitive response that included a widespread dermal rash after dipping sheep in a solution, the active component of which was flumethrin (Box and Lee 1996). The relative contributions of dermal and inhalation exposure were not indicated in the report. See Section 3.2.1.3 for information regarding immunological effects in humans following exposures to pyrethrins or pyrethroids that were likely mixed (inhalation, dermal, and possibly oral).

No reports were located regarding immunological effects in animals following dermal exposure to pyrethrins or pyrethroids.

#### 3.2.3.4 Neurological Effects

Paresthesia (an abnormal cutaneous sensation sometimes described as tingling, burning, stinging, numbness, and itching) has been widely reported among individuals occupationally exposed to pyrethroids (Flannigan and Tucker 1985; Flannigan et al. 1985b; Knox et al. 1984; LeQuesne and Maxwell 1980; Tucker and Flannigan 1983; see also Vijverberg and van den Bercken 1990 for a summary of available information on occupationally-induced paresthesia). This effect is considered to be the result of a direct effect on intracutaneous nerve endings following dermal exposure to pyrethroids (LeQuesne and Maxwell 1980; Wilks 2000). In a double-blind study of volunteers exposed to fenvalerate via application to the earlobe (0.081 mg/cm$^2$), the onset of cutaneous sensations occurred at 1 hour postapplication, peaked at 3–6 hours, and lasted approximately 24 hours (Knox et al. 1984). Sensations included numbness, itching, burning, tingling, and warmth. A similar time-course for paresthesia was noted among agricultural workers exposed during or shortly following the spraying of fenvalerate on field crops (Tucker and Flannigan 1983). Type I (permethrin) and Type II (cypermethrin, fenvalerate, and flucythrinate) pyrethroids have been shown to induce differing severity in paresthesia responses in volunteers exposed on separate days to each pyrethroid in doses of 0.13 mg/cm$^2$ (Flannigan and Tucker 1985). The mildest responses were elicited by permethrin. Both cypermethrin and fenvalerate induced

significantly more severe responses than those of permethrin. Responses to cypermethrin were significantly more severe than those induced by the other three pyrethroids (see Section 3.5.2 for a discussion of mechanisms responsible for differences in toxicity among various pyrethroids).

Signs of mild acute pyrethroid poisoning include dizziness, headache, and nausea, in addition to paresthesia. These signs have been associated with acute occupational (inhalation and dermal) exposure to various pyrethroids during outdoor or indoor spraying (Chen et al. 1991; Moretto 1991; Shujie et al. 1988; Zhang et al. 1991). Based on measurements of pyrethroids deposited on gauze pads during spraying, estimates of dermal deposits on exposed skin ranged from 0.013 to 0.347 μg/cm$^2$ (Chen et al. 1991) and from <0.01 to 141.61 μg/cm$^2$ (Zhang et al. 1991). Although dermal exposure was considered to be the major source of exposure, inhalation exposure was also likely. Facial paresthesia, dizziness, fatigue, miliary red facial papules, and sniffles and sneezes were noted in subjects exposed to deltamethrin and fenvalerate while packaging the insecticides (He et al. 1988). Both inhalation and dermal exposures were likely, although increased toxicity during summer months was indication that dermal exposure may have been increased when greater areas of skin were exposed due to warmer weather. He et al. (1991) reported increased peripheral nerve excitability in individuals following 3 days of exposure to deltamethrin during spraying, in the absence of other clinical signs of acute pyrethroid poisoning. Higher levels of exposure to pyrethroids result in additional clinical signs such as listlessness, muscular fasciculations, and mild disturbance of consciousness, indicative of moderate acute pyrethroid poisoning (Chen et al. 1991; He et al. 1989). Even higher exposure levels may result in convulsive attacks and coma (severe acute pyrethroid poisoning), effects that may last for several weeks (He et al. 1989).

Limited information was available regarding neurological effects in animals following dermal exposure to pyrethrins or pyrethroids. El-Elaimy (1986) observed signs of pyrethroid poisoning (chewing, licking, and salivation) in groups of rats receiving daily dermal applications of cyfluthrin for up to 7 days. In this study, dose levels were 0, 615, 1,250, 1,845, and 2,460 mg cyfluthrin/kg/day. Pawing, whole body tremors, and choreoathetosis were noted at the two highest dose levels, which were also lethal. The description of the findings did not indicate whether clinical signs of neurotoxicity were seen at all dose levels. Significant increases were noted in grouped total activity and individual nonambulatory (but not ambulatory) activity of male mice observed for 4 hours following single dermal applications of 300 mg permethrin/kg or ≥600 mg fenvalerate/kg (Mitchell et al. 1988). These effects were observed in the absence of typical clinical signs of pyrethroid-induced neurotoxicity. Guinea pigs responded to dermal applications of permethrin or fenvalerate by licking, rubbing, scratching, or biting the area of application

(Cagen et al. 1984). These behavioral responses were indicative of paresthesia (considered to result from a direct action of pyrethroids on sensory nerve endings), since these responses were elicited in the absence of visible signs of dermal irritation.

#### 3.2.3.5 Reproductive Effects

No reports were located regarding reproductive effects in humans or animals following dermal exposure to pyrethrins or pyrethroids.

#### 3.2.3.6 Developmental Effects

No reports were located regarding developmental effects in humans following dermal exposure to pyrethrins or pyrethroids.

Available information regarding developmental effects in animals is limited to a single study in which 1 mL of a 0.018% solution of cyhalothrin was applied daily to the skin of pregnant rats throughout gestation (Gomes et al. 1991a). Assuming a mature dam body weight of 0.32 kg (EPA 1988a), the initial dermal dose to the dams was approximately 56 mg/kg/day. A control group was similarly treated with vehicle only. Relative to controls, treated pups exhibited delays in development of fur, ear and eye opening, and testes descent into the scrotum. At weaning and 90 days of age, the frequency of spontaneous locomotion and active avoidance responses did not differ significantly among treated and control groups of offspring. However, when tested as adults for motivational responses, the total number of head-dips in a hole-board test (an index of motivational state) was decreased in offspring of treated dams, relative to control offspring.

#### 3.2.3.7 Cancer

No reports were located regarding cancer in humans or animals following dermal exposure to pyrethrins or pyrethroids.

## 3.3 GENOTOXICITY

Limited information regarding the genotoxicity of natural pyrethrins was located in the studies available for review. As shown in Table 3-3, natural pyrethrins, tested in the standard Ames test in various *Salmonella* strains and in *Escherichia coli* with or without metabolic activation gave negative results (Moriya et al. 1983).

Much more information has been generated regarding the genotoxic properties of both Type I and Type II pyrethroids. For example, administration of the Type I pyrethroids cismethrin (31 or 40 mg/kg) or bioresmethrin (1,000 mg/kg) to female Sprague-Dawley rats by gavage significantly increased the percentage of micronuclei in bone marrow (Hoellinger et al. 1987). In male and female CD-1 mice, intraperitoneal administration of a single dose of permethrin at up to 275 mg/kg failed to increase the percentage of micronuclei in bone marrow (Chruścielska and Kalhorn 1999). In a 28-day study in male Wistar rats, daily administration of permethrin (12.6, 50.3, or 125.7 mg/kg) by gavage significantly increased the number of chromosome aberrations in a dose-related manner (Institóris et al. 1999b). A commercial formulation of permethrin fed to the larva of *Drosophila* was mutagenic in the sex-linked recessive lethal mutation assay in *Drosophila*, affecting the DNA of both spermatogonia and spermatocytes (Kale et al. 1995). In contrast, in a study by Gupta et al. (1990), treating adult males resulted in no significant differences in frequencies of spontaneous mutations. The genotoxicity of Type I pyrethroids *in vivo* is summarized in Table 3-4.

Several Type II pyrethroids have been tested for genotoxicity in mammalian systems (mostly to rats and mice) following oral, parenteral, or dermal administration of the compounds (Table 3-5). Tests conducted with cypermethrin showed that doses ≥30 mg/kg administered intraperitoneally significantly increased the incidence of chromosomal aberrations and micronuclei in bone marrow and the percent of sperm with head abnormalities (Bhunya and Pati 1988). A dose of 50 mg/kg by gavage, but not dermally, also induced chromosomal aberrations in bone marrow (Bhunya and Pati 1988). Of the three assays used by these investigators, the sperm abnormality test was found to be the most sensitive and the micronucleus test was determined to be the least sensitive. Chromosomal aberrations in mouse bone marrow and spleen cells have also been observed in other studies with higher doses of cypermethrin (Amer et al. 1993). Increased incidences of sister chromatid exchanges were also reported by Amer et al. (1993) in mouse bone marrow after an intraperitoneal dose of 180 mg cypermethrin/kg and by Chauhan et al. (1997) after a gavage dose of 32 mg cypermethrin/kg, but not 21.1 mg cypermethrin/kg. Experiments conducted with cypermethrin-dosed rats showed increased chromosomal aberrations in bone marrow after administration

## Table 3-3. Genotoxicity of Pyrethrins *In Vitro*

| Species (test system) | Chemical | End point | With activation | Without activation | Reference |
|---|---|---|---|---|---|
| Prokaryotic organisms: | | | | | |
| *Salmonella typhimurium* (TA100, TA98, TA1535, TA1537, TA1538) | Pyrethrins | Gene mutation | – | – | Moriya et al. 1983 |
| *Escherichia coli* (WP2 *hcr*) | Pyrethrins | Gene mutation | – | – | Moriya et al. 1983 |

– = negative result

## Table 3-4. Genotoxicity of Type I Pyrethroids *In Vivo*

| Species (test system) | Chemical | End point | Results | Reference |
|---|---|---|---|---|
| *Eukaryotic organisms:* | | | | |
| *Drosophila* | Permethrin | Sex linked recessive lethal | + | Kale et al. 1995 |
| *Drosophila* | Permethrin | Sex linked recessive lethal | – | Gupta et al. 1990 |
| Mammalian cells: | | | | |
| Rat bone marrow | Bioresmethrin | Micronuclei | + | Hoellinger et al. 1987 |
| Rat bone marrow | Cismethrin | Micronuclei | + | Hoellinger et al. 1987 |
| Rat bone marrow | Permethrin | Chromosomal aberrations | + | Institóris et al. 1999b |
| Rat bone marrow | Permethrin | Micronuclei | + | Hoellinger et al. 1987 |
| Mouse bone marrow | Permethrin | Micronuclei | – | Chruścielska and Kalhorn 1999 |

– = negative result; + = positive result

## Table 3-5. Genotoxicity of Type II Pyrethroids *In Vivo*

| Species (test system) | Chemical | End point | Results | Reference |
|---|---|---|---|---|
| Eukaryotic organisms: | | | | |
| *Drosophila* | Cypermethrin | Sex-linked recessive lethal | ± | Batiste-Alentorn et al. 1986 |
| *Drosophila* | Cypermethrin | Sex-chromosome loss | – | Batiste-Alentorn et al. 1986 |
| *Drosophila* | Cypermethrin | Non-disjunction | – | Batiste-Alentorn et al. 1986 |
| *Drosophila* | Supercyper-methrin | Sex-linked recessive lethal | – | Miadoková et al. 1992 |
| *Drosophila* | Supercyper-methrin | Sex-chromosome loss, non-disjunction, frequency of deletion | – | Miadoková et al. 1992 |
| Mammalian systems: | | | | |
| Rat bone marrow | Cypermethrin | Chromosomal aberrations | + | Institóris et al. 1999b |
| Rat bone marrow | Cypermethrin | Chromosomal aberrations | – | Nehéz et al. 2000 |
| Mouse bone marrow | Cypermethrin | Chromosomal aberrations | +, – | Bhunya and Pati 1988 |
| Mouse bone marrow | Cypermethrin | Chromosomal aberrations | + | Amer et al. 1993 |
| Mouse spleen cells | Cypermethrin | Chromosomal aberrations | + | Amer et al. 1993 |
| Mouse bone marrow | Cypermethrin | Sister chromatid exchange | + | Chauhan et al. 1997 |
| Mouse bone marrow | Cypermethrin | Sister chromatid exchange | + | Amer et al. 1993 |
| Rat bone marrow | Cypermethrin | Micronuclei | – | Hoellinger et al. 1987 |
| Mouse bone marrow | Cypermethrin | Micronuclei | + | Bhunya and Pati 1988 |
| Mouse sperm | Cypermethrin | Cellular abnormalities | + | Bhunya and Pati 1988 |
| Rat bone marrow | Deltamethrin | Chromosomal aberrations | + | Agarwal et al. 1994 |
| Mouse bone marrow | Deltamethrin | Chromosomal aberrations | + | Bhunya and Pati 1990 |
| Mouse bone marrow | Deltamethrin | Chromosomal aberrations | – | Poláková and Vargová 1983 |
| Mouse bone marrow | Deltamethrin | Sister chromatid exchange | + | Chauhan et al. 1997 |
| Rat bone marrow | Deltamethrin | Micronuclei | + | Agarwal et al. 1994 |
| Rat bone marrow | Deltamethrin | Micronuclei | – | Hoellinger et al. 1987 |
| Mouse bone marrow | Deltamethrin | Micronuclei | + | Bhunya and Pati 1990 |
| Mouse bone marrow | Deltamethrin | Micronuclei | + | Gandhi et al. 1995 |
| Rat testes | Deltamethrin | DNA fragmentation | + | El-Gohary et al. 1999 |
| Mouse sperm | Deltamethrin | Cellular abnormalities | + | Bhunya and Pati 1990 |
| Mouse | Deltamethrin | Dominant lethal mutations | – | Shukla and Taneja 2000 |

## Table 3-5. Genotoxicity of Type II Pyrethroids *In Vivo*

| Species (test system) | Chemical | End point | Results | Reference |
|---|---|---|---|---|
| Rat bone marrow | Fenpropathrin (Meothrin) | Micronuclei | + | Oraby 1997 |
| Mouse bone marrow | Fenpropathrin | Micronuclei | – | Ryu et al. 1996 |
| Rat bone marrow | Fenvalerate | Chromosomal aberrations | + | Chatterjee et al. 1982 |
| Mouse bone marrow | Fenvalerate | Chromosomal aberrations | + | Ghosh et al. 1992 |
| Mouse bone marrow | Fenvalerate | Chromosomal aberrations | + | Pati and Bhunya 1989 |
| Mouse sperm | Fenvalerate | Cellular abnormalities | + | Pati and Bhunya 1989 |
| Mouse bone marrow | Flumethrin | Chromosomal aberrations | +, – | Nakano et al. 1996 |
| Mouse bone marrow | Flumethrin | Micronuclei | +, – | Nakano et al. 1996 |

– = negative result; + = positive result; ± = weak positive result; +, – = both positive and negative results;
DNA = deoxyribonucleic acid

at 22.2 mg/kg/day for 28 days, but not at 11.1 mg/kg/day (Institóris et al. 1999b). However, Nehéz et al. (2000), also in a 4-week gavage study, did not find increases in chromosomal aberrations in bone marrow from rats treated with up to 22 mg cypermethrin/kg/day. No significantly increased incidences of micronuclei were observed in rat bone marrow following acute treatment by gavage with 15 mg cypermethrin/kg (Hoellinger et al. 1987).

Studies of deltamethrin-dosed mice showed increased chromosomal aberrations and micronuclei in bone marrow cells as well as sperm abnormalities following acute intraperitoneal treatment with ≥10 mg/kg (Bhunya and Pati 1990). Increased sister chromatid exchanges were detected after a single 20 mg/kg dose, but not after doses of 13.2 mg/kg or lower (Chauhan et al. 1997). No statistically significant increase in dominant lethal mutation rate was seen in mice treated orally with 0.36, 0.72, or 1.08 mg deltamethrin/kg (Shukla and Taneja 2000). In rats, acute intraperitoneal administration of deltamethrin at ≥5.6 mg/kg induced micronuclei in bone marrow cells (Agarwal et al. 1994), but gavage administration of up to 20 mg/kg did not (Hoellinger et al. 1987). This is consistent with other experiments conducted by Agarwal et al. (1994) in which intraperitoneal and subcutaneous administration of deltamethrin (≥11.2 mg/kg) proved to be more efficient routes for inducing chromosomal aberrations than gavage. Deltamethrin also was shown to induce DNA fragmentation in sections of rat testes following intraperitoneal administration of 1 mg/kg/day (only level tested) for 21 days (El-Gohary et al. 1999).

