

2. HEALTH EFFECTS

2.1 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 of the toxicology of chlorpyrifos. 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 guidance.

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

2.2 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

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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 (LOAEL) 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.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for chlorpyrifos. 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-duration 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.

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Chlorpyrifos (O,O-diethyl O-[3,5,6-trichloro-2-pyridyl] phosphorothioate) is a clear to white crystalline solid pesticide (EPA 1988b) with a strong mercaptan odor (Worthing 1987). Chlorpyrifos is widely used to control insects in the home, workplace, and in agriculture; it has also been found in at least 7 current and former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1996). Thus, the potential for chlorpyrifos exposure is significant.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No information was found concerning the potential for death in humans following acute-, intermediate-, or chronic-duration inhalation exposure. For animals, no data were located for death following intermediate- or chronic-exposure to chlorpyrifos, but limited LD₅₀ (lethal dose, 50% kill) studies were available.

The LD₅₀ for acute-duration inhalation exposure to chlorpyrifos aerosol has been determined for mice and female rats (Berteau and Deen 1978). In mice, an LD₅₀ of 94 mg/kg (milligrams per kilogram of body weight) was determined after whole-body inhalation exposure to 6,700-7,900 mg/m³ chlorpyrifos in 65% xylene. In that study, the dose range was achieved by varying the length of exposure from 27 to 50 minutes. Virgin female Sprague-Dawley rats were similarly exposed to 5,900-7,500 mg/m³ chlorpyrifos in 65% xylene, and an acute-exposure inhalation LD₅₀ of 78 mg/kg was determined by varying the exposure duration from 60 to 180 minutes. Numerous assumptions about minute ventilation and pulmonary absorption were made in this study, and no correction was made for the large amount of xylene in the formulation or for the percutaneous and oral absorption of chlorpyrifos entrapped in the fur. Thus, the LD₅₀ values are crude estimates.

Mortality was also observed in 5 male and 5 female Sprague-Dawley rats acutely exposed to a lower concentration of chlorpyrifos but for a longer duration (Dow 1983a). In males, 80% mortality was observed following a single 4-hour, whole-body exposure to an atmosphere containing 5,300 mg/m³ of the commercial chlorpyrifos preparation Pyrenone-Dursban[®]. In similarly exposed females, 20% mortality was observed. However, no mortality was observed in 5 male or 5 female Sprague-Dawley rats exposed to 2,500 mg/m³ of Pyrenone-Dursban[®] W.B. Pressurized Spray for 4 hours (Dow 1984).

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It should be noted that in these and other animal whole-body inhalation studies, exposure may include ingestion as a route of exposure because the compound gets on the fur of the animals and may then be ingested during grooming.

The LOAEL values for lethality in each reliable study for each species and duration category are shown in Table 2-1 and Figure 2-1.

2.2.1.2 Systemic Effects

No studies were located concerning endocrine or metabolic effects of chlorpyrifos in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to chlorpyrifos. The highest NOAEL value and all LOAEL values for systemic effects in each reliable study for each species and duration category are shown in Table 2-1 and Figure 2- 1.

Respiratory Effects. No information was located concerning the potential respiratory effects of inhaled chlorpyrifos in humans following acute- or intermediate-duration exposure. In a chronicduration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos and 335 matched controls with no history of exposure to organophosphorus chemicals were compared. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. The prevalence of respiratory illness or other respiratory symptoms were compared. There were no statistically significant differences in the number of subjects with respiratory illness or other respiratory symptoms between the exposed and control groups. Exposure was assumed to be via inhalation and dermal routes.

The respiratory effects of acute-duration exposure to the commercial chlorpyrifos preparation, Pyrenone-Dursban®, were investigated in 5 male and 5 female Sprague-Dawley rats (Dow 1983a). One male rat was observed gasping the day after a single 4-hour whole-body exposure to 5,300 mg/m³. The animal was found dead later that day. Two additional males were found dead 2 days post-exposure and one male was found dead three days post-exposure. Scattered dark red areas ranging from 2 mm to extensive hepatization involving up to 75% of lung tissue were observed in these rats. Fibrinous pleurisy was observed in 1 female rat that died 14 days post-exposure (Dow 1983a). No respiratory effects were observed, however, in male or female Sprague-Dawley rats

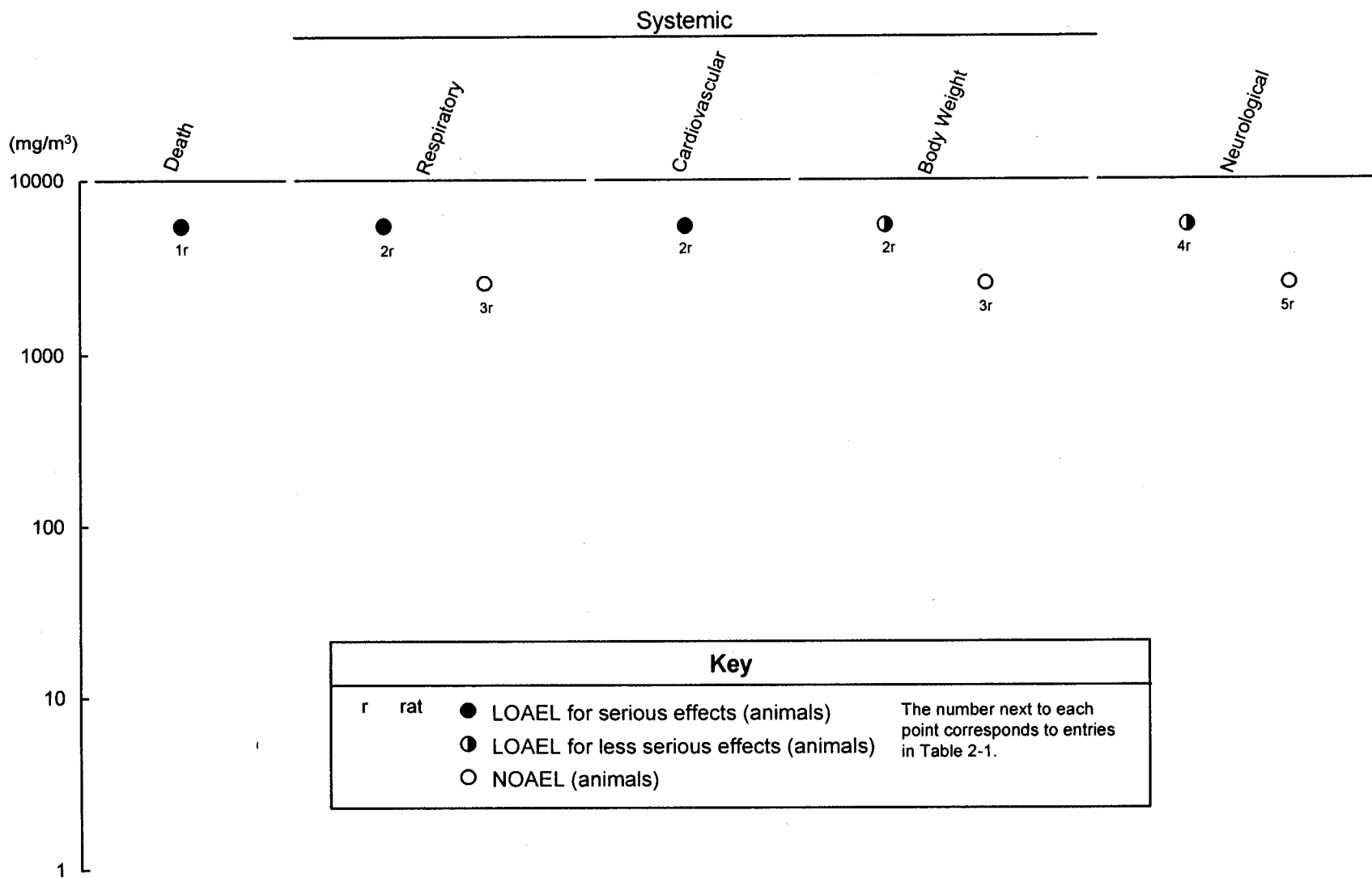
Table 2-1. Levels of Significant Exposure to Chlorpyrifos - Inhalation

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference
					Less serious (mg/m3)	Serious (mg/m3)	
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	4 hr				5300	(80% mortality in males, 20% mortality in females) Dow 1983a
Systemic							
2	Rat (Sprague-Dawley)	4 hr	Resp			5300	(gasping and pneumonia in males, fibrinous pleuritis in females) Dow 1983a
			Cardio			5300 F	(pericarditis)
			Bd Wt	5300	(9-11% decreased Day 2 weight)		
3	Rat (Sprague-Dawley)	4 hr	Resp	2500			Dow 1984
			Bd Wt	2500			
Neurological							
4	Rat (Sprague-Dawley)	4 hr			5300		(reduced locomotor activity up to Day 2) Dow 1983a
5	Rat (Sprague-Dawley)	4 hr		2500			Dow 1984

^aThe number corresponds to entries in Figure 2-1.

Bd Wt = body weight; Cardio = cardiovascular; F = female; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; Resp = respiratory

**Figure 2-1. Levels of Significant Exposure to Chlorpyrifos - Inhalation
Acute (≤ 14 days)**



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exposed to an atmosphere containing 2,500 mg/m³ Pyrenone-Dursban[®] Pressurized Spray for 4 hours (Dow 1984).

The effects of intermediate-duration exposure to chlorpyrifos on lung histology were assessed in male and female Fischer 344 rats (Corley et al. 1989). The rats were exposed nose-only to 0, 0.075, 0.148, or 0.295 mg/m³ chlorpyrifos for 6 hours a day, 5 days a week for 13 weeks. Histopathological evaluation of lungs from the control and 0.295 mg/m³ groups revealed normal lung histology. The exposure levels in this study did not inhibit erythrocyte or plasma cholinesterase activity.

No data were located for respiratory effects in animals following chronic-exposure to chlorpyrifos.

Cardiovascular Effects. No information was located concerning the cardiovascular effects of inhaled chlorpyrifos in humans following intermediate- or chronic-duration exposure. Unstable blood pressure and pulse were noted in a 33-year-old male acutely exposed to an unspecified concentration of Dursban[®] that was accidentally sprayed into the ventilating system at his place of work. The symptoms began approximately 6 weeks after exposure and slowly resolved over 8-10 weeks (Kaplan et al. 1993). Exposure was assumed to be via inhalation and dermal routes. While cardiovascular effects are possible after acute-duration exposure to chlorpyrifos because of cholinergic overstimulation, the 6-week interval between a single exposure and onset of symptoms raises doubts as to whether chlorpyrifos was the causative agent in this case.