In mice dosed intraperitoneally, fenvalerate induced chromosomal aberrations in bone marrow cells at ≥32.5 mg/kg (Ghosh et al. 1992; Pati and Bhunya 1989), micronuclei at 150 mg/kg, and sperm abnormalities at 100 mg/kg (Pati and Bhunya 1989). Fenvalerate also induced chromosomal aberrations in rat bone marrow cells following gavage dosing at ≥50 mg/kg/day for 21 days (Chatterjee et al. 1982). Studies conducted with flumethrin in mice showed induction of chromosomal aberrations in bone marrow cells after a single dermal application of 5,325 mg/kg to a shaved area or a single intraperitoneal injection of 2,083 mg/kg, but not after repeated intraperitoneal injections of 128 mg/kg (Nakano et al. 1996). In contrast, micronuclei frequency was not significantly affected after a single dermal dose of 5,325 mg/kg, but was increased after repeated intraperitoneal doses of 128 mg/kg (Nakano et al. 1996). Additional studies found no significant change in chromosomal aberrations in mouse bone marrow following a single gavage administration of deltamethrin by gavage at up to 6.8 mg/kg (Poláková and Vargová 1983) or of micronuclei after an intraperitoneal dose of up to 105 mg fenpropathrin/kg (Ryu et al. 1996). However, 14 daily doses of fenpropathrin by gavage at ≥0.074 mg/kg/day increased the frequency of micronuclei in rat bone marrow (Oraby 1997); a dose of 0.0074 mg/kg/day was without significant effect.

A limited number of studies of Type II pyrethroids in *Drosophila* show mostly nonmutagenic results under the experimental conditions of the tests. Batiste-Alentorn et al. (1986) showed a significant increase in the frequency of sex-linked recessive lethal mutations after adult ingestion or larval feeding of cypermethrin. However, there were no significant increases in the frequency of sex-chromosome loss or nondisjunction. Similar negative results were reported by Miadoková et al. (1992).

Many *in vitro* studies have also been conducted on both Type I and Type II pyrethroids (Tables 3-6 and 3-7). Many papers investigated gene mutations in various *Salmonella* strains both with and without metabolic activation and, for the most part, the results did not indicate a mutagenic response. In yeast, results were inconsistent, although there was some evidence of mutations of mitochondrial DNA, particularly when commercial formulations were tested, but not when only the active ingredient was tested (Chruścielska et al. 1999).

*In vitro* experiments in mammalian cells show a greater percentage of mutagenic effects than the bacteria and yeast studies (Tables 3-6 and 3-7). Investigations of human, pig, and cattle lymphocytes, Chinese and Syrian hamster cells, and mouse spleen cells were positive for several genetic end points. Chromosomal aberrations, sister chromatid exchange, increased micronuclei, DNA damage, C-mitosis induction, and other damage were all observed. However, as with the bacteria studies, no consistent pattern was seen that could relate genotoxicity to the presence or absence of metabolic activation of the pyrethroids by liver cells or enzymes.

## 3.4 TOXICOKINETICS

Pyrethroids have been classified into two major categories, Type I or Type II, based on distinct toxicological mechanisms (see Section 3.5.2 for details regarding the classification of pyrethroids). Although synthetic pyrethroids are all derivatives of the natural pyrethrins, they exhibit a wide structural diversity and some differences in their toxicokinetics. The differences are most apparent in the metabolism of individual pyrethroid compounds (see Section 3.4.3). Thus, while generalizations are made in the profile regarding the toxicokinetics of the major pyrethroid classes and the basis for these generalizations is provided, the reader is cautioned about applying these generalizations too strictly to specific pyrethroid compounds, even within a class. Relevant literature regarding the toxicokinetics of specific pyrethroid compounds is cited where appropriate to this review, and the reader is encouraged to pursue such literature if information is needed regarding specific pyrethroid compounds.

## Table 3-6. Genotoxicity of Type I Pyrethroids *In Vitro*

| Species (test system) | Chemical | End point | With activation | Without activation | Reference |
|---|---|---|---|---|---|
| Prokaryotic organisms: | | | | | |
| *Escherichia coli* (WP2 *her*) | Allethrin | Gene mutation | | –[a] | Moriya et al. 1983 |
| *Salmonella typhimurium* (TA98, JK1) | Allethrin | Gene mutation | | –[b] | Hour et al. 1998 |
| *S. typhimurium* (JK3, JK947) | Allethrin | Gene mutation | | +[b] | Hour et al. 1998 |
| *S. typhimurium* (TA98, TA1535, TA1537, TA1538) | Allethrin | Gene mutation | | –[a] | Moriya et al. 1983 |
| *S. typhimurium* (TA100) | Allethrin | Gene mutation | + | + | Moriya et al. 1983 |
| *S. typhimurium* (TA97, TA100, TA104) | Allethrin | Gene mutation | + | – | Herrera and Laborda 1988 |
| *S. typhimurium* (TA98, TA1535, TA1538, TA1537) | Allethrin | Gene mutation | – | – | Herrera and Laborda 1988 |
| *S. typhimurium* (TA98, TA100) | Bioresmethrin | Gene mutation | – | – | Pluijmen et al. 1984 |
| *S. typhimurium* (TA98, T100) | Cismethrin | Gene mutation | – | – | Pluijmen et al. 1984 |
| *E. coli* (WP2 *her*) | Permethrin | Gene mutation | | –[a] | Moriya et al. 1983 |
| *S. typhimurium* (TA98, TA100) | Permethrin | Gene mutation | – | – | Pluijmen et al. 1984 |
| *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) | Permethrin | Gene mutation | | –[a] | Moriya et al. 1983 |
| *S. typhimurium* (TA98, TA100) | Permethrin | Gene mutation | – | | Bartsch et al. 1980 |
| *S. typhimurium* (TA97, TA98, TA100, TA104, TA1535, TA1537, TA1538) | Permethrin | Gene mutation | – | – | Herrera and Laborda 1988 |
| *S. typhimurium* (TA98, TA100) | Resmethrin | Gene mutation | – | – | Pluijmen et al. 1984 |
| *S. typhimurium* (TA97, TA98, TA100, TA104, TA1535, TA1537, TA1538) | Resmethrin | Gene mutation | – | – | Herrera and Laborda 1988 |
| Eukaryotic organisms: | | | | | |
| Yeast (Strain A and HB) | Ambush 25EC (Permethrin) | Mitochondrial mutation | | + | Chruścielska et al. 1999 |

## Table 3-6. Genotoxicity of Type I Pyrethroids *In Vitro*

| Species (test system) | Chemical | End point | With activation | Without activation | Reference |
|---|---|---|---|---|---|
| Yeast (Strain A and HB) | Permethrin | Mitochondrial mutation | | – | Chruścielska et al. 1999 |
| Mammalian cells: | | | | | |
| Chinese hamster ovary cells | Bioresmethrin | Gene mutation | | – | Pluijmen et al. 1984 |
| Chinese hamster ovary cells | Cismethrin | Gene mutation | | – | Pluijmen et al. 1984 |
| Chinese hamster ovary cells | Permethrin | Chromosomal aberrations | | + | Barrueco et al. 1994 |
| Human lymphocytes | Permethrin | Chromosomal aberrations | – | + | Barrueco et al. 1992 |
| Human lymphocytes | Permethrin | Chromosomal aberrations | | + | Barrueco et al. 1994 |
| Human lymphocytes | Permethrin | Sister chromatid exchange | ± | ± | Barrueco et al. 1992 |
| Human lymphocytes | Permethrin | Micronuclei | | + | Barrueco et al. 1992 |
| Human lymphocytes | Permethrin | Micronuclei | | – | Surrallés et al. 1995 |
| Human whole blood | Permethrin | Micronuclei | | – | Surrallés et al. 1995 |
| Chinese hamster ovary cells | Permethrin | Gene mutation | | – | Pluijmen et al. 1984 |
| Chinese hamster ovary cells | Resmethrin | Gene mutation | | – | Pluijmen et al. 1984 |

[a]Not clear whether tests were performed with or without activation.
[b]Tests assumed to be performed without activation because use of activation was not discussed in the study.

– = negative result; + = positive result; ± = weak positive result

## Table 3-7. Genotoxicity of Type II Pyrethroids *In Vitro*

| Species (test system) | Chemical | End point | With activation | Without activation | Reference |
|---|---|---|---|---|---|
| Prokaryotic organisms: | | | | | |
| *Salmonella typhimurium* (TA98, 100) | Cypermethrin | Gene mutation | – | – | Pluijmen et al. 1984 |
| *S. typhimurium* (TA98) | Deltamethrin | Gene mutation | – | | Bartsch et al. 1980 |
| *S. typhimurium* (TA100) | Deltamethrin | Gene mutation | – | + | Bartsch et al. 1980 |
| *S. typhimurium* (TA98, TA100) | Deltamethrin | Gene mutation | – | – | Pluijmen et al. 1984 |
| *S. typhimurium* (TA98, TA100, TA1535, TA1537) | Fenpropathrin | Gene mutation | – | – | Ryu et al. 1996 |
| *S. typhimurium* (TA98, TA100) | Fenvalerate | Gene mutation | – | – | Pluijmen et al. 1984 |
| *S. typhimurium* (TA97, TA98, TA100, TA1535, TA1538) | Supercyper-methrin | Gene mutation | – | – | Miadoková et al. 1991 |
| Eukaryotic organisms: | | | | | |
| Yeast (Strains A and HB) | Cypermethrin | Mitochondrial mutation | | – | Chruścielska et al. 1999 |
| Yeast (Strains A and HB) | Fastac 10EC (10% alpha-cypermethrin) | Mitochondrial mutation | | ± | Chruścielska et al. 1999 |
| Yeast (Strains A and HB) | Deltamethrin | Mitochondrial mutation | | – | Chruścielska et al. 1999 |
| Yeast (Strains A and HB) | Decis 2.5EC (2.5% delta-methrin) | Mitochondrial mutation | | + | Chruścielska et al. 1999 |
| Yeast (Strains A and HB) | Karate 025EC (25 g/L lambda-cyhalothrin) | Mitochondrial mutation | | + | Chruścielska et al. 1999 |
| Yeast Strain D7 | Supercyper-methrin | Mitotic cross-over | | ± or – | Vlčková 1991 |
| Yeast Strain D7 | Supercyper-methrin | Conversion at the tryptophan locus | | ± or – | Vlčková 1991 |
| Yeast Strain D7 | Supercyper-methrin | Conversion at the tryptophan locus | | + | Miadoková et al. 1992 |
| Yeast Strain D7 | Supercyper-methrin | Gene reversion mutations | | + | Vlčková 1991 |
| Yeast Strain D7 | Supercyper-methrin | Point mutations at isoleucine locus | | + | Miadoková et al. 1992 |

## Table 3-7. Genotoxicity of Type II Pyrethroids *In Vitro*

| Species (test system) | Chemical | End point | With activation | Without activation | Reference |
|---|---|---|---|---|---|
| Mammalian systems: | | | | | |
| Human lymphocytes | Cypermethrin | Sister chromatid exchange | | – | Puig et al. 1989 |
| Human lymphocytes | Cypermethrin | Micronuclei | | ± | Surrallés et al. 1995 |
| Human whole blood | Cypermethrin | Micronuclei | | ± | Surrallés et al. 1995 |
| Mouse spleen cells | Cypermethrin | Chromosomal aberrations | | + | Amer et al. 1993 |
| Mouse spleen cells | Cypermethrin | Sister chromatid exchange | | + | Amer et al. 1993 |
| Chinese hamster ovary cells | Cypermethrin | Gene mutation | | – | Pluijmen et al. 1984 |
| Human lymphocytes | Deltamethrin | Sister chromatid exchange | | ± | Dolara et al. 1992 |
| Human lymphocytes | Deltamethrin | Sister chromatid exchange | – | – | Villarini et al. 1998 |
| Human lymphocytes | Deltamethrin | Micronuclei | | ± | Surrallés et al. 1995 |
| Human lymphocytes | Deltamethrin | Micronuclei | – | – | Villarini et al. 1998 |
| Human lymphocytes | Deltamethrin | DNA damage | + | ± | Villarini et al. 1998 |
| Human whole blood | Deltamethrin | Micronuclei | | ± | Surrallés et al. 1995 |
| Chinese hamster ovary cells | Deltamethrin | Gene mutation | | – | Pluijmen et al. 1984 |
| Chinese hamster lung fibroblasts | Fenpropathrin | Chromosomal aberrations | – | – | Ryu et al. 1996 |
| Human lymphocytes | Fenpropathrin | Micronuclei | | ± | Surrallés et al. 1995 |
| Human whole blood | Fenpropathrin | Micronuclei | | ± | Surrallés et al. 1995 |
| Human lymphocytes | Fenvalerate | Chromosomal aberrations | | + | Puig et al. 1989 |
| Chinese hamster ovary cells | Fenvalerate | Chromosomal aberrations | + | – | Caballo et al. 1992 |
| Chinese hamster ovary cells | Fenvalerate | Sister chromatid exchange | + | + | Caballo et al. 1992 |
| Human lymphocytes | Fenvalerate | Micronuclei | | – | Surrallés et al. 1995 |

## Table 3-7. Genotoxicity of Type II Pyrethroids *In Vitro*

| Species (test system) | Chemical | End point | With activation | Without activation | Reference |
|---|---|---|---|---|---|
| Human whole blood | Fenvalerate | Micronuclei | | – | Surrallés et al. 1995 |
| Human lymphocytes | Fenvalerate | C–mitosis induction | | + | Carbonell et al. 1989 |
| Chinese hamster ovary cells | Fenvalerate | Gene mutation | | – | Pluijmen et al. 1984 |
| Pig lymphocytes | Supermethrin | Chromosomal aberrations | | + | Dianovský and Šiviková 1997 |
| Cattle lymphocytes | Supermethrin | Chromosomal aberrations | | + | Dianovský and Šiviková 1997 |
| Pig lymphocytes | Supermethrin | Sister chromatid exchange | | – | Dianovský and Šiviková 1997 |
| Cattle lymphocytes | Supermethrin | Sister chromatid exchange | | ± | Dianovský and Šiviková 1997 |
| Syrian hamster embryo cells | Supercyper-methrin | Morphological transformation | | + | Slameňová et al. 1992 |
| BHK21 (baby hamster kidney cells) | Supercyper-methrin | Anchorage independent growth | + | + | Slameňová et al. 1992 |

– = negative result; + = positive result; ± = weak positive result; DNA = deoxyribonucleic acid

Results of studies of volunteers and laboratory animals indicate that Type I and Type II pyrethroid compounds are absorbed from the gastrointestinal tract following oral exposure. Absorption is incomplete, with minimum estimates for absorption between 40 and 60% of an orally or intragastrically administered dose. However, first-pass metabolism may contribute significantly to under-estimation of the absorption of pyrethroids. Pyrethroids are rapidly absorbed in humans following inhalation exposure, but no estimates are available regarding how much of an inhaled dose is absorbed. Only small amounts (<2% of the applied dose) of pyrethroids are absorbed following dermal exposure, and the rate of absorption from this route is much slower than by the oral or inhaled routes. Pyrethroids may be stored in skin and then slowly released into the systemic circulation. Distribution of pyrethroids has not been well studied in humans; most of the available information is based on the results of studies in animals. Following absorption, pyrethroids are widely and rapidly distributed to most tissues, particularly to tissues with a high lipid content, and are concentrated in central and peripheral nervous tissues. Although there is little information on the metabolism of pyrethroids in humans, metabolism of pyrethroids has been extensively studied in animal models. The major metabolic pathways for pyrethroids are hydrolysis of the central ester bond, oxidative attacks at several sites, and conjugation reactions, to produce a complex array of primary and secondary water-soluble metabolites that undergo urinary excretion. Information on the specific enzymes involved in the metabolism of pyrethroid compounds is limited, but it appears to involve nonspecific microsomal carboxyesterases and microsomal mixed function oxidases, which are located in nearly all tissue types, with particularly high activities in the liver. Since microsomal enzymes play an important role in the metabolism of pyrethroids, it is expected that many tissue types are potentially capable of rapidly metabolizing these compounds. Elimination and excretion of pyrethroids in humans have not been extensively studied. Elimination appears to follow first-order kinetics, with elimination half-times in humans ranging from 6.4 to 16.5 hours, depending upon the specific pyrethroid and the exposure route studied. For most pyrethroids, elimination is nearly complete within 5 days of exposure, although certain isomers can persist in the body for a longer period of time. Pyrethroids have been shown to undergo urinary and fecal excretion in humans, but other routes of excretion, such as exhalation of volatile products, have not been studied. In animals, Type I and Type II pyrethroids undergo urinary, fecal, and biliary excretion, with urinary and fecal excretion as the primary routes; small quantities are also excreted in milk. Pyrethroids do not appear to be excreted as parent compounds via expired air of animals.