The cardiovascular effects of acute-duration exposure to the commercial chlorpyrifos preparation Pyrenone-Dursban[®] were investigated in 5 male and 5 female Sprague-Dawley rats (Dow 1983a). Pericarditis was observed in one female rat that died 14 days after a single 4-hour whole-body exposure to 5,300 mg/m³. No cardiovascular effects were noted in the male rats. Intermediate-duration exposure caused cardiovascular effects in a female domestic short-hair cat (Jaggy and Oliver 1992). The cat was exposed to an unspecified amount of chlorpyrifos used to spray the apartment for fleas. The apartment was sprayed 6 times (every 3 days) during an 1% day period. The cat was kept in another apartment during the first 2-3 hours after the spraying on each day. The cat became anorexic and lethargic, and was taken for treatment. The cat was found to have elevated levels of creatine kinase, but the electrocardiogram was negative. It is assumed that exposure was via inhalation, although oral exposure from grooming may also have occurred. No data were located for cardiovascular effects in animals following chronic-exposure to chlorpyrifos.

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Gastrointestinal Effects. Gastrointestinal effects following acute-duration exposure to chlorpyrifos have been observed in humans (Kaplan et al. 1993). A family became ill and complained of feeling nauseated after their house was sprayed with Dursban[®] (Kaplan et al. 1993). The time from exposure to the onset of symptoms and exposure-level data were not reported. Exposure was assumed to be via inhalation and dermal routes. Intermediate-duration exposure to chlorpyrifos may be associated with diarrhea in humans. Diarrhea developed in a 40-year-old male exterminator who was repeatedly exposed to an unknown concentration of Dursban[®] in a closed environment over a 6-month period (Kaplan et al. 1993). Exposure was assumed to be via inhalation and dermal routes. Erythrocyte cholinesterase levels determined at the onset of symptoms were initially low (value not given). The diarrhea probably resulted from stimulation of the parasympathetic nervous system as a consequence of cholinesterase inhibition. Stimulation of the parasympathetic nervous system increases gastrointestinal motility, thereby decreasing food transit times. The net result is that there is less time for water to be absorbed by the gastrointestinal tract and diarrhea results. In a chronic-duration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos were compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. No statistically significant differences in the prevalence of illnesses of the gastrointestinal tract were found in the exposed groups compared to matched controls. Exposure was assumed to be via inhalation and dermal routes.

No data were located for gastrointestinal effects for animals following acute-, intermediate-, or chronic-duration inhalation exposure to chlorpyrifos.

Hematological Effects. A 33-year-old man acutely exposed to an undetermined amount of chlorpyrifos after it was sprayed into the ventilation system of his place of work was examined 2 weeks later because of neurological problems (Kaplan et al. 1993). Routine blood chemistry and hematological evaluations were performed and found to be within normal limits. Similar tests performed on a 40-year-old male exterminator repeatedly exposed to Dursban[®] in a closed environment over a 6-month interval were also negative. In both cases, exposure was assumed to be via inhalation and dermal routes. No information was located concerning the hematological effects of chronic-duration exposure to inhaled chlorpyrifos in humans.

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No information was located concerning the hematological effects of inhaled chlorpyrifos after acute- or chronic-duration exposure in animals. No effects on hematological parameters were seen in Fischer 344 rats exposed to up to 0.295 mg/m³ chlorpyrifos 6 hours a day, 5 days a week for 13 weeks (Corley et al. 1989).

Musculoskeletal Effects. In humans, acute- and intermediate-duration exposures have been associated with musculoskeletal effects. A family became ill, and family members complained of muscle cramps, after their house was sprayed with Dursban[®] (Kaplan et al. 1993). Exposure-level data and the time from exposure to the onset of symptoms were not reported. Muscle twitching developed in a 40-year-old male exterminator who was repeatedly exposed to an unknown concentration of Dursban[®] in a closed environment over a 6-month interval (Kaplan et al. 1993). In both cases, exposure was assumed to be via inhalation and dermal routes. In a chronic-duration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. No statistically significant differences in the prevalence of illnesses or symptoms involving the musculoskeletal system were found in the exposed groups compared to matched controls. Exposure was assumed to be via inhalation and dermal routes.

For animals, no data were located for musculoskeletal effects following acute- or chronic-duration exposure to chlorpyrifos. Musculoskeletal effects have been observed following intermediate-duration oral exposure in cats. Creatine kinase activity increased an undetermined amount in a female cat exposed to an unspecified amount of chlorpyrifos every third day for 18 days via inhalation (Jaggy and Oliver 1992). It is assumed that all exposure was via inhalation, although oral exposure may also have occurred through grooming.

Hepatic Effects. No information was located concerning hepatic effects of inhaled chlorpyrifos in humans following acute- or intermediate-duration exposure. In a chronic-duration exposure study (Brenner et al. 1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. No statistically significant

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differences in the prevalence of liver illnesses were found in the exposed groups compared to matched controls or among the three exposure subgroups. Exposure was assumed to be via inhalation and dermal routes.

The effect of intermediate-duration exposure to chlorpyrifos on liver histology was assessed in male and female Fischer 344 rats (Corley et al. 1989). The rats were exposed nose-only to 0, 0.075, 0.148, or 0.295 mg/m³ chlorpyrifos for 6 hours a day, 5 days a week for 13 weeks. Histopathological evaluation of livers from the control and 0.295 mg/m³ groups revealed normal liver histology in the chlorpyrifos-treated rats. The exposure levels in this study were not sufficient to inhibit erythrocyte or plasma cholinesterase. No data were located for hepatic effects in animals following acute- or chronic-duration exposure to chlorpyrifos.

Renal Effects. The acute-duration exposure of a 33-year-old male to an unspecified amount of chlorpyrifos that was sprayed into a workplace ventilation system caused an increase in urinary frequency (Kaplan et al. 1993). Exposure was assumed to be via inhalation and dermal routes. Intermediate-duration inhalation exposure (data collected over a 3-month period) to undetermined amounts of chlorpyrifos in humans was assessed in a survey of pesticide applicators working in a variety of settings (Ames et al. 1989). Exposure was assumed to be via inhalation and dermal routes. The applicators in this study reported an unspecified decrease in urinary frequency. In a chronic-duration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Illnesses and symptoms included those of the kidney. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. No statistically significant differences in the prevalence of renal illnesses were found in the exposed groups compared to matched controls. Exposure was assumed to be via inhalation and dermal routes.

The effects of intermediate-duration exposure to chlorpyrifos on urine chemistry have also been assessed in male and female Fischer 344 rats (Corley et al. 1989). The rats were exposed nose-only to 0, 0.075, 0.148, or 0.295 mg/m³ chlorpyrifos for 6 hours a day, 5 days a week for 13 weeks. Urinary chemistry in the treated groups was comparable to controls. The exposure levels in this study were not sufficient to inhibit erythrocyte or plasma cholinesterase. No effects on kidney weight or histopathology were seen in the rats exposed to up to 0.295 mg/m³ chlorpyrifos for 13 weeks.

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No data were located in for renal effects in animals following acute- or chronic-duration exposure to chlorpyrifos.

Dermal Effects. No information was located concerning dermal effects of inhaled chlorpyrifos in humans following acute-duration exposure. The intermediate-duration inhalation exposure to undetermined amounts of chlorpyrifos in humans was assessed in a survey of pesticide applicators working in a variety of settings (Ames et al. 1989). Exposure was assumed to be via inhalation and dermal routes. The applicators in this study reported an unspecified increase in skin flushing. This effect may be related to a disruption of autonomic function. In a chronic-duration exposure study by Brenner et al. (1984) the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. No statistically significant differences in the prevalence of illnesses of the skin or other integumentary tissue were found in the exposed groups compared to matched controls. Exposure was assumed to be via inhalation and dermal routes.

For other animals, no data were located for dermal effects following acute-, intermediate- or chronicduration inhalation exposure to chlorpyrifos.

Ocular Effects. Intermediate-duration exposure to an undetermined amount of chlorpyrifos caused an unspecified increase in tearing in a 40-year-old male exterminator repeatedly exposed to Dursban[®] over a 6-month period (Kaplan et al. 1993). Exposure was assumed to be via inhalation and dermal routes. Additionally, intermediate-duration inhalation exposure to undetermined amounts of chlorpyrifos in humans was assessed in a survey of pesticide applicators working in a variety of settings (Ames et al. 1989). Exposure was assumed to be via inhalation and dermal routes. The applicators reported an unspecified increase in blurred vision. It should be noted that in the Kaplan et al. (1993) and Ames et al. (1989) studies, exposure concentration data were not available. Additionally, because these incidences occurred in pesticide applicators, the possibility of exposure to other compounds must be considered; blurred vision is a common symptom after high exposure to organophosphate insecticides.

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No information was located concerning ocular effects of inhaled chlorpyrifos in humans following acute- or chronic-duration exposure.

For other animals, no data were located for ocular effects following acute-, intermediate-, or chronic-duration exposure to chlorpyrifos.

Body Weight Effects. No information was located concerning the effects on body weight of inhaled chlorpyrifos in humans following acute-, intermediate-, or chronic-duration exposure.

The effects on body weight of acute-duration exposure to the commercial chlorpyrifos preparation Pyrenone-Dursban[®] were investigated in male and female Sprague-Dawley rats exposed for 4 hours to an atmosphere containing 5,300 mg/m³ (Dow 1983a). Male rats that survived 2 days postexposure lost 9-11% of their body weight. Exposed females also lost weight during the first two days post-exposure. Weight loss ranged from 1 to 33% with a mean of 10%. Surviving male and female rats subsequently gained weight within normal ranges (Dow 1983a). No body weight effects were observed, however, in male or female Sprague-Dawley rats exposed to an atmosphere containing 2,500 mg/m³ Pyrenone-Dursban[®] Pressurized Spray (Dow 1984). The effects of intermediate-duration exposure to chlorpyrifos on body weight were assessed in male and female Fischer 344 rats (Corley et al. 1989). The rats were exposed nose-only to 0, 0.075, 0.148, or 0.295 mg/m³ chlorpyrifos for 6 hours a day, 5 days a week for 13 weeks. Body weight was not affected by any concentration of chlorpyrifos. The exposure levels in this study were not sufficient to inhibit erythrocyte or plasma cholinesterase. No data were located for body weight effects following chronic-duration exposure to chlorpyrifos.

2.2.1.3 Immunological and Lymphoreticular Effects

No data were located for immunological and lymphoreticular effects in humans or animals following acute-, intermediate-, or chronic-duration inhalation exposure to chlorpyrifos.