### 3.4.1 Absorption

Pyrethrins and pyrethroids are used to control insects in agricultural, commercial, and houshold environments. Since aerial application is the typical method by which pyrethrin- and pyrethroid-containing substances are dispersed, the use of such substances may result in combinations of inhalation, oral, and dermal exposure.

#### 3.4.1.1 Inhalation Exposure

Several studies demonstrate absorption of Type I and Type II pyrethroids following occupational exposure through identification of pyrethroid metabolites in urine (Aprea et al. 1997; Chester et al. 1987, 1992; Kühn et al. 1999; Leng et al. 1996, 1997b). In some cases, plasma levels of pyrethroids were below the limits of detection (5 µg/L) (Leng et al. 1997a, 1997b). Absorption of cyfluthrin in workers was confirmed by measurement of plasma cyfluthrin levels, although estimates of total exposure levels of cyfluthrin in these workers were not available (Leng and Lewalter 1999). It appears that pyrethroids are rapidly absorbed following inhalation, based on the appearance of urinary metabolites within 30 minutes of exposure (Leng et al. 1997a). In this study, an increase in the amount of urinary metabolites correlated with increasing exposure levels, indicating that absorption by the inhalation route is not capacity-limited, at least over the range of exposures studied (10–160 mg/m$^3$). However, occupational exposure of humans to pyrethroids may include inhalation, oral, and/or dermal routes. Studies providing estimates for total absorption of pyrethroids following inhalation or occupational exposure were not identified.

No information was located regarding absorption of pyrethroids following inhalation exposure in animals.

#### 3.4.1.2 Oral Exposure

Available information regarding oral exposure of humans indicates that both Type I and Type II pyrethroids are absorbed from the gastrointestinal tract. A 59-year-old male attempted suicide by drinking approximately 600 mL of 20% permethrin emulsion (143 grams) (Gotoh et al. 1998). The emulsion contained a mix of cis and trans isomers (43.5% cis and 56.5% trans). Maximal plasma concentrations of permethrin occurred 3–4 hours after ingestion. Both isomers were detected in plasma, indicating that both cis and trans isomers of permethrin are absorbed following oral administration. It is not possible to determine the fraction of the administered dose that was absorbed in this patient. Oral

exposure of a single volunteer demonstrated absorption of cyfluthrin by measurement of cyfluthrin metabolites in the urine, with an estimated minimum oral absorption of 40%, based on recovery of urinary cyfluthrin metabolites (Leng et al. 1997b). Similar results were observed in male volunteers exposed to cypermethrin, with absorption estimates ranging from 36 to 63% of the administered dose (Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Woollen et al. 1992). Estimates of absorption following oral exposure to pyrethroids may be low, however, since they are based on the appearance of metabolites in the urine and do not consider other routes of excretion, such as biliary excretion.

Observations in humans are supported by the results of animal studies. In several mammalian species, absorption of Type I pyrethroids following oral administration has been demonstrated by the presence of pyrethroid compounds in plasma, urine, and milk (Anadón et al. 1991b; Elliott et al. 1976; Gaughan et al. 1977, 1978; Hunt and Gilbert 1977; Ohsawa and Casida 1980; Tomigahara et al. 1994a, 1994b; Ueda et al. 1975a, 1975b). Following oral administration of a single dose of permethrin to rats, peak plasma levels of permethrin occurred 3–4 hours after ingestion, with an estimated total absorption of approximately 60% of the administered dose (Anadón et al. 1991b). In cows administered resmethrin orally, 43% of the administered dose was excreted in the urine as resmethrin metabolites, indicating a minimum absorption of 43% of the administered dose (Ridlen et al. 1984). Absorption of several Type II pyrethroids following oral administration has been demonstrated by the presence of pyrethroid compounds in plasma, urine, and milk (Anadón et al. 1996; Quistad and Selim 1983; Quistad et al. 1982, 1983). In Rhesus monkeys exposed to oral doses of $^{14}$C-fluvalinate, peak plasma levels were observed 2–3 hours after administration, with 37% of the administered dose eliminated in the urine as metabolites (Quistad and Selim 1983). Khan et al. (1986, 1990) demonstrated that $^{14}$C-labeled deltamethrin was absorbed by rats following the ingestion of plant material containing bound residues of the pyrethroid.

Differences in the rate and extent of absorption in young versus older rats were demonstrated in one study of rats administered $^{14}$C-fluvalinate by gavage (Quistad et al. 1983). In younger rats (7 weeks old), peak plasma levels of $^{14}$C occurred at 7 hours, compared to 14 hours in older rats. However, lower plasma $^{14}$C levels were observed in younger compared to older rats; thus, it is not clear whether fractional absorption was lower or higher in the younger rats. No information was located that could serve as a basis for predicting the effects of age on absorption of pyrethroids from the human gastrointestinal tract.

No information was located regarding possible sex-related differences in absorption of ingested pyrethroids in humans or animals.

### 3.4.1.3 Dermal Exposure

Limited information is available regarding absorption of Type I or Type II pyrethroids following dermal exposure in humans. Following dermal application of permethrin to patients for treatment of scabies, the estimated absorption of permethrin was 0.5% of the applied dose, based upon the urinary excretion of permethrin metabolites (van der Rhee et al. 1989). Urinary excretion of metabolites persisted for 7–10 days following a single dermal application, suggesting that pyrethroids may be stored in skin and slowly released into the systemic circulation. A study using an *in vitro* preparation of human skin indicated that only a small fraction (approximately 0.7%) of a topically applied dose of permethrin fully penetrated the skin after a single 48-hour exposure, with small amounts of permethrin identified in the epidermal and dermal layers (Franz et al. 1996). Two studies evaluated the absorption of cypermethrin following dermal application of a single dose to volunteers (Eadsforth et al. 1988; Woollen et al. 1992). Based upon the recovery of urinary metabolites of cypermethrin, it was estimated that 0.3–1.8% of the applied dose was absorbed. Peak urinary excretion of metabolites was observed between 14 and 36 hours after application. This is in contrast to observations following oral exposure of cypermethrin in humans in which the urinary excretion rate of metabolites was highest during the first 24 hours after dosing (Woollen et al. 1992).

Limited animal data are available regarding absorption of Type I or Type II pyrethroids following dermal exposure. Results of one study in rats are consistent with findings in humans; approximately 0.7% of a dermal application of fluvalinate was absorbed (Quistad et al. 1983). A single study indicates that fenvalerate is absorbed more quickly following dermal exposure to goats compared with other mammalian species, with peak plasma concentrations reached 2 hours after dosing (Mandal et al. 1996). The total percutaneous absorption of fenvalerate was not determined in that study. Percutaneous absorption of permethrin was demonstrated in guinea pigs *in vivo* following a single dermal application (Franz et al. 1996). In this study, absorption was found to be 20-fold greater than that measured in a preparation of human skin. The percutaneous absorption of permethrin in rats, as measured by recovery of $^{14}C$ in urine and feces, was estimated to be 46% of the applied dose (Shah et al. 1987). This finding is not consistent with lower estimates from other studies in humans and animals and may be attributed to lack of restraint of the animals, allowing for oral exposure from licking of the application site. However, insufficient information is provided in the report to confirm this possibility. In this same study, there was no difference in the absorption of young (33 days) versus adult rats exposed to a single dermal application of permethrin.

No additional information was located regarding sex- or age-related differences in absorption of pyrethroids following dermal exposure in humans or animals. There is no obvious structural basis for predicting substantial differences in the percutaneous absorption of Type I and Type II compounds in humans.

### 3.4.2 Distribution

No information is available regarding the distribution of Type I and Type II pyrethroid compounds or pyrethroid metabolites in humans, except for information regarding the distribution of pyrethroids and pyrethroid metabolites into excretory compartments. Given the lipophilic nature of pyrethroids, it is expected that, in humans, they are widely distributed and undergo rapid distribution to tissues with a high lipid content, including fat and central and peripheral nervous tissues. Based upon observations of central and peripheral nervous system toxicity in humans exposed to pyrethroid compounds, it is apparent that distribution of pyrethroids to these tissues occurs (Aldridge 1990; Casida et al. 1983; Vijverberg and van den Bercken 1990). Since pyrethroid metabolites are less lipid soluble than the parent compounds, it is expected that distribution of metabolites to central and peripheral nervous tissues would be decreased compared to that of the parent compounds. Studies in several mammalian species confirm that pyrethroids are widely and rapidly distributed to many tissues, including liver and kidney, and are concentrated in central and peripheral nervous tissues. In pregnant and lactating animals, pyrethroids are distributed into milk. Although animal studies of placental transfer of pyrethroids indicate that pyrethroids do not cross the placenta in substantial amounts or accumulate in the fetus (Kaneko et al. 1984b; Quistad et al. 1982; Shiba et al. 1990), other animal studies indicate that *in utero* exposure to pyrethroids may result in persistent effects on neurotransmitters (Malaviya et al. 1993; Santoni et al. 1999) and on the immune system (Santoni et al. 1997, 1998, 1999). Interpretation of results obtained from many of the distribution studies in animals is limited by the study design; the distribution of pyrethroids was typically evaluated in tissues collected from animals after most of the chemical had been excreted from the body (1–8 days after treatment with the last dose).

#### 3.4.2.1 Inhalation Exposure

No information was located regarding the distribution of pyrethroids in humans or animals following inhalation exposure.

### 3.4.2.2 Oral Exposure

Limited information is available on the distribution of Type I or Type II pyrethroids in humans following oral exposure, and most of the available information describes the distribution of pyrethroids and pyrethroid metabolites into excretory compartments (reviewed in Section 3.4.3.2). Based on the results of a study in which plasma permethrin concentrations were measured in an adult male who ingested permethrin in a suicide attempt, permethrin appears to follow a two-compartment model, with distribution half-times for the trans and cis compounds of 5.08 and 4.82 hours, respectively (Gotoh at el. 1998). One study that investigated the elimination of $^{14}$C-deltamethrin in volunteers following oral administration showed that small amounts of deltamethrin or its metabolites were distributed to saliva (Stockis et al. 1985). In this same study, evaluation of the distribution of $^{14}$C in plasma indicated that approximately 25% of the plasma $^{14}$C was associated with red blood cells.

In rats, permethrin was rapidly distributed to nervous tissues after administration of a single oral dose, with a distribution half-time of 4.85 hours (Anadón et al. 1991b). Plasma levels of permethrin exhibited a bi-phasic decline, which can be represented by a two-compartment model with a rapid distribution phase. Based on a large apparent volume of distribution, it appears that permethrin is distributed in both extracellular and intracellular fluids, indicating that pyrethroids can easily cross cell membranes. Permethrin concentrations in nervous tissue were higher than those measured in plasma, indicating that permethrin is concentrated in nerve tissue relative to plasma. Concentrations in nerve tissue were highest in the sciatic nerve, followed by (in decreasing order) hypothalamus, frontal cortex, hippocampus, caudate putamen, cerebellum, and medulla oblongata. Peak concentrations were observed to occur within 4 hours of dosing in both nerve tissue and plasma. Permethrin was also distributed to the liver, with peak concentrations observed within 4 hours of dosing. Concentrations of permethrin metabolites (*m*-phenoxy-benzyl alcohol and *m*-phenoxybenzoic acid) in nerve tissues were lower than those observed for the parent compound. Although it is not possible to determine if the permethrin metabolites entered the nerve tissue from blood or if permethrin was metabolized to its metabolites in nerve tissue, distribution of the more lipid soluble parent compounds into nerve tissue is considered more likely (Anadón et al. 1991a, 1991b). $^{14}$C-Permethrin or its metabolites are also rapidly distributed to the kidney following oral administration to rats, with levels of $^{14}$C in the kidney peaking approximately 4 hours after dosing (Miyamoto et al. 1968). Studies in lactating cows indicate that very low levels of Type I pyrethroids (e.g., <0.5% of the administered dose) are distributed into milk (Gaughan et al. 1978; Ridlen et al. 1984). Following oral exposure, permethrin or its metabolites have also been detected in fat of cows and rats up to12 days after dosing (Gaughan et al. 1977, 1978).

Fluvalinate was widely distributed in rats following oral exposure to $^{14}$C-fluvalinate, based on detection of small amounts of $^{14}$C in nearly all tissue types (Ruzo et al. 1978). However, interpretation of these results must be made with caution, since tissue levels of $^{14}$C were measured in animals that had been sacrificed 8 days after oral dosing and nearly all of the $^{14}$C had been eliminated from the body by that time. In rats, deltamethrin was rapidly distributed to nerve tissues after administration of a single oral dose, with a distribution half-time of 2.1 hours (Anadón et al. 1996). Plasma levels of deltamethrin exhibited a bi-phasic decline, which can be represented by a two-compartment model with a rapid distribution phase. Deltamethrin concentrations in nerve tissue were higher than those measured in plasma, indicating that deltamethrin is concentrated in nervous tissue relative to plasma. Concentrations in nerve tissue were highest in the hypothalamus, followed by (in decreasing order) hippocampus, cerebellum, frontal cortex, caudate putamen, and medulla oblongata, with peak concentrations occurring between 4 and 6 hours after oral administration. Similar distribution was observed for the 4-OH-metabolite of deltamethrin but, in general, the concentrations of metabolite measured in each tissue were less than those measured for the parent compound. It is not possible to determine if the metabolite entered the nervous tissue from blood or if deltamethrin was metabolized to the 4-OH-metabolite by nervous tissue. However, distribution of the more lipid soluble parent compounds into nerve tissue is considered more likely due to the lower lipid solubility of the metabolites (Anadón et al. 1996). Deltamethrin and its 4-OH metabolite were also detected in vas deferens and anococcygeus muscle at concentrations that were greater than plasma but less than those observed in nervous tissue (Anadón et al. 1996). Residual amounts of pyrethroids have been measured in fat several days after oral exposure to lambs and cows (Quistad et al. 1982; Wszolek et al. 1981a, 1981b). Studies in lactating cows indicate that Type II pyrethroids are rapidly distributed into milk after exposure to a single oral dose, but that only small amounts of the total dose are distributed to milk (0.4–0.9% of the administered dose) (Quistad et al. 1982; Wszolek et al. 1980). Pyrethroids do not appear to cross the placenta in substantial amounts or accumulate in the fetus of animals, as evidenced by the results of dosing of pregnant rats and a single cow. Measurements of radioactivity in fetuses of rats administered radiolabeled pyrethroids indicated that <0.004% of the administered dose of the Type I pyrethroid, tetramethrin, was recovered in the fetus (Kaneko et al. 1984b). Recovered activity from radiolabeled fenvalerate (a Type II pyrethroid) was <0.07% (Shiba et al. 1990). Eight days after a pregnant cow was given a single dose of $^{14}$C-fluvalinate, only trace amounts of $^{14}$C were detected in the fetus (Quistad et al. 1982).

The results of Anadón and coworkers (Anadón et al. 1991b, 1996) indicate that the Type II pyrethroid, fluvalinate, may be more rapidly distributed than permethrin, a Type I pyrethroid, following dermal

exposure in rats. These apparent differences in distribution of permethrin and fluvalinate could be the result of chemical or toxicokinetic differences in these pyrethroids or Type I and Type II pyrethroids in general, although no data are presently available to confirm or refute this possibility.

No information was located regarding distribution within tissues of pyrethroid compounds following oral exposure of humans or animals. No information was located regarding sex- or age-related differences in distribution of Type I and Type II pyrethroids following oral exposure of humans or animals.

#### 3.4.2.3 Dermal Exposure

No information is available regarding distribution of Type I or Type II pyrethroids in humans following dermal exposure, and available data from animal studies are limited. In guinea pigs exposed to dermally applied permethrin, the concentration of permethrin measured in brain tissue 24 hours after dosing was 7-fold higher than that of plasma (Franz et al. 1996). Residual tissue concentrations of fenvalerate, but not of its metabolites, were determined 4 days after administration of a single dermal dose to goats (Mandal et al. 1996). The highest concentration was observed in the adrenal gland, followed by (in decreasing order) biceps muscle, omental fat, liver, kidney, lung, and cerebrum. Interpretation of these data is hindered because at the time of fenvalerate tissue content measurement, the majority of the dose had been eliminated (only small amounts of fenvalerate remained in plasma at 3 days after dosing). No additional studies were located concerning distribution of Type I or Type II pyrethroids, and no information was available regarding age- or sex-related differences in distribution.

#### 3.4.2.4 Other Routes of Exposure

No information was located regarding distribution of pyrethroids in humans following exposure by other routes.

Following intravenous administration in rats, Type I and Type II pyrethroids are rapidly and widely distributed to tissues and are concentrated in nervous tissue (Anadón et al. 1991b, 1996; Gray and Rickard 1982; Gray et al. 1980a; Silver and Dauterman 1989a). Plasma levels of parent compound exhibit a bi-phasic decline and fit a two-compartment model with rapid distribution phase (Anadón et al. 1991b, 1996). Distribution to the central nervous system is very rapid, with concentrations reaching peak levels

within 5 minutes of administration (Gray et al. 1980a). Following intraperitoneal injection of rats with Type I pyrethroids, pyrethroids are rapidly distributed to the liver and are found to be associated with several subcellular fractions, including microsomes, indicating that pyrethroids are rapidly distributed to a detoxifying organ (Graillot and Hoellinger 1982). Results of these studies provide supportive evidence for the expectedly rapid and wide distribution of pyrethroids after absorption in humans.

No information was located regarding sex- or age-related differences in distribution of pyrethroids following parenteral exposure.

### 3.4.3 Metabolism

Extensive study of the metabolic pathways involved in the biotransformation of pyrethroids in humans has not been undertaken. Information on the metabolism of Type I and Type II pyrethroid compounds in humans is based upon identification of pyrethroid metabolites in urine and blood obtained in a small number of studies conducted under controlled conditions or following occupational exposures. In contrast, the metabolism of Type I and Type II pyrethroid compounds has been extensively studied in several mammalian animal models. Since the metabolites that have been identified in humans have also been identified in other mammalian species, it is unlikely that there are significant qualitative differences between humans and other mammals in the major metabolic pathways for pyrethroids, although some species differences do undoubtedly exist (Anadón et al. 1991b; Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Elliott et al. 1976; Gaughan et al. 1977; Leng et al. 1997a, 1997b; Woollen et al. 1992). The following summary of pyrethroid metabolism is based on the results of extensive investigations of the metabolism of pyrethroids in mammalian models. It is presumed that these metabolic pathways pertain to human metabolism of pyrethroid compounds, although there may be important quantitative differences between species.

All synthetic pyrethroid compounds appear to be degraded by similar metabolic processes in mammals. Upon administration of pyrethroids to mammals, biotransformation takes place through hydrolysis of the central ester bond, oxidative attacks at several sites, and conjugation reactions to produce a complex array of primary and secondary water-soluble metabolites that undergo urinary and biliary excretion (Casida et al. 1983; Gray and Soderlund 1985; Leng et al. 1999a). It is widely accepted that metabolism results in the formation of compounds that have little or no demonstrable toxicity, although the formation of reactive or toxic intermediates cannot be ruled out, and it appears that cleavage of the ester bond results in substantial detoxification (Gray and Soderlund 1985; Hutson 1979). For halogenated pyrethroids (such as

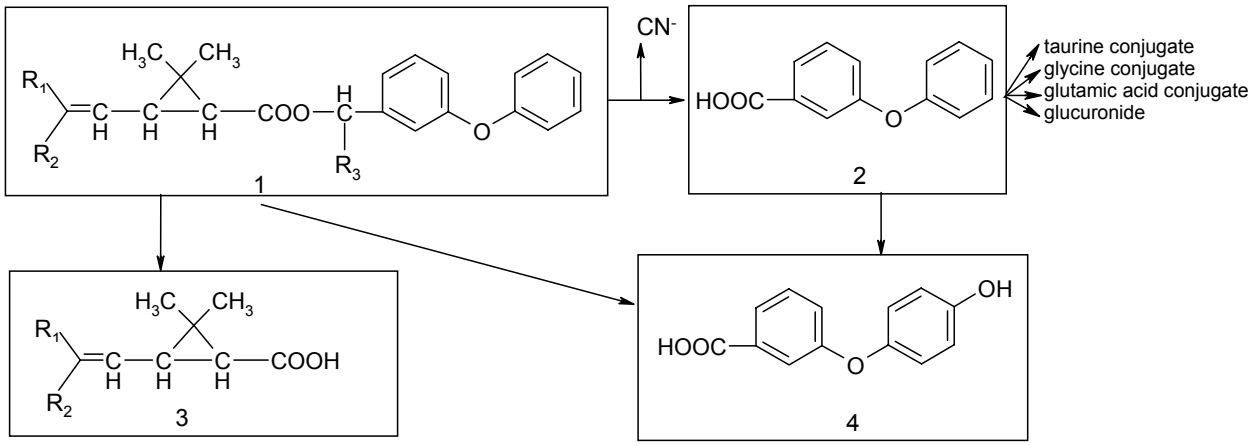
cyfluthrin, cypermethrin, and permethrin), rapid hydrolytic cleavage of the ester bond is followed by oxidation to yield carboxylic acid derivatives and phenoxybenzoic acid derivatives (Leng et al. 1997a, 1997b). These metabolites are, in general, excreted as alcohols, phenols, carboxylic acids, and their glycine, sulfate, glucuronide, or glucoside conjugates (Aprea et al. 1997; Casida et al. 1983). Metabolic pathways for permethrin, cypermethrin, and deltamethrin are shown in Figure 3-3. However, depending upon the type of pyrethroid compound, either oxidation or hydrolysis may predominate (Miyamoto 1976). The presence of the alpha-cyano group of the Type II pyrethroid compounds has been shown to decrease the rate of hydrolytic cleavage of the ester bond (Casida et al. 1983). Many of the trans enantiomers of pyrethroid compounds are metabolized mainly through hydrolytic cleavage of the ester linkage, with subsequent oxidation and/or conjugation of the component alcohol and acid moieties, whereas certain cis enantiomers are more resistant to hydrolytic attack and are degraded via oxidation at various sites of the molecule (Miyamoto 1976; Shono et al. 1979). For pyrethroids containing an alpha-cyanophenoxybenzyl substituent (Type II pyrethroids), cleavage of the ester bond results in the release of cyanide, which is rapidly converted mainly to thiocyanate (Casida et al. 1983; Gray and Soderlund 1985; Ohkawa et al. 1979). It does not appear that there is significant additional metabolic fragmentation of the acid and alcohol moieties, since metabolism studies with $^{14}C$-labeled pyrethroid compounds yield little or no detectable $^{14}CO_2$ (Ohkawa et al. 1979; Ruzo et al. 1978).

Information on the specific enzymes involved in the metabolism of pyrethroid compounds is limited. Metabolism appears to involve nonspecific microsomal carboxyesterases and microsomal mixed function oxidases, which are located in nearly all tissue types (Casida et al. 1983; Miyamoto 1976; Shono et al. 1979). Since microsomal enzymes play an important role in the metabolism of pyrethroids, it is expected that many tissue types are potentially capable of rapidly metabolizing these compounds, with a particularly important role for the liver. Pyrethroids are metabolized in blood *in vitro* (Gray and Rickard 1982). Metabolism of pyrethroids may also occur in the brain (Anadón et al. 1996; Ghiasuddin and Soderlund 1984), which may contribute to the detoxification of some pyrethroids in mammals (Ghiasuddin and Soderlund 1984).

Information on the effects of induction or inhibition of microsomal enzymes by other chemicals or drugs on the rate of metabolism of pyrethroid compounds in humans or animals was not identified.

No information was located regarding sex- or age-related differences in metabolism of pyrethroids following exposure in humans or animals.

## Figure 3-3. Metabolic Diagram for Deltamethrin, Permethrin, and Cypermethrin




1 { deltamethrin $R_1 = R_2 = Br$ $R_3 = CN$
permethrin $R_1 = R_2 = Cl$ $R_3 = H$
cypermethrin $R_1 = R_2 = Cl$ $R_3 = CN$

2 { 3-phenoxybenzoic acid (3-PBA)

3 { 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (DCVA)
3-(2,2-dibromovinyl)-2,2-dimethy-cyclopropane carboxylic acid (DBVA)

4 { 3-(4-hydroxy)-phenoxybenzoic acid (4-OHPBA)

### 3.4.3.1 Inhalation Exposure

The results of a single study of cyfluthrin in humans demonstrate that, when administered by the inhalation route, pyrethroids are rapidly metabolized, with metabolites appearing in the urine by 30 minutes after exposure (Leng et al. 1997a).

No studies were located regarding metabolism of pyrethroids following inhalation exposure to animals.

### 3.4.3.2 Oral Exposure

Given the important role of hepatic microsomal enzymes in the biotransformation of xenobiotics, accurate estimates of absorption following oral administration of pyrethroid compounds must take into account first-pass metabolism. Studies in humans indicate that the absorption of orally administered pyrethroids is incomplete; however, these studies do not provide evidence for first pass metabolism (Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Woollen et al. 1992). Results of a study in isolated perfused rat liver are supportive for an important role for first-pass metabolism of pyrethroid compounds (Silver and Dauterman 1989b). In this study, the hepatic extraction ratios for both cis and trans isomers of tetramethrin were approximately 0.9, and both the cis and trans isomers were rapidly metabolized by the liver. If the high *in vitro* extraction is indicative of *in vivo*, then first-pass extraction from the hepatic portal circulation and metabolism would be likely. Incomplete absorption of pyrethroids following oral exposure may also result from metabolism within the gastrointestinal tract or binding to poorly absorbed components of the ingesta. Results of studies in rats indicate that pyrethroid metabolites are produced within the gastrointestinal tract (Tomigahara et al. 1994b). Metabolites from permethrin were recovered in the feces following oral administration to rats, suggesting the possibility of metabolism in the gastrointestinal tract or fecal elimination of metabolites formed after absorption (Gaughan et al. 1977).

Although no information is available regarding sex-related differences in metabolism following oral administration of pyrethroids in humans, no differences in metabolism were observed in male and female rats orally exposed to pyrethroids (Quistad et al. 1983).

#### 3.4.3.3 Dermal Exposure

Little information is available regarding metabolism of pyrethroid compounds following dermal exposure. Following dermal application of permethrin to patients for treatment of scabies, permethrin metabolites were recovered from urine (van der Rhee et al. 1989). Results of a single study in volunteers comparing urinary metabolite profiles following oral and dermal exposure to cis- and trans-cypermethrin isomers demonstrated a difference in the urinary metabolite profiles following exposure by each route (Woollen et al. 1992). Following oral exposure, urine contained a higher proportion of trans-metabolites compared to that obtained following dermal exposure. These results could indicate differences in absorption or metabolism between these two routes of exposure.

No information was located regarding sex- or age-related differences in metabolism following dermal administration of pyrethroids to humans or animals.

### 3.4.4 Elimination and Excretion

#### 3.4.4.1 Inhalation Exposure

The results of a single study examining urinary metabolites in humans following inhalation exposure to cyfluthrin indicate that elimination follows first-order kinetics, with 93% of the urinary elimination complete within 24 hours of exposure (Leng et al. 1997a). Elimination half-times for the cyfluthrin metabolites cis-/trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (DCCA), 4-fluoro-3-phenoxybenzoic acid (FPBA), and their isomers ranged from 5.3 to 6.9 hours. These elimination half-times remained constant over a range of exposure levels, providing supportive evidence that pyrethroids exhibit first-order elimination kinetics. The amounts of cyfluthrin metabolites excreted in urine correlated with increasing exposure levels, demonstrating that urinary levels of pyrethroid metabolites may be a useful indicator of exposure level.

Several studies of occupational exposure of humans to pyrethroids were located; however, the exposures may have been by the inhalation, oral, or dermal routes, or a combination of these routes. Following occupational exposure to Type I and Type II pyrethroid compounds, excretion of pyrethroid metabolites in the urine occurs and is nearly complete within 4 days of exposure (Aprea et al. 1997; Chester et al.

1987; Kühn et al. 1999). Based on elimination of cyfluthrin from plasma, the elimination half-time is estimated to be between 0.5 and 2 hours (Leng and Lewalter 1999). Based on elimination of metabolites into the urine, the elimination half-times are 5 hours for cyfluthrin and 8 hours for cypermethrin (Kühn et al. 1999). No information was provided in these studies regarding the amount of pyrethroid eliminated by nonurinary routes.

No information was located regarding sex- or age-related differences, or other factors, that might affect the elimination and excretion of pyrethroids following inhalation exposure of humans or animals.

#### 3.4.4.2 Oral Exposure

Limited information is available regarding the elimination and excretion of Type I and Type II pyrethroid compounds following oral exposure in humans. The elimination half-time of cis-permethrin in plasma following ingestion of a mix of cis and trans isomers of permethrin in a suicide attempt was approximately 67 hours (Gotoh et al. 1998). Trans-permethrin was eliminated from the blood more quickly than the cis isomer and was undetectable in blood after 25 hours. However, an estimate of the plasma elimination half-time for the trans isomer was not reported. This patient was noted to have a history of chronic renal dysfunction, but no specific details were reported. Therefore, it is not possible to determine how this patient's renal status may have affected the elimination of permethrin from the plasma. In humans exposed to single oral doses of Type II pyrethroids, the elimination half-time based on the appearance of metabolites in the urine has been estimated to be between 6 and 13 hours (Leng et al. 1997b; Woollen et al. 1992). Approximately 35–50% of the administered dose was excreted in the urine as metabolites during the first 5 days after dosing, with peak urinary excretion rates observed during the first 24 hours after dosing (Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Leng et al. 1997b; Woollen et al. 1992). It is not possible to determine the percentage of the administered dose that was eliminated in the urine in these studies since only the urinary pyrethroid metabolites, and not total urinary pyrethroids (parent compound plus metabolites), were measured. Fecal elimination following oral dosing of Type II pyrethroids in humans has been confirmed based on the results of one study in humans, but neither the fraction of the administered dose excreted in feces nor the identity of the compounds excreted in feces were determined (Stockis et al. 1985).

Results of animal studies indicate that Type I and Type II pyrethroids are almost completely eliminated from the body within 4–12 days following oral exposure, with the majority of the dose eliminated within the first 12–48 hours (Anadón et al. 1996; Elliott et al. 1976; Gaughan et al. 1977; Hunt and Gilbert 1977;

Lee et al. 1985; Quistad and Selim 1983; Quistad et al. 1982; Ridlen et al. 1984; Ruzo et al. 1978; Staiger and Quistad 1984; Wszolek et al. 1980). Type I and Type II pyrethroids exhibit first-order elimination kinetics. An estimate for the elimination half-time of permethrin in rats is approximately 8 hours (Anadón et al. 1991b). In oral studies, the plasma elimination half-time for fluvalinate in Rhesus monkeys was 2–3 hours, whereas, in rats, the elimination half-time of deltamethrin was 38.5 hours, although the time from administration to peak levels of the pyrethroids in both studies was similar (approximately 2–3 hours) (Anadón et al. 1996; Quistad and Selim 1983). It is not known if the differences in the elimination half-times observed in these studies are related to species differences, differences in dose, or differences in the elimination kinetics of the specific pyrethroid compounds.