2.2.1.4 Neurological Effects

The majority of the neurological symptoms associated with chlorpyrifos exposure result from its inhibition of acetylcholinesterase and the subsequent cholinergic overstimulation. Common symptoms

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related to excessive cholinergic activity include headache, diaphoresis, nausea, vomiting, diarrhea, epigastric cramping, bradycardia, blurred vision, miosis, bronchoconstriction and excess mucous secretions, pulmonary edema, dyspnea, muscle fasciculations, salivation, lacrimation, and urination (Ballantyne and Marts 1992). In adults and children, acute-duration inhalation exposure to unspecified concentrations of chlorpyrifos is associated with paresthesia and lightheadedness (Kaplan et al. 1993; Sherman 1995). Headache is also a common occurrence (Kaplan et al. 1993; Sherman 1995). Additionally, in the Sherman (1995) report, acute-duration chlorpyrifos exposure may produce signs of neurological toxicity weeks or months after the initial symptoms have resolved. For example, a family which became ill after an unspecified concentration of chlorpyrifos was applied in their home initially presented with headaches, nausea, and muscle cramps (Kaplan et al. 1993). However, numbness, paresthesia (most prominent in the legs), and memory impairment were reported by the family 1 month later. The children also showed a decline in scholastic performance that lasted for approximately 6 months. Neurological exams conducted 6 months post-exposure revealed mild short-term memory loss on all routine mental status testing of recall of multiple objects. Neuropsychological testing was declined by the subjects, all other neurological exams were normal. Nerve conduction studies revealed low-amplitude sural nerve action potentials in all family members. Motor and upper-extremity sensory nerve action potentials were normal. Sural nerve amplitudes in all but one family member had returned to normal 6 months later. Although inhalation was the most likely route of exposure, the family could also have been exposed dermally.

Other patients in the compilation of case reports by Kaplan et al. (1993) presented with similar deferred neurotoxicity that resolved after a period of weeks or months. In a review of the physical, neurotoxic, and respiratory problems suffered by people exposed to organophosphate pesticidal products, similar symptoms of severe organophosphate poisoning were reported in men and women exposed to unspecified amounts of chlorpyrifos at home or at work (Sherman 1995). However, in the Kaplan et al. (1993) and Sherman (1995) reports, no exposure-level data were presented, and the cognitive complaints were nonspecific, nonquantitative, and possibly attributable to a wide variety of possible causes. Additionally, measurements of erythrocyte acetylcholinesterase, a biomarker for chlorpyrifos exposure, were not taken.

Intermediate-duration inhalation exposure to unspecified concentrations of chlorpyrifos in humans have been associated with deferred neurotoxicity similar to that observed after acute-duration exposure (Kaplan et al. 1993). For example, sensory loss, mild distal weakness, and are flexia in the lower

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extremities were revealed in a neurological evaluation of a man 6 weeks after being exposed to Dursban® in a closed environment for over a 6-month interval. Nerve conduction studies and quantitative sensory threshold studies revealed changes consistent with peripheral neuropathy of the distal axonopathy type. However, follow-up one year later revealed normalization of the results of the neurological examination, nerve conduction studies, and quantitative sensory threshold studies, and remission of all symptoms (Kaplan et al. 1993).

In a chronic-duration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. No statistically significant differences in the prevalence of central and peripheral nervous system symptom were found in the exposed groups compared to matched controls. Exposure was assumed to be via inhalation and dermal routes.

In female mice, acute-duration inhalation exposure to 95.6 mg/kg chlorpyrifos (total dose received during 5 hours of exposure) caused an approximate 90% decrease in plasma cholinesterase, a marker for exposure, 3 days after exposure (Berteau and Deen 1978). Fourteen days after exposure, plasma cholinesterase had returned to within 20% of predosing levels. The effects of acute-duration inhalation exposure to the commercial chlorpyrifos Pyrenone-Dursban® on behavior were investigated in male and female Sprague-Dawley rats exposed for 4 hours to an atmosphere containing 5,300 mg/m³ (Dow 1983a). Locomotor activity was reduced for up to 2 days post-exposure (Dow 1983a). No behavioral effects were observed, however, in male or female Sprague-Dawley rats exposed to an atmosphere containing 2,500 mg/m³ Pyrenone-Dursban® Pressurized Spray (Dow 1984). The effects of intermediate-duration exposure to chlorpyrifos on brain weight and brain cholinesterase were assessed in male and female Fischer 344 rats (Corley et al. 1989). The rats were exposed nose-only to 0, 0.075, 0.148, or 0.295 mg/m³ chlorpyrifos for 6 hours a day, 5 days a week for 13 weeks. Brain weight and brain acetylcholinesterase activity were not affected by any concentration of chlorpyrifos. The concentrations of chlorpyrifos used in this study were not sufficient to inhibit erythrocyte or plasma cholinesterase activity. No data were located for neurological effects in animals following chronic-duration exposure to chlorpyrifos.

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All LOAEL values for neurological effects in each reliable study for each species and duration category are shown in Table 2-1 and Figure 2-1.

2.2.1.5 Reproductive Effects

No information was located concerning reproductive effects of inhaled chlorpyrifos in humans following acute-, intermediate-, or chronic-duration exposure.

The effect of intermediate-duration exposure to chlorpyrifos on testicular weight and histology was assessed in male Fischer 344 rats (Corley et al. 1989). The rats were exposed nose-only to 0, 0.075, 0.148, or 0.295 mg/m³ chlorpyrifos for 6 hours a day, 5 days a week for 13 weeks. No effects of treatment on testes weight or histology were detected. The air concentrations of chlorpyrifos used in this study were not sufficient to inhibit erythrocyte or plasma cholinesterase activity. No data were located for reproductive effects in animals following acute- or chronic-duration exposure to chlorpyrifos.

2.2.1.6 Developmental Effects

No information was located concerning developmental effects of inhaled chlorpyrifos in humans or other animals following acute-, intermediate-, or chronic-duration exposure.

2.2.1.7 Genotoxic Effects

No information was located concerning genotoxic effects of inhaled chlorpyrifos in humans following acute-, intermediate-, or chronic-duration exposure.

Chlorpyrifos was tested for its ability to induce complete and partial chromosome losses in *Drosophila melanogaster* males (Woodruff et al. 1983). Initial attempts were made to identify an approximate LD₅₀ (lethal dose, 30% kill) dose prior to treatment, with toxicity defined as the number of dead flies out of the total number treated over a 3-day period. Mortality was recorded at 24, 48, and 72 hours. At 72 hours, males were removed and mated with *mus*-302 repair-defective females, and F₁ male progeny were screened for complete and partial chromosome loss. Treated and control males that had a ring-X chromosome and a doubly-marked Y chromosome were used in a screen for ring

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chromosome loss and for loss of Y-chromosome markers. A significant increase in complete chromosome loss was induced by 0.717 mg/m³ chlorpyrifos, but no effect on partial chromosome loss was observed. No information was located concerning genotoxic effects of inhaled chlorpyrifos in animals following intermediate- or chronic-duration exposure. Genotoxicity studies are also discussed in Section 2.5.

2.2.1.8 Cancer

No information was located concerning the cancer risk of inhaled chlorpyrifos in humans or other animals following acute-, intermediate-, or chronic-duration exposure.

2.2.2 Oral Exposure

2.2.2.1 Death

No information was found concerning death in humans following acute-, intermediate-, or chronic-duration oral exposure.

Acute oral LD₅₀ has been assessed in rodents (El-Sebae et al. 1978; Gaines 1969; McCollister et al. 1974). In rats, chlorpyrifos appears to be more toxic to females than males. Gaines (1969) reported an LD₅₀ of 82 mg/kg for female Sherman rats and an LD₅₀ of 155 mg/kg for males. Similarly, McCollister et al. (1974) reported an LD₅₀ of 135 mg/kg for female Dow-Wistar rats and an LD₅₀ of 163 mg/kg for males. However, in contrast to this apparent sex effect suggested by Gaines' (1969) data, an LD₅₀ of 155 mg/kg was reported for female Sherman rats while the male LD₅₀ was 118 mg/kg (McCollister et al. 1974). An LD₅₀ of 60 mg/kg has been determined for mice (unspecified gender) (El-Sebae et al. 1978). In male guinea pigs, an oral LD₅₀ of 504 mg/kg has been reported (McCollister et al. 1974). In chickens, a single oral dose of 75 mg/kg chlorpyrifos caused death in 1 of 3 animals following regurgitation and aspiration within 8 hours of dosing (Richardson et al. 1983a). However, no hens exposed to 150 or 300 mg/kg died in that study, although at the time of sacrifice, 1 of 3 in the 150 mg/kg group and all in the 300 mg/kg group appeared moribund. In other chicken studies, LD₅₀ values of 32 mg/kg (McCollister et al. 1974) and 34.8 mg/kg (Miyazaki and Hodgson 1972) were reported in male Leghorns. In adult hens, acute-duration oral administration of "pure" chlorpyrifos resulted in deaths within 48 hours in all dose groups (20-60%). In hens dosed

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with 4, 6, 16, or 32 mg/kg chlorpyrifos, 1 of 5, 1 of 5, 3 of 5, and 3 of 5, respectively, died (Capodicasa et al. 1991). In pregnant CF-1 mice, 25 mg/kg/day Dursban F[®] (96.8% chlorpyrifos) as a solution in cottonseed oil administered via gavage from gestation day (Gd) 6-15 caused death in 4 of 47 of the treated mice (Deacon et al. 1980); one death was observed at each 1 mg/kg/day and 10 mg/kg/day chlorpyrifos dose.

Intermediate-duration oral exposure to chlorpyrifos has also been shown to cause death in rodents (Chiappa et al. 1995). Death was observed in 6 of 10 male Long-Evans rats exposed to 100 mg/kg/day chlorpyrifos in corn oil via gavage for 3 days, followed by 75 mg/kg/day chlorpyrifos for 2-4 weeks (Chiappa et al. 1995), time to death was not specifically reported. No treatment-related deaths were observed in a multigeneration study where rats (30 males and 30 females per dose group) received 0, 0.1, 1, or 5 mg/kg/day chlorpyrifos in feed (Breslin et al. 1996). In another multigeneration study, no deaths were observed in male and female Sprague-Dawley rats (30/sex/group) exposed to 0.5, 0.8, or 1.2 mg/kg/day Dursban[®] in feed for 120-135 days (Dow 1983b). Similarly, exposure to up to 15 mg/kg/day Dursban[®] in feed for 13 weeks caused no deaths in Fischer 344 rats (Dow 1993). Intermediate-duration (90 days) oral exposure did not cause deaths in two Leghorn hens exposed to 10 mg/kg/day chlorpyrifos in capsules. In chronic-duration oral exposure studies, no deaths were observed in Sherman rats or Beagle dogs exposed to up to 3 mg/kg/day chlorpyrifos in feed for up to 2 years (McCollister et al. 1974).

The LOAEL and LD₅₀ values for lethality in each reliable study for each species and duration category are shown in Table 2-2 and Figure 2-2.

2.2.2.2 Systemic Effects

The highest NOAEL value and all LOAEL values for systemic effects in each reliable study for each species and duration category are shown in Table 2-2 and Figure 2-2.