In monkeys, cows, and rats, a large portion of the orally administered dose (43–56%) is excreted in the urine (Quistad and Selim 1983; Quistad et al. 1982; Ridlen et al. 1984; Staiger and Quistad 1984), primarily as metabolites. In rats subject to oral exposure, almost all of the pyrethroids recovered in the urine are metabolites, with urine containing very little of the unchanged compound (Ueda et al. 1975b). In monkeys, cows, and rats, approximately 45–60% of the orally administered dose is excreted in the feces as a mix of parent compound and metabolites (Miyamoto et al. 1968; Quistad and Selim 1983; Quistad et al. 1982; Ridlen et al. 1984; Staiger and Quistad 1984; Ueda et al. 1975b). The urinary excretion route appears to be more important for trans-permethrin metabolites, while the fecal excretion route appears to be more important for cis-permethrin metabolites (Elliott et al. 1976; Hunt and Gilbert 1977).

Studies performed using cows, rats, and monkeys indicate that pyrethroids undergo biliary excretion, although estimates for the amount of biliary excretion were not available in these studies (Quistad and Selim 1983; Quistad et al. 1982, 1983). Based on the results of a study in isolated perfused rat liver, it appears that tetramethrin may undergo extensive biliary excretion (Silver and Dauterman 1989b). Studies in lactating cows and goats indicate that only very low levels of Type I pyrethroids are excreted (<1% of the administered dose) in milk (Gaughan et al. 1978; Hunt and Gilbert 1977; Quistad et al. 1982; Ridlen et al. 1984; Wszolek et al. 1980). In one study, one pregnant cow was administered a single oral dose of $^{14}$C-fluvalinate and tissues were examined for radioactivity 8 days after dosing (Quistad et al. 1982). Analysis of the $^{14}$C content of the fetus indicates minimal transfer of fluvalinate or its metabolites to the fetus (approximately $1x10^{-5}$% of the administered dose). It does not appear that pyrethroids are excreted in significant amounts via expired air (Gaughan et al. 1977; Ohkawa et al. 1979; Ruzo et al. 1978; Ueda et al. 1975b).

Apart from the finding that pyrethroids may be excreted in milk, no additional information was located regarding sex-related differences, and no information was located regarding age-related differences, which might affect the elimination and excretion of pyrethroids following oral exposure of humans or animals.

#### 3.4.4.3 Dermal Exposure

Limited information is available regarding elimination and excretion of pyrethroids following dermal exposure in humans. Results of two studies in humans exposed to single dermal doses of cypermethrin indicate that a small fraction (0.1–1.2%) of the administered dose is excreted in the urine as metabolites (Eadsforth et al. 1988; Woollen et al. 1992). Peak urinary excretion rates were observed between 12 and 36 hours after dosing (Woollen et al. 1992). Following dermal application of a single permethrin dose to patients for treatment of scabies, permethrin metabolites were excreted in urine, with urinary excretion persisting for 7 days after exposure (van der Rhee et al. 1989).

In rats exposed to single dermal doses of permethrin, >90% of the absorbed dose was excreted in urine and feces, with a urine-to-fecal ratio of approximately 4:1 (Shah et al. 1987). While results of this study may provide evidence for fecal excretion following exposure by a nonoral route, it is possible that oral exposure occurred through licking of the application site if the animals were not properly restrained. In this study, no differences were noted in urinary excretion between young and adult rats. No other studies were located in which age-related differences in elimination and excretion of pyrethroids or their metabolites were assessed following dermal exposure. Following dermal exposure of rats to $^{14}$C-fluvalinate, 0.7 and 0.8% of the administered radioactivity was excreted in the urine and feces, respectively (Quistad et al. 1983). In this study, one group of animals was not restrained and the animals were able to lick the application site, which may have resulted in oral exposure and higher urinary and fecal excretion of $^{14}$C.

No information was located regarding sex-related differences, or other factors, that might affect the elimination and excretion of pyrethroids following dermal exposure in humans or animals.

#### 3.4.4.4 Other Routes of Exposure

No information was located regarding the elimination and excretion of Type I or Type II pyrethroids in humans following parenteral exposure. In rats administered a mix of cis- and trans-tetramethrin intravenously, the elimination half-time for the cis isomer was less (72 minutes) than that observed for the trans isomer (125 minutes) (Silver and Dauterman 1989a). Following intravenous administration to the rats, tetramethrin metabolites were recovered from both urine and, to a lesser extent, feces, providing evidence for biliary excretion. No unmetabolized tetramethrin was recovered in the urine. Only a small amount of the parent cis isomer was identified in the feces. Fecal excretion appears to be the major excretory pathway for the cis isomer, whereas urinary excretion appears to be the major excretory route for the trans isomer. Thus, biliary elimination appears to be more important for the cis isomer than for the trans isomer. In rats administered deltamethrin and its metabolite (4-OH-deltamethrin) intravenously, elimination half-times were 33 and 25 hours, respectively. In another phase of this study involving gavage administration, similar elimination rates were observed (Anadón et al. 1996).

No information was located regarding age- or sex-related differences that might affect the excretion and elimination of pyrethroids following parenteral exposure in humans or animals.

### 3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can

be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

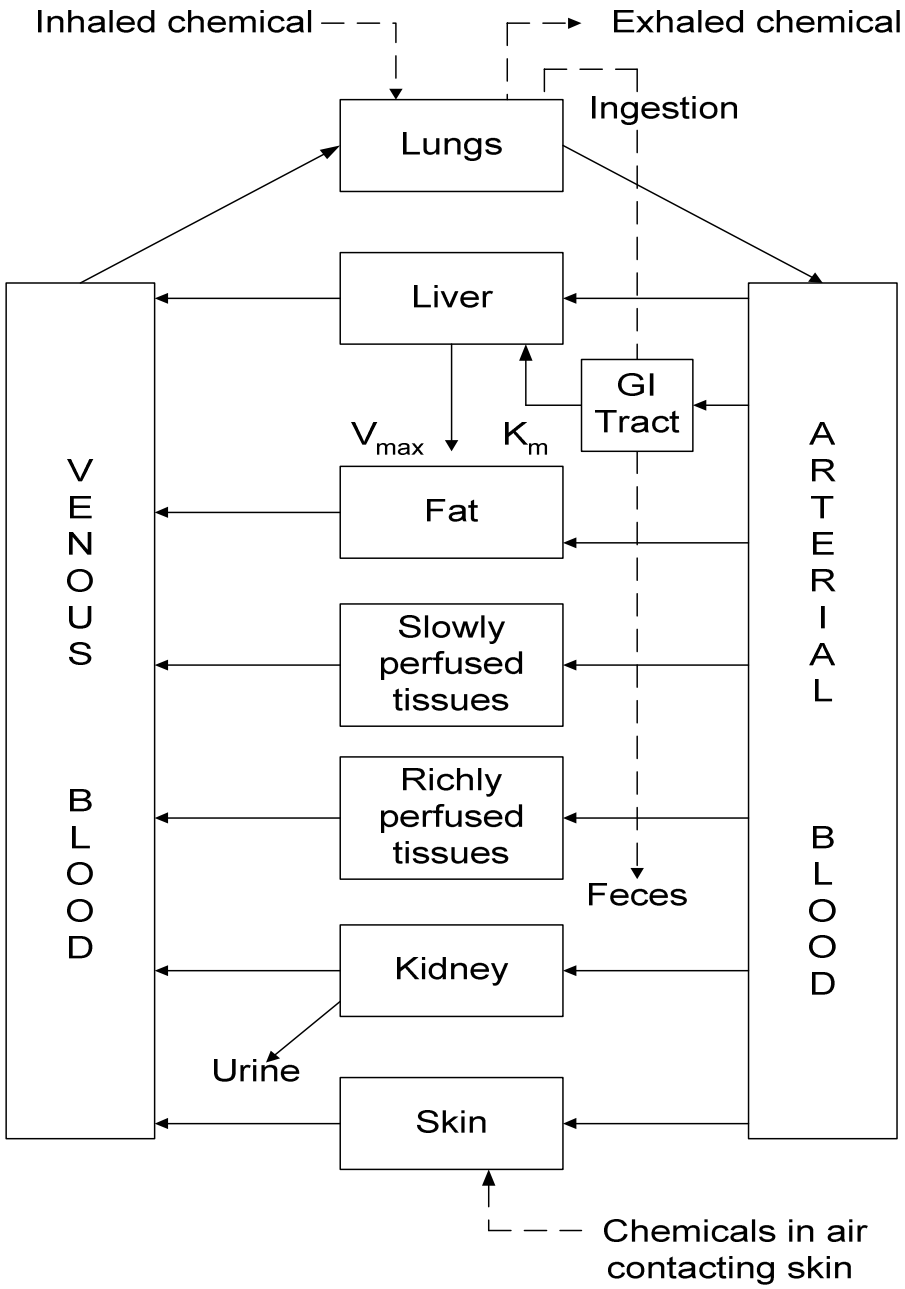
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

No PBPK models for exposure to pyrethroid compounds were identified. Thorough study of the toxicokinetic profiles of Type I and Type II pyrethroids in humans or experimental animals has not been undertaken. Empirical models for exposure to Type I (permethrin) and Type II (deltamethrin) pyrethroids have been developed based upon the results of two studies in rats (Anadón et al. 1991b, 1996). The

**Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance**




Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

empirical models developed from these toxicokinetic studies yielded similar results for both compounds, indicating that the biodisposition of Type I and Type II compounds is similar. Pyrethroids are rapidly absorbed following oral exposure. Following oral and intravenous exposure, permethrin and deltamethrin plasma kinetics are described by a two-compartment model with a relatively rapid distribution phase, followed by a slower elimination phase. Following intravenous administration, the distribution and elimination half-times were 0.46 and 8.67 hours for permethrin, respectively, and 1.39 and 33.0 hours for deltamethrin, respectively. Under these experimental conditions, permethrin was eliminated more rapidly than deltamethrin.

## 3.5 MECHANISMS OF ACTION

### 3.5.1 Pharmacokinetic Mechanisms

**Absorption.** No information was located regarding the mechanism of absorption of pyrethroids from the gastrointestinal tract. Since pyrethroids are lipophilic compounds, it is presumed that they cross intestinal cells and pass into the circulation by diffusion across lipid membranes. No information was identified on the location of absorption of pyrethroids within the gastrointestinal tract. However, it is presumed that most of the absorption takes place in the intestines due to the large exposed surface area. Although no information was located regarding the mechanism of absorption through the skin or across alveolar membranes, it is presumed that pyrethroids cross these barriers by diffusion across lipid membranes.

**Distribution.** No information was located regarding the transport of pyrethroid compounds in blood. Pyrethroids are distributed to nearly all tissues and are concentrated in tissues with high lipid contents, such as fat and nerve tissue (Anadón et al. 1991b, 1996). It is likely that the pattern of concentration in lipid-rich tissues is due to the high lipid solubility of pyrethroid compounds. Since metabolism of pyrethroids results in products that are more water-soluble than the parent compounds, it is likely that the metabolites are less able to cross the blood-brain barrier, unless there are facilitated mechanisms for transport of pyrethroid metabolites that have not yet been characterized.

**Metabolism.** Upon administration of pyrethroids to mammals, biotransformation takes place through hydrolysis of the central ester bond, oxidative attacks at several sites, and conjugation reactions to produce a complex array of primary and secondary water-soluble metabolites that undergo urinary excretion (Casida et al. 1983; Gray and Soderlund 1985; Leng et al. 1999a, 1999b). It is well accepted

that these metabolites have little or no demonstrable toxicity, although the formation of reactive or toxic intermediates cannot be ruled out, and it appears that cleavage of the ester bond results in detoxification (Gray and Soderlund 1985). For halogenated pyrethroids (such as cyfluthrin, cypermethrin, and permethrin), rapid hydrolytic cleavage of the ester bond is followed by oxidation to yield carboxylic acid derivatives and phenoxybenzoic acid derivatives (Leng et al. 1997a, 1997b). These metabolites are then generally metabolized further and form conjugated products with compounds such as glycine, sulfate, and glucuronic acid (Aprea et al. 1997; Casida et al. 1983). Information on the specific enzymes involved in metabolism of pyrethroid compounds is limited. Metabolism appears to involve nonspecific microsomal carboxyesterases and microsomal mixed function oxidases, which are located in nearly all tissue types.

**Excretion.** No information was located regarding the specific mechanisms of excretion of pyrethroid compounds. However, metabolism of pyrethroids results in products that are water soluble and, therefore, are more readily eliminated from the body by renal and biliary excretion. No information is available regarding the mechanisms of excretion of pyrethroids and pyrethroid metabolites by the kidney, but it is expected that pyrethroids and their metabolites are eliminated, at least in part, by glomerular filtration since their molecular size is not restrictive for passage though the glomerular membrane. However, there is no information on the extent to which these compounds bind to plasma proteins, which might restrict their glomerular filtration. No information was located regarding mechanisms of excretion for the biliary or salivary routes of elimination. No information was located regarding mechanisms involved in the passage of pyrethroids into milk, although excretion into milk most likely occurs via lipid diffusion across membranes with retention in milk fat.

### 3.5.2 Mechanisms of Toxicity

The primary site of action for pyrethrins and pyrethroids is the sodium channel of nerve cells, as is also the case for DDT and its analogs (for reviews, see Cassida et al. 1983; Coats 1990; Narahashi 1985; Sattelle and Yamamoto 1988; Soderlund 1995; Soderlund et al. 2002; Valentine 1990; Vijverberg and van den Bercken 1990). Using a variety of methods, including voltage clamp and patch clamp techniques, it has been shown that pyrethrins and pyrethroids slow the closing of sodium channel gates following an initial influx of sodium during the depolarizing phase of an action potential, which results in a prolonged sodium tail current (Narahashi 1986; Vijverberg and Van den Bercken 1982). 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 (Coats 1990; Verschoyle and Aldridge 1980). Type I pyrethroids do not include a cyano group; their effects in rodents 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. Type II pyrethroids include a cyano group; their effects in rodents are usually characterized by pawing and burrowing behavior, followed by profuse salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremor that progresses to sinuous writhing (choreoathetosis). Clonic seizures may be observed prior to death. Body temperature is not increased, but may decrease. The term CS-syndrome (from choreoathetosis and salivation) has been applied to Type II responses. Two of the cyano-pyrethroids, fenpropathrin and cyphenothrin, have been shown to trigger responses intermediate to those of T-syndrome and CS-syndrome, characterized by both tremors and salivation (Miyamoto et al. 1995; Wright et al. 1988). Mechanisms underlying this intermediate response type have not been elucidated. Occupational exposure to pyrethroids (particularly Type II pyrethroids containing the cyano group) frequently leads to paresthesia (abnormal cutaneous sensations such as tingling, burning, numbness, and itching). This response is considered to be the result of the direct action of pyrethroids on sensory nerve endings (LeQuesne and Maxwell 1980; Wilks 2000), causing repetitive firing in these fibers (Vijverberg and van den Bercken 1990).

Marked differences exist in the duration of action on the sodium channel gate, particularly between Type I and Type II pyrethroids. These differences may account for the differences observed in toxic effects elicited in laboratory animals. Measurements of sodium tail currents in frog nerve fibers treated with Type I pyrethroids measure approximately 6–150 milliseconds in duration, whereas those generated from Type II pyrethroids last much longer (290 milliseconds to as long as several seconds) (Narahashi 1986; Vijverberg et al. 1986). The shorter-duration sodium tail current generated by Type I pyrethroids results in an elevated after potential that may cause repetitive discharges. The longer-duration sodium tail current generated by Type II pyrethroids may result in summation of after potentials, which can cause gradual depolarization of the nerve and frequency-dependent suppression of action potentials. For both Type I and Type II pyrethroids, the magnitude of effect on sodium influx is strongly dependent on temperature, increasing markedly with cooling (Narahashi 1971, 1976; Vijverberg et al. 1983). The action of pyrethroids on as little as 0.6% of the sodium channel gates results in repetitive after-discharges that could lead to neurotoxic symptoms in animals (Narahashi 1996; Song and Narahashi 1996).

Pyrethroids appear to bind to the membrane lipid phase in the immediate vicinity of the sodium channel, thus modifying the channel kinetics. Results of radioligand binding assays indicate that the actions of DDT and pyrethroids on the sodium channel are site-specific, functionally distinct from, but allosterically

coupled to, sites 2, 3, and 5 of the 5 known neurotoxin-binding domains of the sodium channel (Lombet et al. 1988). Pyrethroids do not appear to influence sodium channel properties such as cation selectivity and cation binding (Yamamoto et al. 1986).

Stereochemistry dictates the degree of toxicity that will be expressed by a given pyrethroid formulation or mixture. In the case of tetramethrin, like all other Type I pyrethroids, the 1R conformation is considerably more toxic than the 1S conformation. The 1S isomer can also inhibit toxicity by competitive inhibition at a number of stereospecific pyrethroid binding sites, thus preventing binding of the more toxic 1R isomer (Narahashi 1986). Furthermore, it has been observed that the cis isomers possess greater mammalian toxicity than the trans isomers. For these reasons, recent formulations of tetramethrin (d-tetramethrin) contain predominantly the 1R cis and 1R trans isomers in a ratio of 20:80 (Tomlin 1997).

Type II pyrethroids have been shown to inhibit specific binding at or near the picrotoxin site of $GABA_A$ receptors in mouse brain (Crofton et al. 1987; Lawrence and Casida 1983), specifically inhibiting GABA-dependent chloride flux (Bloomquist et al. 1986). However, taken together, the results of a number of studies that investigated the actions of pyrethrins and pyrethroids on ligand-gated ion channels indicate a limited role for the $GABA_A$ receptor in pyrethroid-induced neurotoxicity (Bloomquist 1993).

Recently, Forshaw et al. (2000) demonstrated that voltage-gated chloride channels may play a role in Type II, but not Type I, pyrethroid poisoning. Their patch test experiments showed that ivermectin and pentobarbitone significantly increased open chloride channel probability in mouse neuroblastoma cells. When rats were pretreated with ivermectin or pentobarbitone and subsequently administered the Type II pyrethroid deltamethrin, comparatively reduced severity of neurotoxic effects was observed. This was an indication that these chemicals effectively antagonized Type II pyrethroid poisoning. Changes in neurotoxic effects were not observed when the Type I pyrethroid, cismethrin, was used.

Other pyrethroid-induced effects include altered concentrations of catecholamines, blood glucose, and lactate, and marked changes in cerebral blood flow. However, these effects may be secondary effects arising from neural dysfunction resulting from the action of pyrethroids on the sodium and chloride channels.

### 3.5.3 Animal-to-Human Extrapolations

Limited information is available regarding the specific mechanisms involved in the toxicokinetics of pyrethroids in either humans or animals. Therefore, it is difficult to assess how the toxicokinetic data obtained from studies in laboratory animals may differ from that obtained in humans. It is presumed that the toxicokinetic mechanisms involved are generally similar in all mammalian species, although quantitative interspecies differences most certainly exist. Absorption and distribution of pyrethroids appear to be largely determined by the lipid-soluble nature of these compounds. Therefore, it is expected that the absorption and distribution of pyrethroids in humans will be similar to that observed in other mammalian species. In both humans and animals, pyrethroids appear to be metabolized by nonspecific microsomal carboxyesterases and microsomal mixed function oxidases, which are located in nearly all tissue types and are common to all mammalian species. Since the metabolites that have been identified in humans have also been identified in other mammalian species, it is unlikely that there are significant qualitative differences between humans and most animal species for the major metabolic pathways for pyrethroids (Anadón et al. 1991b; Eadsforth and Baldwin 1983; Eadsforth et al. 1988; Elliott et al. 1976; Gaughan et al. 1977; Leng et al. 1997b; Woollen et al. 1992). The cat appears to be an exception, exhibiting increased sensitivity to the toxic actions of pyrethroids. This increased sensitivity may be the result of less efficient hepatic glucuronidation in the cat (Whittem 1995), a second step in the metabolism of pyrethroids in mammalian systems. Pyrethroids and their metabolites are excreted primarily in the urine and feces, and it is likely that mechanisms involved are the same in all mammalian species. If interspecies differences exist in sodium channel kinetics, such differences could increase the uncertainty related to interspecies extrapolation.

## 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made

recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

The potential for pyrethroids to act as endocrine disruptors has been investigated in a limited number of studies *in vitro* (Eil and Nisula 1990; Garey and Wolff 1998; Go et al. 1999). Using Ishikawa Var-I human endometrial cancer cell line and the T47D human breast cancer cell line, cell lines that produce phosphatase as an indicator of hormonal activity, Garey and Wolff (1998) demonstrated that fenvalerate and phenothrin induced significant estrogenicity at concentrations of 10 μM. Similar tests performed using d-trans-allethrin and permethrin did not result in apparent estrogenicity. None of the four pyrethroids showed significant estrogen antagonist activity or acted as progestins, but fenvalerate and d-trans-allethrin significantly antagonized the action of progesterone in T47D cells. Go et al. (1999) found that micromolar concentrations of phenothrin or fenvalerate induced pS2 expression in the MCF-7 human breast cell carcinoma cell line by 5-fold, indicating that these pyrethroids may induce estrogenic activity. The fact that phenothrin-induced pS2 expression was suppressed by antiestrogen co-treatment is a further indication that phenothrin may affect endocrine function. Other pyrethroids (fenvalerate, permethrin, and cypermethrin) were also found to induce pS2 expression (Chen et al. 2002). Several pyrethroids have been shown to interact with androgen binding sites in dispersed intact human genital skin fibroblasts, with varying degrees of potency, but at levels comparable to those resulting in the same order of binding observed using cimetidine, a known inhibitor of androgen receptor binding (Eil and

Nisula 1990). Pyrethrins and bioallethrin were found to displace [$^3$H]testosterone from sex hormone binding globulin in human plasma, at inhibitory levels up to 50% (Eil and Nisula 1990).

Data regarding potential for pyrethrins and pyrethroids to act as endocrine disruptors *in vivo* include findings of reduced reproductive organ weights, significantly altered sperm characteristics, and reduced plasma testosterone levels in male rats administered oral doses of pyrethroids for up to 65 days (Abd El-Aziz et al. 1994; Abd El-Khalek et al. 1999; Hassan et al. 1993). However, there was no evidence of androgenicity or estrogenicity following repeated oral gavage exposure of castrated male rats (5-day Hershberger assay) and ovariectomized female rats (3-day uterotrophic assay) to esfenvalerate, fenvalerate, or permethrin at doses high enough to elicit classical clinical signs of neurotoxicity (Kunimatsu et al. 2002).

## 3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to

body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Differences between children and adults regarding the toxicokinetics of pyrethroid compounds have not been investigated in humans, and there is insufficient information from studies conducted in immature laboratory animals to allow for prediction of particular sensitivities in children. However, based on what is known about the toxicokinetics of pyrethroid compounds, some general areas of concern for exposure of children to pyrethroids can be identified.

Limited information is available regarding the ability of pyrethroid compounds to cross the placenta and be distributed to the fetus. Measurements of radioactivity in fetuses of rats administered radiolabeled pyrethroids indicated that <0.004% of the administered dose of the Type I pyrethroid, tetramethrin, was recovered in the fetus (Kaneko et al. 1984b). Recovered activity from radiolabeled fenvalerate (a Type II

pyrethroid) was <0.07% (Shiba et al. 1990). Eight days after a pregnant cow was given a single dose of $^{14}$C-fluvalinate, only trace amounts (approximately 1x10$^{-5}$% of the administered dose) of $^{14}$C were detected in the fetus (Quistad et al. 1982). However, given the fact that exposure of rat fetuses to pyrethroids via their mothers resulted in persistent alterations in brain neurotransmitter numbers (Malaviya et al. 1993), it would appear that concentrations that reached the fetal brain were sufficient to cause a consistent effect.

Pyrethroids are eliminated from the body primarily by metabolism and subsequent excretion of metabolites via the urine and feces. Hepatic metabolism of pyrethroids is of critical importance for the detoxification and, ultimately, the excretion of these compounds. Although biotransformation reactions are catalyzed largely by microsomal enzymes, and enzymatic activity is involved in conjugation reactions, the specific enzymes involved in pyrethroid metabolism have not been identified. The ability of children to detoxify pyrethroid compounds through metabolic pathways may be different from that of adults (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Using lethality as an indicator of toxicity in a study designed to assess age-related susceptibility to pyrethroids, Sheets et al. (1994) found that adult rats were approximately 16 and 7 times less sensitive to orally administered deltamethrin than 11- and 21-day-old rats, respectively. Cantalamessa (1993) administered acute oral doses of permethrin or cypermethrin to 8-, 16-, and 21-day-old rats, as well as adult rats. For both permethrin and cypermethrin, acute oral $LD_{50}$ values increased with increasing age, indicating greater sensitivity in younger rats. No significant changes in $LD_{50}$ values were seen in young rats pretreated with either tri-o-tolyl phosphate (TOTP, an esterase inhibitor) or piperonyl butoxide (PB, a monooxygenase inhibitor). However, TOTP pretreatment in adult rats resulted in a significant increase in pyrethroid-induced lethality. Increased lethality in adult rats pretreated with PB did not reach the level of statistical significance. These results suggest the possibility that increased susceptibility of young animals to pyrethroid poisoning may be related to less efficient enzyme production than in adult animals. If children have a decreased metabolic capacity compared to adults, altered distribution and excretion of pyrethroids could result. However, age-related differences in responses of animals to near-lethal doses of pyrethroids do not provide a firm basis for human risk assessment.

Since pyrethroid metabolites are water-soluble compounds, it is likely that their ability to cross the blood-brain barrier is limited. In children, a decrease in the production of these polar metabolites could result in an increased distribution of unmetabolized pyrethroids to the central nervous system. There also could be an increase in the distribution of pyrethroids to the central nervous system due to immature development of the blood-brain barrier. Very little unmetabolized pyrethroid is excreted in the urine, most likely

because pyrethroid compounds are very lipid soluble and, if filtered by the glomerulus, are likely to undergo extensive renal reabsorption via lipid diffusion. If the metabolism of pyrethroids is decreased in children, a decrease in the renal excretion of pyrethroids may occur. Since specific details on the mechanisms of the renal handling of pyrethroids are not known, it is unclear how immature renal functions may affect the excretion of pyrethroids and pyrethroid metabolites in newborns and young children.

Exposure to pyrethroids through ingestion of breast milk in nursing infants has not been investigated in humans. However, only very low levels of pyrethroids (<1% of the orally administered dose) are excreted into milk of lactating cows and goats, which would suggest that exposures in human by this route may be similarly low (Gaughan et al. 1978; Hunt and Gilbert 1977; Quistad et al.1982; Ridlen et al. 1984; Wszolek et al. 1980). The relatively low transfers of lipophilic pyrethroids to milk presumably reflects competing pathways of elimination, including relatively rapid and extensive metabolism to more water-soluble metabolites and excretion in urine and feces.

Pyrethroids do not appear to impair gross morphological development in animals. Some investigators have suggested that repeated oral exposure of neonatal mice to selected pyrethroids may result in altered locomotor behavior and changes in brain neurotransmitter receptor densities as adults (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Talts et al. 1998a). However, limitations in study design and the inability to duplicate the results (Ray et al. 2002) render the findings of Eriksson and coworkers of questionable toxicological significance.

Children may be more likely to be exposed to pyrethroids than adults. Behavioral patterns of children can result in higher rates of ingestion of soil and dust, which may contain pyrethroid compounds following spraying. Examples of activities that tend to promote soil and dust ingestion preferentially in children include playing and crawling on the ground and floor, hand-to-mouth activity, mouthing of objects, and indiscriminate eating of food items on the ground or floor. Pyrethroids are also used in shampoos and creams for treatment of patients with lice and scabies. Hand-to-mouth behavior may increase the risk of exposure in children under these conditions of use.

## 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to pyrethrins and pyrethroids are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by pyrethrins and pyrethroids are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 "Populations That Are Unusually Susceptible."

### 3.8.1 Biomarkers Used to Identify or Quantify Exposure to Pyrethrins and Pyrethroids

Measurement of urinary metabolites of pyrethroids may serve as biomarkers of exposure. In several studies in humans exposed to pyrethroids occupationally, the presence of pyrethroid metabolites in urine has been used to confirm exposure (Aprea et al. 1997; Kühn et al. 1999; Leng et al. 1996, 1997a, 1997b). Chemically, synthetic pyrethroids are esters of chrysanthemic acid and specific alcohols, such as 3-phenoxybenzyl alcohol. Hydrolytic cleavage of the ester bond *in vivo* yields chrysanthemic acid derivatives and 3-phenoxybenzoic (3-PBA) (Aprea et al. 1997; Kühn et al. 1999; Leng et al. 1997a, 1997b). The specific pyrethroid metabolites found in urine vary depending upon the parent compound, which may have some modifications to the chrysanthemic acid moiety (Kühn et al. 1999). Results of a single study in humans following inhalation exposure to cyfluthrin indicate that the amounts of cyfluthrin metabolites excreted in urine correlate with increasing exposure levels (Leng et al. 1997a). Thus, urinary levels of pyrethroid metabolites may be a useful indicator of exposure level; however, at this time, there is insufficient information to allow for correlation of the amount of metabolites measured in the urine to the body burden of pyrethroids or to the level of exposure to pyrethroids.

### 3.8.2 Biomarkers Used to Characterize Effects Caused by Pyrethrins and Pyrethroids

Paresthesia (an abnormal cutaneous sensation sometimes described as tingling, burning, stinging, numbness, and itching) has been widely reported among individuals occupationally exposed to pyrethroids (see Vijverberg and van den Bercken 1990 for a summary of available information on occupationally-induced paresthesia). Other symptoms associated with occupational exposure to pyrethroids include dizziness, headache, nausea, loss of appetite, blurred vision, and tightness of the chest. Mild acute pyrethroid poisoning is characterized in part by listlessness and muscular fasciculations. Increased peripheral nerve excitability was measured in cotton workers following 3 days of exposure to deltamethrin during spraying. Whereas paresthesia may be a biomarker of effect for humans occupationally exposed to pyrethroids, other reported symptoms are not specifically indicative of pyrethrin or pyrethroid poisoning.

## 3.9 INTERACTIONS WITH OTHER CHEMICALS

Pyrethroids are eliminated through biotransformation reactions that are catalyzed by microsomal enzymes, although the specific enzymes involved have not been identified. Results from studies of laboratory animals show that inhibition of hydrolytic reactions and of oxidative metabolism increases the toxicity of pyrethroids, while induction of microsomal oxidases decreases the toxicity of pyrethroids (Hutson 1979). Therefore, it appears that chemicals or drugs capable of inducing or inhibiting the enzymes involved in pyrethroid biotransformation reactions can alter the metabolism of pyrethroids. Since the metabolites of pyrethroids are more water soluble than the parent compounds, they are less likely to cross the blood-brain barrier and are more easily excreted by the kidney and liver than the parent compounds. Thus, alterations in the metabolism of pyrethroids through inhibition or induction of microsomal enzymes could alter the distribution and excretion of pyrethroids. For example, piperonyl butoxide, a common insecticide synergist, inhibits microsomal enzymes and potentiates the toxic effects of pyrethrins and pyrethroids to mammals.

Limited evidence exists to suggest that some Gulf War veterans with chronic, nonspecific symptoms may be experiencing neurological dysfunction due to low-level exposures to mixtures of anti-cholinesterase agents, insect repellents, and pyrethroids that might have additive or synergistic effects (Haley and Kurt 1997; Haley et al. 1997a, 1997b). To test this hypothesis, McCain et al. (1997) administered rats oral doses of a short-acting anti-cholinesterase agent (pyridostigmine bromide), an insect repellent (DEET), and permethrin, alone or in combination, and found that combined exposure resulted in a higher degree of lethality than that which would be expected from additive lethal values obtained for each chemical separately. Abu-Qare and Abou-Donia (2001a) demonstrated that co-administration of DEET and permethrin to the skin of rats resulted in significantly increased release of brain mitochondrial cytochrome c, whereas no significant effect was seen following applications of either chemical alone. The effects of combined exposure may be the result of synergistic effects that are expressed following absorption since results of an *in situ* assay of mouse skin revealed that DEET appeared to inhibit the dermal absorption of permethrin (Baynes et al. 1997). Synergistic effects could potentially occur in workers who spray a variety of pesticides, although no data were available to indicate such effects.