Respiratory Effects. In humans, acute-duration oral exposure to chlorpyrifos has been shown to cause respiratory distress resulting from cholinesterase inhibition. A 3-year-old boy was taken to the hospital in respiratory distress following the ingestion of an unknown amount of chlorpyrifos (Aiuto et al. 1993). He lapsed into a coma and was placed on a respirator. After 3 days, the endotracheal tube was removed, but the boy soon developed severe stridor and respiratory distress. Upper-airway edema

Table 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
ACUTE EXPOSURE						
Death						
1	Rat (Sherman)	once (GO)				82 F (LD ₅₀) 155 M (LD ₅₀) Gaines 1969
2	Rat (Dow- Wistar)	once (GO)				163 M (LD ₅₀) 135 F (LD ₅₀) McCollister et al. 1974
3	Rat (Sherman)	once (GO)				118 M (LD ₅₀) 155 F (LD ₅₀) McCollister et al. 1974
4	Mouse (CF-1)	Gd 6-15 1x/d (GO)				1 F (1/40 died) Deacon et al. 1980
5	Gn Pig (NS)	once (GO)				504 M (LD ₅₀) McCollister et al. 1974
Systemic						
6	Rat (Fischer- 344)	Gd 6-15 1x/d (GO)	Hepatic Bd Wt	3 F 3 F	15 F (porphyrin deposits)	15 F (44% decreased body weight gain on Gd 12-16) Breslin et al. 1996
7	Rat (Long- Evans)	once (GO)	Bd Wt Metab	50 M 20 M	100M (13.3% decreased body weight) 50M (hypothermia)	Moser 1995
8	Mouse (CF-1)	Gd 6-15 1x/d (GO)	Hepatic Bd Wt	25 F 10 F	25 F (14% mean body weight gain decrease Gd 6-17)	Deacon et al. 1980

Table 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
9	Mouse (CF-1)	Gd 6-15 1x/d (GO)	Hepatic Bd Wt	10 F 10 F			Deacon et al. 1980
Neurological							
10	Human	9 d (C)		0.03 ^b	0.10 M (rhinorrhea; blurred vision)		Coulston et al. 1972
11	Rat (Fischer- 344)	Gd 6-15 1x/d (GO)		0.1 F	3 F (26% decreased erythrocyte ChE)	15 F (excessive salivation, tremors, urine staining of the perineal region)	Breslin et al. 1996
12	Rat (Long- Evans)	once (GO)			20M (unspecified decreased motor activity)		Moser 1995
13	Mouse (CF-1)	Gd 6-15 1x/d (GO)		1 F	10 F (increased salivation in 5/44)	25 F (symptoms of severe ChE inhibition in 32/47 mice)	Deacon et al. 1980
14	Mouse (CF-1)	Gd 6, 6-10, or 6-15 1x/d (GO)		0.1 F	1 F (25-29% decreased erythrocyte ChE Gds 6-10 and 6-15)		Deacon et al. 1980
15	Cat (Domestic Short-hair)	once (GO)				40 M (hypersalivation, muscular tremors, mild ataxia; decr. brain ChE activity)	Hooser et al. 1988
Reproductive							
16	Rat (Fischer- 344)	Gd 6-15 1x/d (GO)		3 F	15 F (vaginal bleeding)		Breslin et al. 1996

Table 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
17	Mouse (CF-1)	Gd 6-15 1x/d (GO)		25 F			Deacon et al. 1980
Developmental							
18	Rat (Fischer- 344)	Gd 6-15 1x/d (GO)		15			Breslin et al. 1996
19	Mouse (CF-1)	Gd 6-15 1x/d (GO)		1	10	(35% decreased fetal homogenate ChE activity)	Deacon et al. 1980

Table 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Death							
20	Rat (Long- Evans)	2-4 wk 5 d/wk 1x/d (GO)				75 M (6/10 died)	Chiappa et al. 1995
Systemic							
21	Rat (Sprague- Dawley)	multigen (F)	Endocr	1	5	(slight vacuolation of adrenal gland zona fasiculata in both sexes, altered tinctorial properties in females)	Breslin et al. 1996
			Bd Wt	5			
22	Rat (Sprague- Dawley)	135 d ad lib (F)	Renal	1.2			Dow 1983b
			Bd Wt	1.2			
23	Rat (Sprague- Dawley)	120 d ad lib (F)	Bd Wt	1.2			Dow 1983b
24	Rat (Fischer- 344)	13 wk 7 d/wk (F)	Gastro	1 F 15 M	5 F (perineal soiling)		Dow 1993
			Musc/skel	15			
			Ocular	15			
			Bd Wt	15			

Table 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
25	Human	20 d (C)		0.03 ^c M	0.10 M (runny nose; blurred vision)		Coulston et al. 1972
26	Rat (Sprague- Dawley)	multigen (F)		0.1		1 (65-69% decreased erythrocyte ChE)	Breslin et al. 1996
27	Rat (Long- Evans)	2-4 wk 5 d/wk 1x/d (GO)				75 M (73-91% decreased AChE activity in all regions examined; 26-56% increased AChE-IR in all regions examined)	Chiappa et al. 1995
28	Rat (Fischer- 344)	13 wk 7 d/wk (F)		5	15 (decreased motor activity)		Dow 1993
29	Chicken (Leghorn)	90 d 1x/d (C)				10 F (extreme debilitation, weakness and lethargy 35-60 days postdosing)	Francis et al. 1985
Reproductive							
30	Rat (Sprague- Dawley)	multigen (F)		5			Breslin et al. 1996
31	Rat (Sprague- Dawley)	135 d ad lib (F)		1.2			Dow 1983b

Table 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
32	Rat (Sprague- Dawley)	120 d ad lib (F)		1.2			Dow 1983b
Developmental							
33	Rat (Sprague- Dawley)	multigen (F)		1	5	(10-11% decreased pup body weight)	Breslin et al. 1996
34	Rat (Sprague- Dawley)	135 d ad lib (F)		1.2			Dow 1983b
35	Rat (Sprague- Dawley)	120 d ad lib (F)		1.2			Dow 1983b

Table 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Systemic							
36	Rat (Sherman)	2 yr (F)	Resp	3.0			McCollister et al. 1974
			Cardio	3.0			
			Gastro	3.0			
			Hemato	3.0			
			Musc/skel	3.0			
			Hepatic	3.0			
			Renal	3.0			
			Ocular	3.0			
			Bd Wt	3.0			
37	Dog (Beagle)	1 yr (F)	Resp	3.0			McCollister et al. 1974
			Cardio	3.0			
			Gastro	3.0			
			Hemato	3.0			
			Musc/skel	3.0			
			Hepatic	3.0			
			Renal	3.0			
			Ocular	3.0			
			Bd Wt	3.0			

Table 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (continued)

Key to figure ^a	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
38	Dog (Beagle)	2 yr (F)	Resp	3.0			McCollister et al. 1974
			Cardio	3.0			
			Gastro	3.0			
			Hemato	3.0			
			Musc/skel	3.0			
			Hepatic	3.0			
			Renal	3.0			
			Ocular	3.0			
			Bd Wt	3.0			
Immunological/Lymphoreticular							
39	Rat (Sherman)	2 yr (F)		3.0			McCollister et al. 1974
40	Dog (Beagle)	1 yr (F)		3.0			McCollister et al. 1974
41	Dog (Beagle)	2 yr (F)		3.0			McCollister et al. 1974
Neurological							
42	Rat (Sherman)	2 yr (F)		0.1 ^d		1.0 (65-70% decreased red blood cell ChE activity)	McCollister et al. 1974
43	Dog (Beagle)	1 yr (F)		0.1M	1.0M (red blood cell ChE decreased 42-45% of pretest and control values)		McCollister et al. 1974

Table 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
44	Dog (Beagle)	2 yr (F)		0.1	1.0 (27% decreased RBC ChE activity - females only)	McCollister et al. 1974
Reproductive						
45	Rat (Sherman)	2 yr (F)		3.0		McCollister et al. 1974
46	Dog (Beagle)	1 yr (F)		3.0		McCollister et al. 1974
47	Dog (Beagle)	2 yr (F)		3.0		McCollister et al. 1974

^aThe number corresponds to entries in Figure 2-2.

^bUsed to derive an acute oral minimal risk level (MRL) of 0.003 mg/kg/day; dose divided by an uncertainty factor of 10 for human variability.

^cUsed to derive an intermediate oral MRL of 0.003 mg/kg/day; dose divided by an uncertainty factor of 10 for human variability.

^dUsed to derive a chronic oral MRL of 0.001 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

AChE = acetylcholinesterase; ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; ChE = cholinesterase; d = day(s); Endocr = endocrine; F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn Pig = guinea pig; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; IR = immunoreactivity; LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; Musc/skel = musculoskeletal; multigen = multigenerational; NOAEL = no-observable-adverse-effect level; NS = not specified; RBC = red blood cell; Resp = respiratory; wk = week(s); x = times; yr = year(s)

Figure 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral
Acute (≤ 14 days)