Another indication of an adverse toxic interaction between pyrethroids and other chemicals is the finding of significantly increased chromosomal aberrations in bone marrow cells of rats orally administered repeated doses of cypermethrin and lead, in combination (Nehéz et al. 2000). This effect was significant

when compared with both control animals and those administered cypermethrin or lead separately, and appeared to be greater than an additive effect.

See Section 3.11.3 for information regarding chemicals used to reduce the toxic effects of pyrethrins and pyrethroids.

## 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to pyrethrins or pyrethroids than will most persons exposed to the same level of pyrethrins or pyrethroids in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of pyrethrins or pyrethroids, or compromised function of organs affected by pyrethrins or pyrethroids. Populations who are at greater risk due to their unusually high exposure to pyrethrins or pyrethroids are discussed in Section 6.7, Populations With Potentially High Exposures.

Pyrethroids are eliminated from the body primarily by metabolism and subsequent excretion of metabolites into the urine. Individuals with impaired liver function that results in decreased ability to metabolize pyrethrins or pyrethroids are likely to have increased susceptibility to the toxic effects of pyrethrins or pyrethroids. Since urine and bile are the major excretory routes for pyrethrin and pyrethroid metabolites, kidney and/or liver disease are likely to delay elimination of metabolites from the body. However, no studies were located in which metabolites of pyrethrins or pyrethroids were shown to exert toxic effects in humans or animals. Young animals may be more susceptible during stages when enzymes responsible for metabolizing absorbed pyrethroids are not fully developed (Cantalamessa 1993) or during critical stages of neonatal brain development (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Talts et al. 1998a). A predisposition for asthma may contribute to pyrethrin- or pyrethroid-induced respiratory effects. Allergic reactions have been observed in a few individuals following exposure to products that contain pyrethrins or pyrethroids. However, such responses may be due, at least in part, to “inert ingredients” in such products.

## 3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to pyrethrins or pyrethroids. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to pyrethrins. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to pyrethrins:

Ellenhorn MJ, Schonwald S, Ordog G, et al., eds. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore: Williams & Wilkins, 1626–1627.

Goldfrank LR, Flomenbaum NE, Lewin NA, et al., eds. 1998. Goldfrank's toxicologic emergencies. 6th edition. Stamford: Appleton & Lange, 1455–1456.

Haddad LM, Shannon MW, Winchester JF, eds. 1998. Clinical management of poisoning and drug overdose. 3rd edition. Philadelphia: W.B. Saunders, 482–483.

### 3.11.1 Reducing Peak Absorption Following Exposure

**Inhalation Exposure.** There is little information regarding the degree of absorption following inhalation exposure to pyrethrins or pyrethroids, although it is presumed that absorption will occur via diffusion across lipid membranes. However, there is no known effective way to reduce absorption following inhalation exposure to pyrethrins or pyrethroids.

**Oral Exposure.** Pyrethrins and pyrethroids are rapidly absorbed following oral exposure and it is presumed that absorption occurs across the intestinal mucosa via diffusion. There is, however, very little information available regarding the rate or extent of absorption following oral administration in humans. Use of lavage and activated charcoal would likely result in reduced absorption following oral exposure, and charcoal may aid in removing compounds undergoing enterohepatic recirculation. It is also presumed that some absorption could occur in the mouth and stomach and, therefore, mouth rinsing may modestly contribute to decreasing absorption following oral exposure.

**Dermal Exposure.** Pyrethrins and pyrethroids are not well absorbed following dermal exposure, but limited absorption through the skin does occur. Washing of the skin with soap and water would reduce dermal absorption. If the eyes are affected, proper rinsing procedures should be followed.

No information was located regarding the effectiveness of various methods intended to reduce peak absorption of pyrethrins or pyrethroids following exposure.

### 3.11.2 Reducing Body Burden

No information was located regarding the effectiveness of various methods intended to reduce pyrethrin or pyrethroid body burden following absorption.

Pyrethrins and pyrethroids are substantially detoxified through biotransformation reactions catalyzed by microsomal enzymes, although the specific enzymes involved have not been identified. It is anticipated that the body burden would be reduced more quickly if these enzymes are induced; however, until the specific enzymes involved are identified, it is not possible to specify protocols to reduce the body burden of pyrethrins or pyrethroids through induction of microsomal enzymes. Metabolites of pyrethrins and pyrethroids are excreted in urine and bile, but no specific information is available regarding the renal or hepatic handling of these metabolites. Increased fluid consumption, which increases the rate of urine production and excretion, may help to decrease the body burden of pyrethroid metabolites since they are water soluble and excreted in the urine. Activated charcoal might aid in removing pyrethrins or pyrethroids undergoing enterohepatic circulation. However, since pyrethrins and pyrethroids are rapidly metabolized by mammalian detoxification systems, such methods for reducing body burden might not effectively shorten the time during which pyrethrins and pyrethroids exert their toxic effects.

### 3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No information was located regarding effective methods for interfering with the mechanism of action for pyrethrin- or pyrethroid-induced toxic effects. Anticonvulsant drugs have varying degrees of therapeutic efficacy in various animal species treated with a variety of pyrethroids, and may not be regarded as specific antidotes for pyrethroid poisoning in general (Vijverberg and van den Bercken 1990). Muscle relaxants such as mephenesin and methocarbamol may be more effective counters to pyrethroid poisoning, but appear to be more effective against Type II than Type I pyrethroids (Bradbury et al. 1981;

Hiromori et al. 1986). Atropine appears to be effective in reducing pyrethroid-induced effects such as salivation and choreoathetosis in animals (Ray and Cremer 1979). Agents such as ivermectin and pentobarbitone, which act as agonists at chloride channels, have been shown to reduce salivation and choreoathetosis, respectively, in animals (Forshaw and Ray 1997). Dermal applications of Vitamin E and local anesthetic creams have effectively reduced symptoms of paresthesia following dermal exposure to pyrethroids (Flannigan et al. 1985b; Malley et al. 1985; Tucker et al. 1984).

## 3.12 ADEQUACY OF THE DATABASE

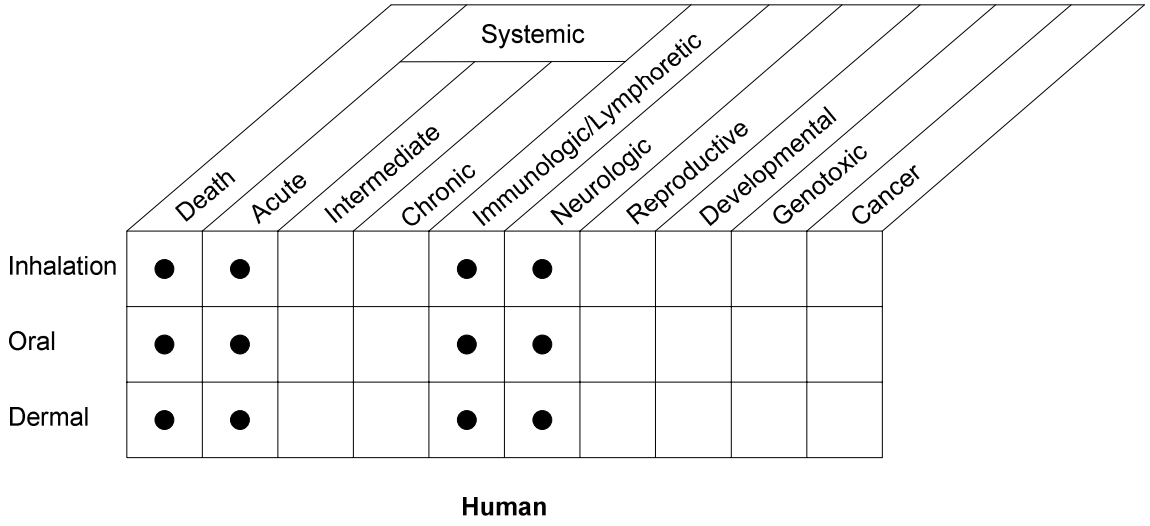
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pyrethrins and pyrethroids is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pyrethrins and pyrethroids.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

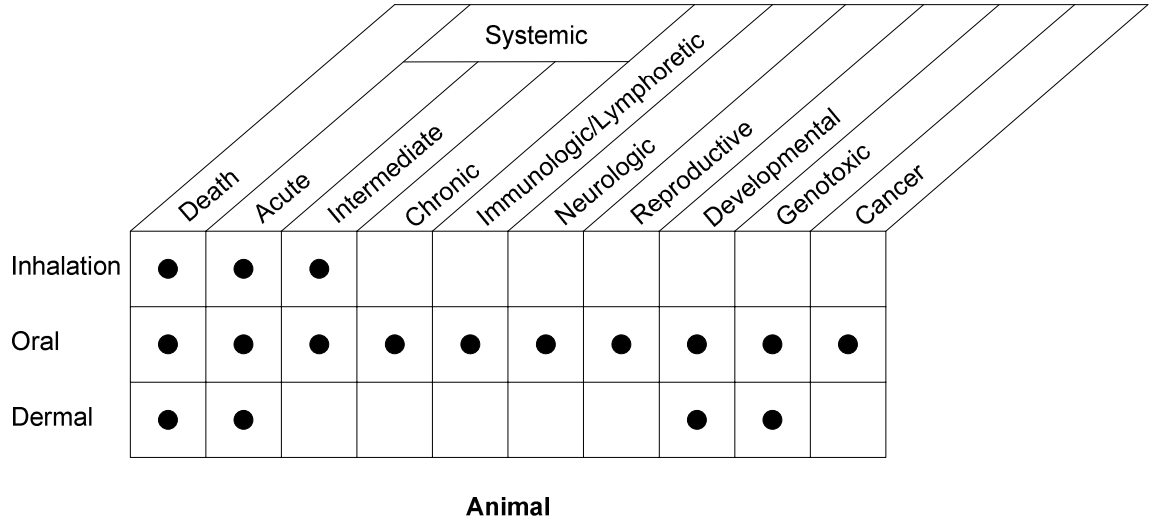
### 3.12.1 Existing Information on Health Effects of Pyrethrins and Pyrethroids

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to pyrethrins and pyrethroids are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of pyrethrins and pyrethroids. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct

## Figure 3-5. Existing Information on Health Effects of Pyrethrins and Pyrethroids




**Human**




**Animal**

● Existing Studies

comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Available data regarding health effects in humans exposed to pyrethrins or pyrethroids largely concern occupational exposure during crop applications in which exposure was considered to have occurred primarily via dermal contact, although inhalation exposure could not be ruled out. Therefore, Figure 3-5 indicates that information exists for both inhalation and dermal exposure routes. A number of human cases involved intentional ingestion of pyrethroids. Both inhalation and dermal exposures were likely in the few reported cases of reactive airway responses. Some occupational exposures were considered to have been of intermediate or chronic duration due to repeated exposures ranging from weeks to years. However, observed health effects following repeated exposure to pyrethrins or pyrethroids were similar to those that characterize acute pyrethroid poisoning.

The database for health effects following oral exposure to pyrethrins or pyrethroids in experimental animals is substantial. However, as can be seen in Figure 3-5, information regarding health effects following inhalation or dermal exposure is more limited. The nervous system appears to be the predominant target of pyrethrin- and pyrethroid-induced toxicity. Genotoxicity data on pyrethrins and pyrethroids are available from studies *in vivo* and *in vitro*; results of genotoxicity tests are predominantly negative. Pyrethrum extract (containing 57.7% pyrethrins) may induce cancer in laboratory animals as evidenced by increased incidences of liver and thyroid tumors in rats exposed orally for a lifetime. Based on currently available animal cancer bioassays, synthetic pyrethroids do not appear to pose a particular carcinogenicity concern.

### 3.12.2 Identification of Data Needs

**Acute-Duration Exposure.** Reports in which inhalation could be considered to be a significant route of exposure to pyrethrins or pyrethroids are mainly available from studies of workers involved in the manufacture or use of the chemicals (Chen et al. 1991; Flannigan and Tucker 1985; Flannigan et al. 1985b; He et al. 1988, 1989, 1991; Knox et al. 1984; Kolmodin-Hedman et al. 1982; LeQuesne and Maxwell 1980; Moretto 1991; Shujie et al. 1988; Tucker and Flannigan 1983; Zhang et al. 1991). Limitations associated with these reports include lack of quantitative exposure data, lack of data on duration of exposure, and the possibility of multiple routes of exposure (i.e., dermal as well as inhalation). Dermal exposure was considered to have been the principal exposure route among individuals involved

with spraying pyrethroids. A limited report in which inhalation exposure was considered to be the primary exposure route did not include exposure levels (Lessenger 1992). Limited animal inhalation toxicity data are available for pyrethrins and pyrethroids (Curry and Bennett 1985; Flucke and Thyssen 1980; Hext 1987; Kavlock et al. 1979; Miyamoto 1976; Pauluhn and Thyssen 1982; Schoenig 1995), but these studies mainly concerned lethality or used exposure levels at which serious neurological effects were elicited. Due to the limited nature of the human and animal data, an acute inhalation MRL could not be derived. Additional peer-reviewed animal studies designed to examine the effects of acute inhalation exposure to pyrethrins and pyrethroids would strengthen the database of currently available information.

The nervous system is the major target of pyrethrin- and pyrethroid-induced toxicity. Numerous reports describe clinical signs of neurotoxicity in humans (Gotoh et al. 1998; He et al. 1989; Peter et al. 1996) and laboratory animals (Eriksson and Nordberg 1990; Hudson et al. 1986; Parker et al. 1983, 1984a, 1984b, 1985; Ray and Cremer 1979; Southwood 1984) following acute oral exposure to relatively high doses of pyrethrins or pyrethroids. One research group (Eriksson and coworkers) has reported neurological effects in adult mice that had been administered acute oral doses of pyrethroids during critical stages of neonatal brain growth (postpartum days 10–16) at exposure levels much lower than those eliciting the classical clinical signs of neurotoxicity (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Eriksson and Nordberg 1990; Talts et al. 1998a). Another group of investigators (Ray et al. 2002) duplicated the study design of Eriksson and coworkers, but did not observe a toxicologically significant neurological effect. Additional studies designed to assess developmental neurotoxic effects at relatively low levels of oral exposure to pyrethrins and pyrethroids could serve to support or refute the findings of Eriksson and coworkers.

Paresthesia (an abnormal cutaneous sensation sometimes described as tingling, burning, stinging, numbness, and itching) has been widely reported by individuals occupationally exposed to pyrethroids (Flannigan and Tucker 1985; Flannigan et al. 1985b; Knox et al. 1984; LeQuesne and Maxwell 1980; Tucker and Flannigan 1983). Higher levels of exposure to various pyrethroids have resulted in mild acute pyrethroid poisoning that included dizziness, headache, and nausea (Chen et al. 1991; Moretto 1991; Shujie et al. 1988; Zhang et al. 1991). However, human studies typically involved the potential for multiple exposure routes and exposure levels were not quantified. Limited available peer-reviewed animal data indicate neurotoxicity following acute dermal exposure to pyrethroids (El-Elaimy 1986; Meyer 1999; Mitchell et al. 1988). Analysis of results of acute dermal toxicity testing by the pesticide industry might preclude the need for additional animal studies.

Acute-duration inhalation MRLs were not derived for pyrethrins or pyrethroids due to the limited available information concerning health effects following inhalation exposure to pyrethrins or pyrethroids. Acute-duration oral MRLs were derived for permethrin, cypermethrin, and cyhalothrin. As information becomes available for additional pyrethroids, acute-duration oral MRLs can be derived for them as well.