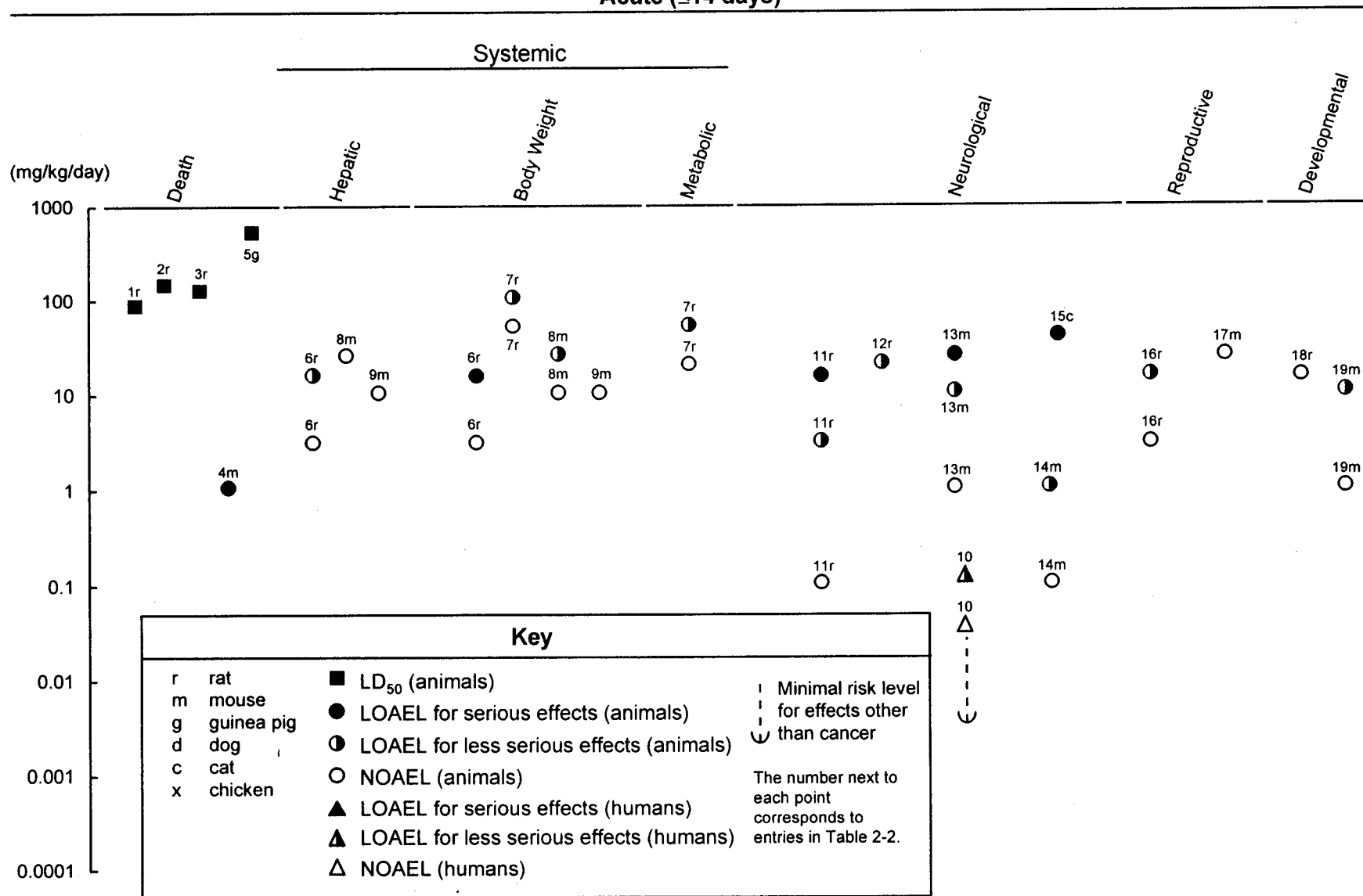


Figure 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (cont.)
Intermediate (15-364 days)

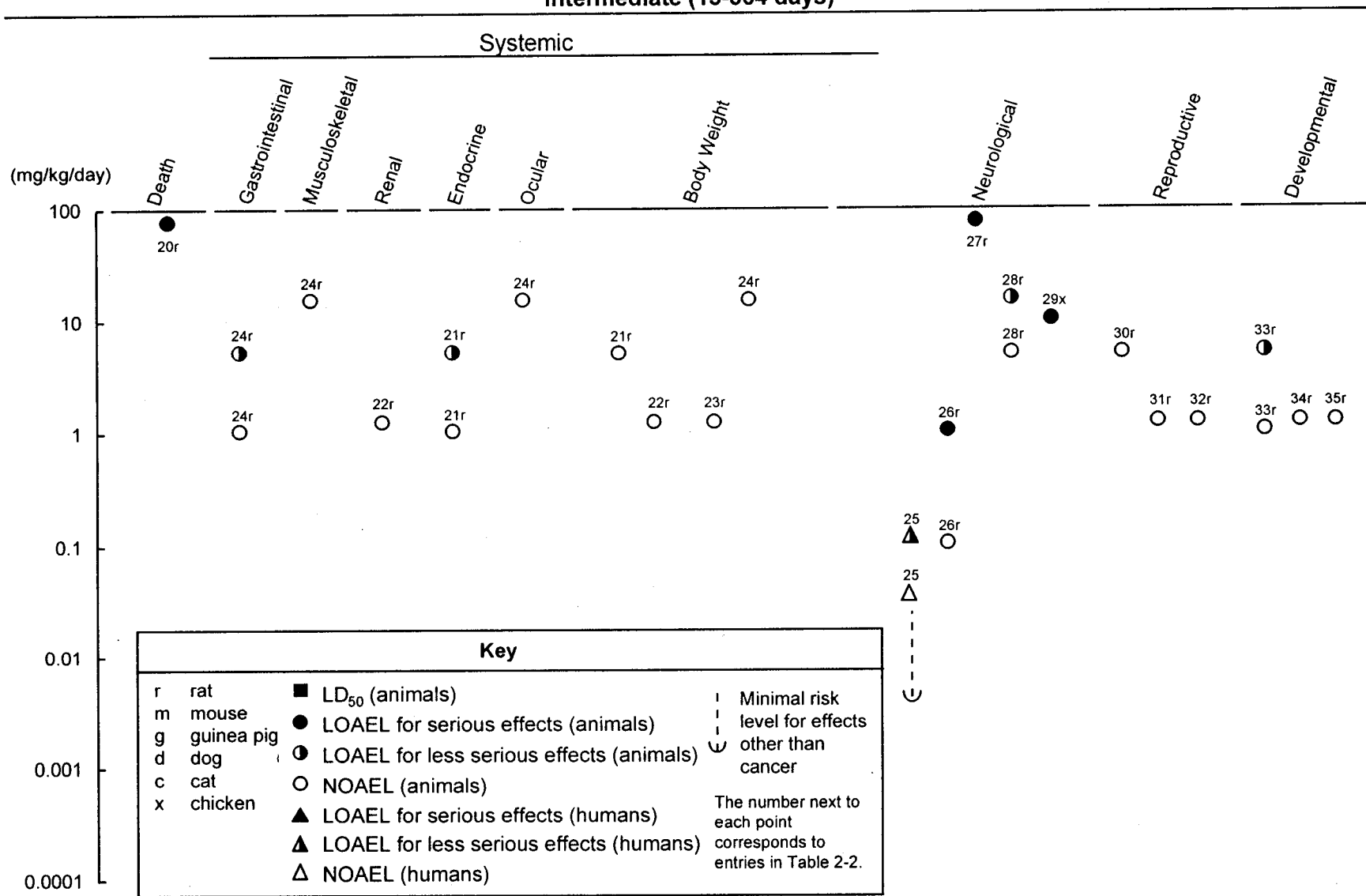
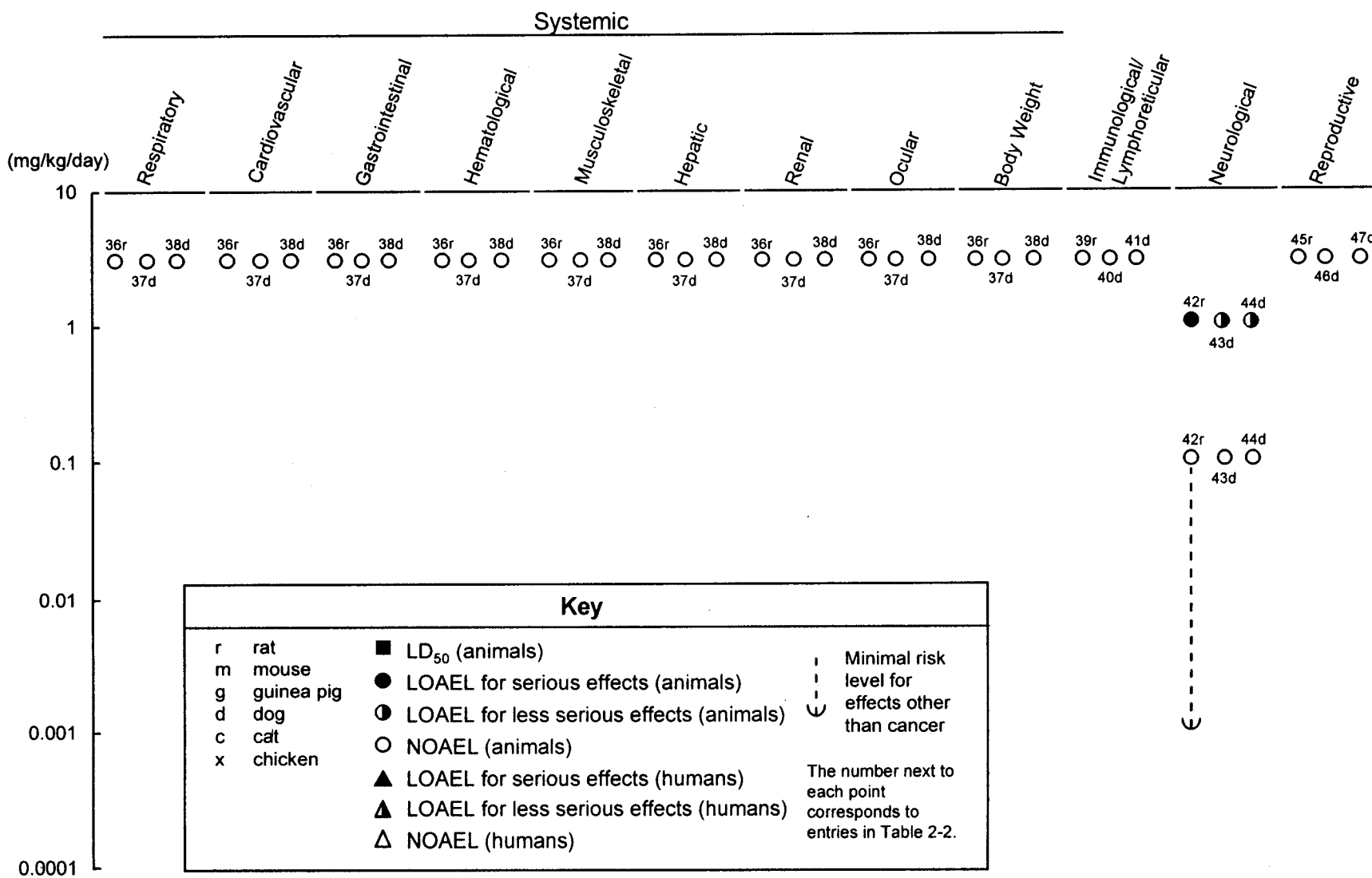


Figure 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (cont.)
Chronic (≥365 days)



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was also evident. It should be noted that stridor often develops in children after they are removed from artificial respirators. Stridor recurred, but the boy responded well to aerosolized racemic epinephrine and cool mist. An acute episode of stridor that did not respond to the aforementioned treatment occurred on day 11 of hospitalization. The airway appeared normal after direct laryngoscopy and bronchoscopy. Bilateral vocal cord paralysis was noted. However, this may have been caused or exacerbated by the intubation. All respiratory symptoms had resolved by day 52 of hospitalization. Similar symptoms were reported in a 5-year-old girl who drank an undetermined amount of Rid-A-Bug[®], a pesticide preparation containing chlorpyrifos. When she arrived at the hospital, she presented with rapid and labored breathing, wheezing, and copious secretions in the nose and mouth that required frequent suctioning (Selden and Curry 1987). The symptoms resolved by day 6 of hospitalization. Respiratory distress was also observed in an adult following acute-duration oral exposure to approximately 300 mg/kg chlorpyrifos (Lotti et al. 1986). No information was found concerning respiratory effects in humans following intermediate- or chronic-duration oral exposure.

No histopathological lesions of the lungs were noted following acute-duration exposure to 40 mg/kg chlorpyrifos dissolved in methylene chloride and administered via gavage in olive oil to male domestic short-hair cats (Hooser et al. 1988) or chronic-duration exposure of Sherman rats and Beagle dogs to as much as 3 mg/kg/day chlorpyrifos in feed (McCollister et al. 1974). No data were located for respiratory effects in animals following intermediate-duration oral exposure to chlorpyrifos.

Cardiovascular Effects. Acute-duration oral exposure to undetermined amounts of chlorpyrifos in humans has been shown to cause tachycardia (Aiuto et al. 1993; Selden and Curry 1987). Although these studies only found tachycardia, the initial response after exposure to an acetylcholinesterase inhibitor is likely to be bradycardia because of stimulation of muscarinic receptors in the heart. No information was found concerning cardiovascular effects in humans following intermediate- or chronic-duration oral exposure to chlorpyrifos.

No histopathological lesions of the heart were noted following acute-duration exposure to 40 mg/kg chlorpyrifos dissolved in methylene chloride and administered in olive oil to cats (Hooser et al. 1988). Similarly, no heart weight changes or histopathological lesions were observed following chronic-duration exposure of Sherman rats and Beagle dogs to as much as 3 mg/kg/day chlorpyrifos in feed (McCollister et al. 1974). Intermediate-duration exposure of a female domestic short-hair cat to an unspecified concentration of chlorpyrifos 2-3 hours after an apartment was sprayed for fleas did result

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in increased creatine kinase levels in the cat. No effect was seen on an electrocardiogram, however (Jaggy and Oliver 1992). It is assumed that at least some of the exposure to this animal was oral through grooming.

Gastrointestinal Effects. No information was found concerning gastrointestinal effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorpyrifos.

Limited gastrointestinal effects have been noted in rats following intermediate-duration oral exposure to chlorpyrifos. In female Fischer 344 rats, perineal soiling was observed in animals exposed to 5 mg/kg/day chlorpyrifos in feed for 13 weeks and may have been related to cholinesterase inhibition (Dow 1993). This effect was not seen in male rats exposed to as much as 15 mg/kg/day in feed for the same duration. This effect may be part of the spectrum of cholinergic effects. No histopathological lesions of the stomach were noted following either acute-duration exposure to 40 mg/kg chlorpyrifos in male domestic short-hair cats (Hooser et al. 1988) or chronic-duration exposure of Sherman rats and Beagle dogs to as much as 3 mg/kg/day chlorpyrifos in feed (McCollister et al. 1974).

Hematological Effects. Acute-duration oral exposure to an undetermined amount of chlorpyrifos by ingestion caused elevated serum glucose and creatinine kinase levels and low lactate dehydrogenase levels in a 3-year-old boy who ingested an unknown amount of Dursban® (Aiuto et al. 1993). No effect on hematological or serum chemistry parameters were seen, however, in adult male volunteers treated with up to 0.1 mg/kg/day chlorpyrifos by capsule for 9 days or up to 0.03 mg/kg/day chlorpyrifos for 20 days (Coulston et al. 1972). No information was found concerning hematological effects in humans following chronic-duration oral exposure to chlorpyrifos. No information was found concerning hematological effects in other animals following acute- or intermediate-duration oral exposure to chlorpyrifos. No effect was seen on hematological parameters monitored in Sherman rats and Beagle dogs exposed to up to 3 mg/kg/day chlorpyrifos in the feed for 1-2 years (McCollister et al. 1974).

Musculoskeletal Effects. Acute-duration oral exposure to an undetermined amount of chlorpyrifos caused increased muscle tone in a 23-year-old woman (Joubert et al. 1984), and fasciculations in a 42-year-old male (Lotti et al. 1986). Bilateral vocal cord paralysis was also

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observed in a 3-year-old boy who swallowed an undetermined amount of chlorpyrifos (Aiuto et al. 1993); the vocal cord paralysis, however, may have been caused or exacerbated by the intubation of this patient. No information was found concerning musculoskeletal effects in humans following intermediate- or chronic-duration oral exposure to chlorpyrifos.

No histopathological lesions of the skeletal muscle were noted following acute-, intermediate-, or chronic-duration exposure to chlorpyrifos. Exposure to 40 mg/kg chlorpyrifos dissolved in methylene chloride and administered in olive oil to male domestic short-hair cats (Hooser et al. 1988), to 15 mg/kg/day Dursban[®] in feed administered to male and female Fischer 344 rats (Dow 1993), or chronic-duration exposure of Sherman rats and Beagle dogs to as much as 3 mg/kg/day chlorpyrifos in feed (McCollister et al. 1974) caused no histopathology of the skeletal muscles. No data were located for musculoskeletal effects in animals following acute- or chronic-duration oral exposure to chlorpyrifos.

Hepatic Effects. No information was found concerning hepatic effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorpyrifos.

The effects on liver weight and relative liver weight (liver weight/body weight) were assessed in pregnant CF-1 mice following acute-duration oral exposure to doses as high as 25 mg/kg/day chlorpyrifos from Gd 6 to 15 (Deacon et al. 1980). Liver weight and relative liver weight determined on Gd 18 were comparable to controls in all treatment groups. Hepatic effects were also noted in pregnant female Fischer 344 rats dosed by gavage with 0, 0.1, 3, or 15 mg/kg/day of the technicalgrade chlorpyrifos Dursban F[®] in corn oil on Gd 6-15. Porphyrin deposits about the eyes were observed during the dosing period in maternal animals exposed to 15 mg/kg/day chlorpyrifos. This effect was not seen at doses of 3 mg/kg/day or below (Breslin et al. 1996). Increased serum total protein and albumin levels were observed in a female domestic short-hair cat exposed to an unspecified amount of chlorpyrifos in an apartment that was sprayed with chlorpyrifos every third day for 18 days (Jaggy and Oliver 1992). It is assumed that some of the exposure was via the oral route as a result of grooming. No histopathological lesions or organ weight changes were observed in livers of Sherman rats or Beagle dogs chronically exposed to as much as 3 mg/kg/day chlorpyrifos in feed (McCollister et al. 1974).

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Renal Effects. No chlorpyrifos-induced renal effects have been observed in humans. Urinalyses conducted for adult male volunteers treated with up to 0.1 mg/kg/day chlorpyrifos by capsule for 9 days or up to 0.03 mg/kg/day chlorpyrifos for 20 days were normal (Coulston et al. 1972). No information was found concerning renal effects in humans following chronic-duration oral exposure to chlorpyrifos.

In laboratory animals, chlorpyrifos-induced renal effects were few. No renal lesions were noted following a single oral exposure to 40 mg/kg chlorpyrifos dissolved in methylene chloride and administered in olive oil to adult male domestic short-hair cats (Hooser et al. 1988). Urine staining of the perineal region was observed in pregnant Fischer 344 rats exposed via gavage on Gd 6-15 to 15 mg/kg/day of the technical-grade chlorpyrifos, Dursban F[®], in corn oil (Breslin et al. 1996). In the same study, no renal effects were noted in rats exposed to 0.1 or 3 mg/kg/day chlorpyrifos. Renal effects have been observed following intermediate-duration oral exposure. Unspecified increases in urea nitrogen, alkaline phosphatase, and alanine aminotransferase were observed in a female domestic short-hair cat orally exposed to an unspecified amount of chlorpyrifos every third day for 18 days (Jaggy and Oliver 1992). It is assumed that some of the exposure was oral through grooming. No renal effects were seen in the parental generation of Sprague-Dawley rats exposed to 0, 0.5, 0.8, or 1.2 mg/kg/day chlorpyrifos in feed for 135 days (Dow 1983b). Chronic-duration oral exposure to up to 3 mg/kg/day chlorpyrifos in feed also caused no organ weight changes or histopathological lesions of the kidneys in either male or female Sherman rats or Beagle dogs exposed to chlorpyrifos in feed for 1-2 years (McCollister et al. 1974).

Endocrine Effects. No information was found concerning endocrine effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorpyrifos.

Acute-duration oral exposure to 40 mg/kg chlorpyrifos dissolved in methylene chloride and administered in olive oil to male domestic short-hair cats caused no microscopic lesions of the thyroid or adrenal glands (Hooser et al. 1988). Mild endocrine effects were, however, observed following intermediate-duration oral exposure (Breslin et al. 1996). In a multigeneration study, rats (30 males and females per dose group) received chlorpyrifos dosages equivalent to 0, 0.1, 1, or 5 mg/kg/day/day in feed. Very slight to slight vacuolation of the adrenal gland fasciculata was observed at 5 mg/kg/day in both males and females in the parental generation. These alterations were characterized by very slight to slight vacuolation in males and very slight vacuolation and altered tinctorial

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properties in females. The toxicological significance of these effects is unclear. No endocrine effects were observed at the 0.1 or 1 mg/kg/day doses (Breslin et al. 1996). No information was found concerning endocrine effects in animals following chronic-duration oral exposure to chlorpyrifos.

Ocular Effects. No information was found concerning ocular effects in humans following intermediate- or chronic-duration oral exposure to chlorpyrifos.

Miosis was observed in a man after a single oral exposure to 300 mg/kg chlorpyrifos (Lotti et al. 1986). No data were located for ocular effects in other animals following acute-duration oral exposure to chlorpyrifos. No ocular histopathology was found in male and female Fisher 344 rats exposed for 13 weeks to 0, 0.1, 1, 5, or 15 mg/kg/day chlorpyrifos in feed (Dow 1993). Chronic-duration oral exposure in feed to as high as 3 mg/kg/day chlorpyrifos caused no ocular effects in either male or female Sherman (30-32/sex/group) rats dosed for 2 years or Beagle dogs (3/sex/group) exposed for 1-2 years (McCollister et al. 1974).

Body Weight Effects. No information was found concerning effects on body weight in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorpyrifos.

The effects on body weight and body weight gain were assessed in pregnant CF-1 mice following acute-duration oral exposure to doses as high as 25 mg/kg/day chlorpyrifos in cottonseed oil on Gd 615 (Deacon et al. 1980). A statistically significant decrease in mean body weight gain for Gd 10-15 (33.3%) and overall (Gd 6-17, 14%) was observed in animals exposed to 25 mg/kg/day chlorpyrifos. Food consumption was unaffected. The body weight gain and food consumption of dams exposed to 1 or 10 mg/kg/day chlorpyrifos were comparable to controls. Additionally, body weights determined on Gd 18 for all the treatment groups were similar to control values. Similar effects have been observed in rats (Breslin et al. 1996; Moser 1995). A single dose of 100 mg/kg technical-grade chlorpyrifos (99%) administered via gavage in corn oil caused a 13.3% decrease in the body weight of male Long-Evans rats by 24 hours post-dosing. Recovery was seen at one week postdosing. Decreased body weight was not seen at doses of 50 mg/kg or less (Moser 1995). Similarly, pregnant Fischer 344 rats exposed via gavage to 15 mg/kg/day Dursban F[®] (technical-grade chlorpyrifos) in corn oil on Gd 6-15 experienced a statistically significant decrease in mean body weight gain for Gd 9-12 (44%). The body weight gain of dams exposed to 0.1 or 3 mg/kg/day chlorpyrifos was comparable to controls (Breslin et al. 1996).