**Intermediate-Duration Exposure.** Available reports of toxicoses in humans occupationally exposed to pyrethrins or pyrethroids include multiple exposure routes (dermal, inhalation, and possibly oral) and lack quantitative exposure data. Oral data and limited inhalation data were available for laboratory animals repeatedly exposed to pyrethrins or pyrethroids (Cabral and Galendo 1990; DOD 1977; Flucke and Schilde 1980; Hext et al. 1986; IRIS 2003a, 2003b, 2003c; Ishmael and Litchfield 1988; Miyamoto 1976; Mohan et al. 1998; Parker et al. 1984a, 1984b; Schoenig 1995), but there were few indications that repeated or continuous exposure result in cumulative neurological effects in animals exposed as adults. Intermediate-duration inhalation MRLs were not derived for pyrethrins or pyrethroids due to the limited available information concerning health effects following inhalation exposure to pyrethrins or pyrethroids. Intermediate-duration oral MRLs were derived for permethrin and cyhalothrin. As information becomes available for additional pyrethroids, intermediate-duration oral MRLs can be derived for them as well.

**Chronic-Duration Exposure and Cancer.** Available reports of toxicity in humans occupationally exposed to pyrethrins or pyrethroids include multiple exposure routes (dermal, inhalation, and possibly oral) and lack quantitative exposure data. Oral data were available for laboratory animals chronically exposed to pyrethrins or pyrethroids (Cabral and Galendo 1990; Hext et al. 1986; IRIS 2003a, 2003b, 2003c; Ishmael and Litchfield 1988; Parker et al. 1984a; Schoenig 1995), but there were no indications that repeated or continuous exposure might result in cumulative neurological effects. Chronic-duration inhalation MRLs were not derived for pyrethrins or pyrethroids due to the limited available information concerning health effects following inhalation exposure to pyrethrins or pyrethroids. Chronic-duration oral MRLs were not derived for pyrethrins or pyrethroids, due to inadequate data.

Available cancer bioassays of animals administered pyrethrins or selected pyrethroids orally provide equivocal evidence of a carcinogenic effect (Cabral and Galendo 1990; EPA 1994c; Ishmael and Litchfield 1988; Miyamoto 1976; Parker et al. 1983, 1984a; Schoenig 1995). Additional information from the pesticide industry should be reviewed in the process of assessing the need for additional studies.

**Genotoxicity.** No information was located regarding the genotoxicity of pyrethrins or pyrethroids in humans. Limited information indicated that pyrethrins were not mutagenic in bacterial test systems *in vitro* (see Table 3-3). Type I and Type II pyrethroids generally tested negative for mutagenicity in prokaryotic test systems, but some positive results were obtained for mutation in yeast cells exposed to selected Type I and Type II pyrethroids (see Tables 3-6 and 3-7). Tests in mammalian systems, both *in vivo* and *in vitro*, indicated that Type I and Type II pyrethroids had the potential to induce chromosomal damage (see Tables 3-6 and 3-7).

**Reproductive Toxicity.** No information was located regarding pyrethrin- or pyrethroid-induced reproductive toxicity in humans. Reproductive toxicity was not observed in rats administered oral doses of pyrethrins in the diet at concentrations resulting in average daily doses of 240 mg/kg for 2 generations (Schoenig 1995). One 3-generation study found no evidence for reproductive toxicity from fenpropathrin at an oral dose level of 25 mg/kg/day (Hend et al. 1979). However, Abd El-Aziz et al. (1994) reported significantly reduced fertility in male rats following intermediate-duration oral exposure to deltamethrin at a dose level of 1 mg/kg/day. Additional reproductive toxicity studies could be designed to support or refute these results.

**Developmental Toxicity.** No information was located regarding pyrethrin- or pyrethroid-induced developmental toxicity in humans. Most available developmental toxicity studies in animals do not indicate that pyrethrins or pyrethroids might be considered to be developmental toxicity hazards. The World Health Organization (WHO 2001), and EPA (IRIS 2003f) reviewed a number of unpublished or proprietary developmental toxicity studies performed for various chemical organizations. The summaries of WHO (2001) and EPA (IRIS 2003f) indicate that classical developmental effects are not elicited following exposure to pyrethroids.

Recent studies by Eriksson and coworkers suggest that exposure to pyrethroids during neonatal stages of development when the brain is rapidly growing, may result in adverse neurological effects (changes in MACh receptor density in the cerebral cortex and increased spontaneous locomotor behavior) that are not apparent until adulthood (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Eriksson and Nordberg 1990; Talts et al. 1998a). However, limitations in study design and lack of success in duplicating the results (Ray et al. 2002; Tsuji et al. 2002) render the studies of Eriksson and coworkers of questionable value for the purpose of risk assessment. Additional studies should be designed to support or refute the findings of Eriksson and coworkers.

**Immunotoxicity.** A few cases of hypersensitive responses in humans exposed to pyrethrins and pyrethroids have been documented in available literature (Box and Lee 1996; Carlson and Villaveces 1977; Wagner 2000; Wax and Hoffman 1994). Available information regarding immunotoxicity in animals was limited to oral studies in which administration of selected pyrethroids resulted in immunotoxic effects such as suppression of the humoral immune response, alterations in lymphocytes, leukopenia, altered natural killer cell activity, and decreased spleen weight (Blaylock et al. 1995; Demian 1998; Demian and El-Sayed 1993; Dési et al. 1986; Lukowicz-Ratajczak and Krechniak 1992; Varshneya et al. 1992). No adequate studies are available in humans to assess the immunotoxic potential of pyrethrins or pyrethroids. Studies measuring specific immunologic parameters in occupationally exposed populations might provide useful information. However, inherent variation among human subjects would necessitate very large sample sizes. Animal studies designed to investigate the mechanism for pyrethroid-induced immunotoxicity might help to identify special populations at risk for such effects.

**Neurotoxicity.** Abundant human data show that exposure to large amounts of pyrethroids, either by accidental or intentional ingestion or by dermal and inhalation exposure during unprotected handling or spraying of pyrethroids, may result in clinical signs of neurotoxicity (Chen et al. 1991; Flannigan and Tucker 1985; Flannigan et al. 1985b; Gotoh et al. 1998; He et al. 1989, 1991; Knox et al. 1984; LeQuesne and Maxwell 1980; Moretto 1991; Peter et al. 1996; Shujie et al. 1988; Tucker and Flannigan 1983; Zhang et al. 1991). Exposure of laboratory rodents to selected Type I and Type II pyrethroids has been shown to trigger typical signs of Type I (aggressive behavior and increased sensitivity to external stimuli, fine tremor, prostration with coarse whole body tremor, elevated body temperature, and coma) and Type II (pawing and burrowing behavior, profuse salivation, increased startle response, abnormal hindlimb movements, and choreoathetosis) pyrethroid poisoning. Although the majority of animal studies reporting neurotoxic effects employed oral exposure (EPA 1988c, 1991a, 1991b, 1992b, 1992c, 1994b; Eriksson and Nordberg 1990; Hudson et al. 1986; McDaniel and Moser 1993; Parker et al. 1983, 1984a, 1984b, 1985; Ray and Cremer 1979; Southwood 1984), these effects were also elicited following inhalation and dermal exposure (Curry and Bennett 1985; El-Elaimy 1986; Pauluhn and Thyssen 1982; Schoenig 1995). Several investigators reported typical signs of Type I or Type II pyrethroid poisoning in laboratory rodents during repeated oral administration of pyrethrins or pyrethroids (from 2 days to 2 years), but there were few indications that repeated or continuous exposure might result in cumulative neurological effects (Cabral and Galendo 1990; DOD 1977; Flucke and Schilde 1980; Hext et al. 1986; IRIS 2003a, 2003b, 2003c; Ishmael and Litchfield 1988; Mohan et al. 1998; Parker et al. 1984a, 1984b; Schoenig 1995). Some investigators have reported signs of neurotoxicity such as altered locomotor

activity, altered acoustic startle response, decreased active avoidance response, and changes in brain neurotransmitter concentrations at pyrethroid exposure levels below those eliciting clinical signs of Type I or Type II pyrethroid poisoning (Crofton and Reiter 1988; Hijzen et al. 1988; Husain et al. 1991; Mandhane and Chopde 1997; Mitchell et al. 1988; Moniz et al. 1994; Spinosa et al. 1999). Additional studies of the neurotoxicity of pyrethrins and pyrethroids should assess sensory function in humans and sensitivity of unique populations such as farm workers, children of farm workers, the elderly, and veterans of the Gulf War.

**Epidemiological and Human Dosimetry Studies.** Available information regarding the health effects of pyrethrins and pyrethroids in humans mainly concerns reports of neurological effects following accidental or intentional ingestion or during unprotected handling or spraying (Chen et al. 1991; Flannigan and Tucker 1985; Flannigan et al. 1985b; Gotoh et al. 1998; He et al. 1989, 1991; Knox et al. 1984; LeQuesne and Maxwell 1980; Moretto 1991; Peter et al. 1996; Shujie et al. 1988; Tucker and Flannigan 1983; Zhang et al. 1991). Occupational exposure to pyrethrins and pyrethroids may be confounded by differences in specific formulations and by concurrent exposures to other pesticides. Pesticide applicators, farm workers, individuals involved in production of pyrethrins or pyrethroids, and individuals exposed in recently sprayed homes or offices might serve as a focus for well-designed epidemiological studies for further assessment of neurological effects of pyrethrins and pyrethroids, as well as assessment of other potential adverse effects, such as immunotoxicity. Studies of dosimetry would be useful in future epidemiological studies.

**Biomarkers of Exposure and Effect.**

***Exposure.*** Measurement of urinary metabolites of pyrethroids can serve as useful markers of exposure (Aprea et al. 1997; Kühn et al. 1999; Leng et al. 1996, 1997a, 1997b). However, there is insufficient information from studies in humans or animals to allow for correlation of the amounts of metabolites measured in the urine to the body burden of pyrethroids or to the level of exposure to pyrethroids. Additional information regarding the relationship of urinary pyrethroid metabolite levels to pyrethroid body burden and to exposure levels could improve the ability to monitor worker's exposure to pyrethroids. Also, residues of pyrethrins and pyrethroids and their metabolites should be determined in blood of humans (antemortem) and in blood, digestive tract contents, liver, kidney, and brain of animals and accidently exposed or suicide victims (postmortem). Without detailed knowledge regarding the appearance and disappearance of parent compounds and metabolites over the course of a toxicosis, confirmed diagnoses will remain elusive to impossible.

***Effect.*** Biomarkers of effect for pyrethrins and pyrethriods include typical neurotoxic signs of acute pyrethroid poisoning (Coats 1990; Verschoyle and Aldridge 1980). Although these clinical signs are distinctive, they are not totally unique to pyrethrin or pyrethroid poisoning.

**Absorption, Distribution, Metabolism, and Excretion.** The absorption, distribution, metabolism, and excretion of pyrethrins or pyrethroids following exposure by any route are not well characterized in humans. While many studies have investigated these processes for pyrethroids in various laboratory animals, in general, toxicokinetics of these compounds are not well defined. No PBPK models of pyrethrins or pyrethroids have been reported. Information to support the development of a PBPK model for pyrethrins or pyrethroids has not been systematically compiled and is currently insufficient to support such models (e.g., mechanisms and kinetic constants and variables of metabolism, tissue partition coefficients). Such models would be useful for predicting body burdens and, if combined with dose-response models, for predicting health effects of pyrethrins and pyrethroids associated with known or projected exposures.

***Absorption.*** Although results of studies in humans and laboratory animals demonstrate that pyrethroids are absorbed following exposure by the inhaled, oral, and dermal routes, further studies would be helpful for quantifying the absorption and time-course of absorption by each exposure route. It has been proposed that pyrethroids are stored in the skin following dermal exposure and are slowly released into the systemic circulation (Eadsforth et al. 1988; Woollen et al. 1992). Given the importance of the dermal route in occupational exposure to pyrethroids, additional information regarding the time-course of absorption following dermal exposure would be helpful. Little information is available concerning roles such factors as diet, age, sex, or other chemicals and drugs might play in the absorption of pyrethroids by any route in humans and animals. Further studies are needed to examine these factors and define potential differences in absorption over a range of pyrethrins and pyrethroids.

***Distribution.*** The distribution of pyrethrins and pyrethroids in humans and animals has not been well studied. From the results of studies in laboratory animals, it is concluded that pyrethroids are rapidly and widely distributed and are concentrated in central and peripheral nerve tissues (Anadón et al. 1991a, 1991b, 1996; Gray and Rickard 1982; Gray et al. 1980). 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.

***Metabolism.*** The metabolism of pyrethrins and pyrethroids in humans has not been well defined. 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 (Gray and Soderlund 1985; Hutson 1979).

***Elimination and Excretion.*** The elimination and excretion of pyrethrins and pyrethroids in humans have not been well defined and information is limited to studies investigating the elimination of pyrethroids from the plasma and excretion of pyrethroids into the urine. Additional information on nonurinary excretory routes and information to quantify excretion by each route in humans would be helpful for predicting routes and elimination kinetics in humans. Based on the limited information available in humans, it is not possible to predict precisely how long pyrethroids will remain in the body following exposure by various routes. Further study on the elimination kinetics of a range of pyrethroids by each route of exposure would be helpful for developing predictive models in humans. There is little information available regarding the mechanisms of excretion in either humans or animals. Further study on these mechanisms would allow assessment of the many potential factors, such as age, sex, and other chemicals and drugs, that could alter the elimination and excretion of pyrethroids.

**Comparative Toxicokinetics.** Insufficient information is available regarding comparative toxicokinetics of pyrethrins or pyrethroids in humans and laboratory animals. Further investigations on potential differences in humans and animals may help to determine appropriate species and strains of animals to use in predicting the toxicokinetics of pyrethroids in humans. Evaluation of mechanisms, character, and extent of human variability in the disposition of pyrethroids is also warranted.

**Methods for Reducing Toxic Effects.** Other than general guidelines of washing the skin with soap and water following dermal exposure and use of gastric lavage and activated charcoal following oral exposure, little additional information is available regarding methods for reducing absorption of

pyrethroids. Additional studies on factors that could affect the absorption and metabolism of pyrethroids, such as diet and concomitant exposure to other chemicals and drugs, would be helpful in understanding the impact of these factors on risks from occupational exposures.

**Children's Susceptibility.** Neurotoxic effects have been well characterized in humans exposed to pyrethrins and pyrethroids. Information mainly derives from individuals occupationally exposed during spraying. No reports on exposed children were found, but it is reasonable to assume that children would exhibit signs and symptoms similar to those in adults under similar exposure conditions. No information was located regarding developmental toxicity in humans exposed to pyrethrins or pyrethroids. Studies in animals have suggested that neonatal exposure to pyrethroids may result in neurological effects first observed in adulthood (Ahlbom et al. 1994; Eriksson and Fredriksson 1991; Eriksson and Nordberg 1990; Talts et al. 1998a). These results could not be confirmed by independent investigators (Ray et al. 2002).

No human data were located regarding age-related differences in the pharmacokinetics of pyrethrins or pyrethroids. Limited animal data suggest that young animals may be more susceptible to pyrethroid poisoning, possibly due to less efficient production of enzymes responsible for detoxification (Cantalamessa 1993).

Extremely limited data suggest that pyrethroids may be minimally transferred across the placenta to the fetus (Quistad et al. 1982). Very low levels of pyrethroids have been measured in the milk of lactating cows and goats (Gaughan et al. 1978; Hunt and Gilbert 1977; Quistad et al.1982; Ridlen et al. 1984; Wszolek et al. 1980).

No data were located regarding pediatric-specific methods to reduce peak absorption of pyrethrins or pyrethroids following exposure, to reduce body burdens, or to interfere with mechanisms of action. Based on available information, it is reasonable to assume that methods recommended for treating adults will also be applicable to children.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

### 3.12.3 Ongoing Studies

The Federal Research In Progress database (FEDRIP 2003) lists an ongoing study in which Dr. B. Wilson, from the University of California, Davis, California has proposed the development of biomarkers of exposure and effect for organophosphorus and pyrethroid insecticidal sprays. Two studies were located in the Computer Retrieval of Information in Scientific Projects database (CRISP 2003). Dr. S. Holladay, from Virginia Polytechnic Institute and State University, Blacksburg, Virginia, is investigating the immunotoxicity of permethrin. Dr. D. Soderlund, from Cornell University, Ithaca, New York, is investigating specific mechanisms of action of pyrethroids in vertebrate systems. Dr. T. Narahashi, from Northwestern University, Chicago, Illinois, is investigating differential actions of Type II pyrethroids on sodium channels.