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Body weight effects have not been seen following intermediate-duration oral exposure of rodents (Breslin et al. 1996; Dow 1983b, 1993). No body weight changes were observed in male and female Fischer 344 rats exposed to up to 15 mg/kg/day Dursban[®] in feed for 13 weeks (Dow 1993). Similarly, in a rat multigeneration study, no body weight or feed intake changes were observed in male and female Sprague-Dawley rats exposed to 0, 0.1, 1, or 5 mg/kg/day chlorpyrifos in feed (Breslin et al. 1996). In another rat multigeneration study, no body weight or feed intake changes were observed in male and female Sprague-Dawley parental animals or first generation offspring exposed to 0, 0.5, 0.8, or 1.2 mg/kg/day Dursban[®] for 135 or 120 days, respectively (Dow 1983b). However, body weight decreases following intermediate-duration chlorpyrifos exposure have been observed in chickens. A dose of 10 mg/kg/day chlorpyrifos for 20 days caused a 25% decrease in body weight in hens by the end of the dosing period (Richardson et al. 1993b). Chronic-duration oral exposure to ≤ 3 mg/kg/day chlorpyrifos in feed also caused no body weight effects in either male or female Sherman rats or Beagle dogs exposed for 1-2 years (McCollister et al. 1974).

Metabolic Effects. No information was found concerning the metabolic effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorpyrifos.

Hypothermia was observed in male Long-Evans rats 3.5 hours after acute-duration exposure to 50 or 100 mg/kg technical-grade (99%) chlorpyrifos in corn oil via gavage (Moser 1995). Hypothermia was present at 24 hours post-dosing only in the 100 mg/kg group and was no longer detectable at 72 hours post-dosing. Hypothermia was not observed in animals exposed to 20 mg/kg. No information was found concerning the potential metabolic effects in animals following intermediate- or chronic-duration exposure to chlorpyrifos.

2.2.2.3 Immunological and Lymphoreticular Effects.

No information was found concerning immunological or lymphoreticular effects in humans following acute-, intermediate-, or chronic-duration oral exposure to chlorpyrifos. No immunological or lymphoreticular effects were observed microscopically in the spleen or mesenteric lymph nodes of 2 male domestic short-hair cats acutely exposed to 40 mg/kg chlorpyrifos (Hooser et al. 1988). Similarly, chickens exposed orally to 10 mg/kg/day chlorpyrifos for 20 days also exhibited no immunological or lymphoreticular effects (Richardson et al. 1993b). Breslin et al. (1996)

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investigated the reproductive and developmental effects of chlorpyrifos at 0.1, 1, and 5 mg/kg/day/day in a 2-generation reproductive study in Sprague-Dawley rats. Their results indicated no treatment-related histopathological changes in thymus, spleen, mesenteric lymph node, or bone marrow in any of the F₀ or F₁ adults. Chronic-duration oral exposure to up to 3 mg/kg/day chlorpyrifos in feed also caused no histopathology of the spleen or organ weight change in either male or female Sherman rats or Beagle dogs orally exposed for 1-2 years (McCollister et al. 1974). Taken together, the available evidence indicates that exposure to chlorpyrifos produces little or no structural changes in the immune system, even when administered chronically at doses causing statistically significant decreases in acetylcholinesterase activity.

2.2.2.4 Neurological Effects

In humans, acute-duration oral exposure to 0.1 mg/kg/day/day of chlorpyrifos for 9 days has been reported to inhibit plasma cholinesterase activity 66% (Coulston et al. 1972). Additionally, acute-duration oral exposure to undetermined amounts of chlorpyrifos has been reported to inhibit both erythrocyte and plasma cholinesterase activity 78-95% (Joubert et al. 1984; Selden and Curry 1987). These latter levels of inhibition were associated with life-threatening cholinergic symptoms requiring hospitalization. Acute-duration oral exposure to undetermined amounts of chlorpyrifos caused stupor in a 23-year-old woman (Joubert et al. 1984), seizure-like motor activity in a 5-year-old girl (Selden and Curry 1987), and coma in a 42-year-old man (Lotti et al. 1986) and a 3-year-old boy (Aiuto et al. 1993). A variety of other symptoms have also been associated with exposure to unspecified amounts of chlorpyrifos: miosis, muscle twitching and fasciculations, hyper- or hyporeflexia, lacrimation, salivation, sweating, bronchorrhea, diaphoresis, and coreo-athetotic motions (Aiuto et al. 1993; Joubert et al. 1984; Selden and Curry 1987). Similar chlorpyrifos-related effects have been observed for CF-1 mice at 25 mg/kg/day, but not at 10 mg/kg/day chlorpyrifos (Deacon et al. 1980); in domestic shorthair cats at 40 mg/kg (Hooser et al. 1988); and in hens at 90 mg/kg (Capodicasa et al. 1991). Plasma and erythrocyte cholinesterase activity in adult humans volunteers following intermediate-duration oral exposure to doses up to 0.03 mg/kg/day chlorpyrifos for 20 days were unaffected (Coulston et al. 1972). No information was found concerning neurological effects in humans following chronic-duration oral exposure to chlorpyrifos.

In male domestic short-hair cats, acute-duration oral exposure to 40 mg/kg chlorpyrifos caused a 43-57% decrease in whole blood acetylcholinesterase activity and a 71% decrease in plasma

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cholinesterase activity (Hooser et al. 1988). Similar effects were observed in pregnant Fischer 344 rats exposed to technical-grade chlorpyrifos Dursban F[®] administered via gavage on Gd 6-15. Erythrocyte acetylcholinesterase activity decreased 74 and 85% compared to control values at the 3 and 15 mg/kg/day body weight doses, respectively (Breslin et al. 1996). The dams exposed to 15 mg/kg/day chlorpyrifos also exhibited classic signs of organophosphate poisoning during the dosing period, including excessive salivation, tremors, and decreased plasma cholinesterase activity. In the same study, no neurological effects were seen at 0.1 mg/kg/day. Female CF-1 mice (40-51 per group) were exposed by gavage to 1, 10, or 25 mg/kg/day/day Dursban F[®] (96.8% chlorpyrifos) as a solution in cottonseed oil on day 6, days 6-10, or Gd 6-15 (Deacon et al. 1980). Plasma and erythrocyte cholinesterase levels were significantly decreased from control values among mice given 10 or 25 mg/kg/day chlorpyrifos on day 6 (plasma, 95 and 97% decrease, respectively; erythrocyte, 20 and 40%, respectively) and, days 6-10 (plasma, 97 and 99%, respectively; erythrocyte, 43 and 71%, respectively), or days 6-15 (plasma, 96 and 98%, respectively; erythrocyte, 43 and 57%, respectively). Plasma cholinesterase levels were significantly reduced among mice given 1 mg/kg/day chlorpyrifos during the same time intervals (69, 78, and 85%, respectively). Erythrocyte cholinesterase levels were also reduced (43%) after 1 mg/kg/day chlorpyrifos, but only after exposure on Gd 6-10 (Deacon et al. 1980). In a concurrent study of cholinesterase inhibition using dosages of 0.1, 1, and 10 mg/kg/day, Deacon et al. (1980) determined a no-effect level of 0.1 mg/kg/day for erythrocyte and plasma cholinesterase inhibition. Similar effects on erythrocyte and plasma cholinesterase activities were noted in a multigeneration study in rats (Breslin et al. 1996). Significantly decreased erythrocyte and plasma cholinesterase levels were seen in first and second generation male and female Sprague-Dawley rats exposed to 1 mg/kg/day Dursban F[®] in feed. In males, erythrocyte cholinesterase was decreased 65-69%, while plasma cholinesterase was decreased 43-44%. In females, erythrocyte cholinesterase was decreased 67%, while plasma cholinesterase was decreased 49-55%. These effects were not observed in rats fed diets containing 0.1 mg/kg/day Dursban F[®] (Breslin et al. 1996).

In one human suicide attempt, acute-duration oral exposure to approximately 300 mg/kg of a commercial formulation of chlorpyrifos caused transient distal polyneuropathy that resolved approximately 90 days after exposure (Lotti et al. 1986). Acute-duration oral exposure to undetermined amounts of chlorpyrifos produced clinical findings in a 3-year-old boy that were consistent with proximal polyneuropathy (Aiuto et al. 1993). Eleven days following exposure, the boy was areflexic, and electromyography demonstrated the absence of voluntary motor units on the 18th

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day of hospitalization. Nerve conduction studies revealed a lack of F latencies. The patient was fully recovered by day 52 of his hospital stay.

In the chicken, the species of choice for the evaluation of the OPIDN (Johnson 1982), a single oral exposure to 150 or 300 mg/kg chlorpyrifos (with atropine prophylaxis to prevent death from acute cholinergic effects) caused a 3880% inhibition of neurotoxic esterase (NTE) 4 days after exposure (Capodicasa et al. 1991; Richardson et al. 1993a). NTE inhibition is believed by some to be directly related to the onset of OPIDN (Johnson 1982). Mild ataxia (indicating OPIDN) was observed in 4 of 7 chickens receiving 5 daily doses of 90 mg/kg/day chlorpyrifos (with atropine prophylaxis) and observed for a further 2 weeks (Capodicasa et al. 1991). A repeated-dose study showed that 20 daily doses of 10 mg/kg/day/day chlorpyrifos in corn oil (the maximally tolerated dose that did not require atropine prophylaxis) followed by a 4-week recovery produced signs of toxicity, including a significant decrease in body weight and brain and blood AChE (Richardson et al. 1993a). It also produced a maximum 18% inhibition of brain NTE, with no significant inhibition of lymphocyte NTE or clinical signs of OPIDN.

In the chicken, brain AChE has also been shown to be inhibited by acute-duration oral exposure to chlorpyrifos. Exposure to 150 or 300 mg/kg caused brain AChE inhibition of >80% 4 days after exposure (Richardson et al. 1993a). Intermediate-duration exposure to 10 mg/kg/day chlorpyrifos inhibited brain AChE 58-70% during days 4-20 of exposure (Richardson et al. 1993b). Similar effects on brain AChE were observed in male Long-Evans rats exposed to 75 mg/kg/day chlorpyrifos in corn oil via gavage for 24 weeks. Brain AChE was decreased 85, 91, 86, and 73% in the whole brain, forebrain, hippocampus, and cerebellum, respectively. Additionally, brain immunoreactive AChE was increased 56, 29, 26, and 26% in the whole brain, forebrain, hippocampus, and cerebellum, indicating increased synthesis of AChE or inhibited degradation to compensate for the effects of chlorpyrifos (Chiappa et al. 1995). In a study to examine the potential for intermediate-duration chlorpyrifos exposure to produce OPIDN (Francis et al. 1985), 2 hens were exposed to 10 mg/kg/day chlorpyrifos for 90 days. Physical deterioration began 30 days after exposure, and extreme debilitation, weakness, and lethargy occurred between 35 and 60 days of dosing. The report indicates that both hens recovered from the chlorpyrifos-induced neurotoxicity after the cessation of dosing, but the time to recovery was not given. The time-course of toxicity and the eventual resolution of neurological symptoms following the exposure indicate that chlorpyrifos did not cause the classic OPIDN, from which recovery would not be expected, in this study. In fact, work by Richardson et al.

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(1993a) indicates that chlorpyrifos-related OPIDN would only be expected at doses that would cause death without aggressive therapy.

Other neurological effects were also noted in acute- and intermediate-duration studies of humans and animals (Aiuto et al. 1993; Dow 1993; Joubert et al. 1984; Lotti et al. 1986; Moser 1995; Selden and Curry 1987). Acute-duration exposure to unspecified amounts of chlorpyrifos in children (a 3-year-old boy [Aiuto et al. 1993] and a 5-year-old girl [Selden and Curry 1987]) and a 23-year-old woman (Joubert et al. 1984) caused miosis. Miosis was also observed in a man who ingested an estimated 300 mg/kg chlorpyrifos in a suicide attempt (Lotti et al. 1986). Decreased motor activity was noted in male Long-Evans rats 3.5 hours after a single gavage exposure to 20, 50, or 100 mg/kg technical-grade chlorpyrifos (99%) in corn oil. At 24 hours post-dosing, decreased motor activity was still present in the 100 mg/kg group, but these effects were no longer evident at 72 hours post-dosing (Moser 1995). Male and female Sprague-Dawley rats exposed to 1.5 mg/kg/day Dursban F® in feed for 13 weeks displayed a transient decrease in motor activity at the fourth week of dosing (Dow 1993). Chronic-duration oral exposure to chlorpyrifos in feed also caused neurological effects in rats and dogs (McCollister et al. 1974). Brain acetylcholinesterase AChE activity was depressed at all sampling times in rats fed 3 mg/kg/day chlorpyrifos for up to 2 years, with overall means averaging 56% of control value for males and 57% for females. There was no overall reduction in brain AChE activity at study termination in rats dosed with 1 mg/kg/day, although there were individually significant differences at some of the sampling times. Rat plasma cholinesterase (ChE) and red blood cell (RBC) AChE activities were significantly depressed for both male and female rats dosed with 1 and 3 mg/kg/day chlorpyrifos. For example, at 1 mg/kg/day, plasma ChE activity was decreased 20-53% while RBC AChE activity was decreased 65-70%. At 0.1 mg/kg/day, the AChE activity of the RBCs for females was significantly different from controls at 2 of the 6 sampling periods only. Otherwise, doses of 0.1 mg/kg/day and below had no effect on either plasma or RBC activity. Cholinesterase activities in plasma, RBC, and brain returned to normal levels in males and females in all dose groups maintained on control diets for 7-8 weeks (McCollister et al. 1974). In Beagle dogs, similar effects were observed in males exposed to 1 mg/kg/day chlorpyrifos in feed for 1 or 2 years or females receiving that same daily dose for 2 years. However, this effect was not seen in females exposed to as much as 3 mg/kg/day chlorpyrifos in feed for 1 year (McCollister et al. 1974), suggesting that there may be a cumulative effect of chlorpyrifos exposure.

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Any sex-dependent toxicity of chlorpyrifos may be due to an increased rate of extrahepatic detoxification of the pesticide in males. A complete discussion of this phenomenon may be found in Section 2.3, Toxicokinetics, of this profile.

The highest NOAEL value and all LOAEL values for neurological effects in each reliable study for each species and duration category are shown in Table 2-2 and Figure 2-2.

2.2.2.5 Reproductive Effects

No information was found concerning reproductive effects in humans following oral acute-, intermediate-, or chronic-duration exposure to chlorpyrifos.

Pregnant CF-1 mice were exposed on Gd 6, Gd 6-10 or Gd 6-15, to 0, 1, 10, or 25 mg/kg/day chlorpyrifos (Deacon et al. 1980). Four of 47 dams exposed to 25 mg/kg/day chlorpyrifos died. That dose also caused a significant decrease in body weight gain during Gd 10-15 (33%) and Gd 6-17 (14%). Despite the deficits in weight gain, overall body weight at study termination was not affected at that dose. Thirty-two of 47 mice exposed to 25 mg/kg/day chlorpyrifos exhibited symptoms (excessive salivation, tremors, urine-soaked coat, ataxia, and lethargy) of cholinergic overstimulation; similar clinical signs were seen in 5 of 44 dams dosed with 10 mg/kg/day/day chlorpyrifos. Food and water intake were also significantly decreased at that dose. Despite the maternal toxicity, chlorpyrifos did not affect the ability of the surviving dams to maintain pregnancy. No overt neurological symptoms were observed at the lower chlorpyrifos doses (1 or 10 mg/kg/day). In a concurrent study, pregnant mice were orally administered 0, 0.1, 1, or 10 mg/kg/day chlorpyrifos. No significant clinical signs of maternal toxicity were noted at any dose of chlorpyrifos. In pregnant Fischer 344 rats exposed by gavage to 0, 0.1, 3, or 15 mg/kg/day technical-grade chlorpyrifos as Dursban F[®], on Gd 6-15, vaginal bleeding was observed in dams exposed to 15 mg/kg/day chlorpyrifos, but no other reproductive organ effects were noted (Breslin et al. 1996). No reproductive effects were seen in rats exposed to 0.1 or 3 mg/kg/day. No adverse effects on fertility, mating, or gestation indices were observed in multigeneration studies conducted using Sprague-Dawley rats (30/sex/group) dosed with 0.1-5 mg/kg/day Dursban[®] feed (Breslin et al. 1996; Dow 1983b). No effects on testes weight or reproductive organ histology were observed in male and female Sherman rats or Beagle dogs exposed to as high as 3 mg/kg/day chlorpyrifos in feed for 1-2 years (McCollister et al. 1974).

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The highest NOAEL values for reproductive effects in each reliable study for each species and duration category are shown in Table 2-2 and Figure 2-2.

2.2.2.6 Developmental Effects

No information was found concerning developmental effects in humans following oral acute-, intermediate-, or chronic-duration exposure to chlorpyrifos.

The potential for chlorpyrifos to cause developmental toxicity was assessed in CF-1 mice exposed to 0, 1, 10, or 25 mg/kg/day chlorpyrifos on Gd 6-15 (Deacon et al. 1980). On Gd 18, all fetuses were weighed, sexed, examined for external malformations and cleft palate, and had their crown-rump length determined. One-third of the fetuses of each litter were also examined for evidence of soft tissue alterations. There was no biologically significant effect of treatment on the number of live fetuses per litter, the number of dead fetuses per litter, the number of resorptions per litter, the average fetal body weight, or average crown-rump length. However, significant increases in skeletal variations were observed in litters exposed to 25 mg/kg/day chlorpyrifos. Increases were seen for the number of fetuses with delayed ossification of the skull bones (6.8-fold increase), delayed ossification of the sternalbrae (2.1-fold increase), and unfused sternalbrae (4-fold increase). These effects, however, may have been due, in part, to maternal toxicity as opposed to a direct effect of chlorpyrifos on the developing offspring. In the same study, 10 and 25 mg/kg/day significantly decreased whole fetal homogenate cholinesterase activity by 35 and 65%, respectively. Similar exposure in rats, however, caused no developmental effects (Breslin et al. 1996). Pregnant Fischer 344 rats exposed to 0.1, 3, or 15 mg/kg/day technical-grade chlorpyrifos Dursban F[®] in corn oil administered via gavage on Gd 6-15 showed no effect on pregnancy rate, number of implantations, preimplantation loss, resorption, number of dead fetuses, litter size, fetal body weight, crown-rump length, or sex ratio in any treatment group. Increased fetal body weight was observed in the 3 and 15 mg/kg groups, but was not considered treatment-related. There were no treatment-related effects on fetal malformations or variations at any exposure level (Breslin et al. 1996).

Few developmental effects have been seen following intermediate-duration oral exposure to chlorpyrifos. No adverse effects on gestation indices; gestation survival indices; total number of live pups per litter on day 1 of lactation; pup survival indices on days 1, 4, 7, 14, and 21 of lactation; sex ratio of pups at day 21; or incidence of external alterations in first and second generation offspring

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between birth and 21 days of age were observed in a multigeneration study conducted using Sprague-Dawley rats (30/sex/dose group) fed the equivalent of 0.5, 0.8, or 1.2 mg/kg/day Dursban[®] (Dow 1983b). However, a 10-11% decrease in pup body weight was observed in first generation pups in a multigeneration study of male and female Sprague-Dawley rats fed diets containing 5 mg/kg/day Dursban F[®] (Breslin et al. 1996). Using a similar study design and numbers of animals, Breslin et al. (1996) did not report offspring body weight deficits in animals fed 1 mg/kg/day or less chlorpyrifos. No data were located for developmental effects in animals following chronic-duration oral exposure to chlorpyrifos.

The LOAEL values for developmental effects in each reliable study for each species and duration category are shown in Table 2-2 and Figure 2-2.

2.2.2.7 Genotoxic Effects

No information was found concerning the potential genotoxic effects in humans following oral acute-, intermediate-, or chronic-duration exposure to chlorpyrifos.

Chlorpyrifos was tested for its ability to induce complete and partial chromosome losses in *D. melanogaster* males (Woodruff et al. 1983). Initial attempts were made to identify an approximate LD₃₀ dose prior to treatment, with toxicity defined as the number of dead flies out of the total number treated over a 3-day period. Mortality was recorded at 24, 48, and 72 hours. At 72 hours, males were removed and mated with mus-302 repair-defective females, and F₁ male progeny were screened for complete and partial chromosome loss. Treated and control males that had a ring-X chromosome and a doubly-marked Y chromosome were used in a screen for ring-chromosome loss and for loss of Y-chromosome markers. A significant increase in complete chromosome loss was induced by 0.05 mg/kg chlorpyrifos, but no effect on partial chromosome loss was observed.

The mutagenic potential of an unspecified dose of Durmet[®] (20% chlorpyrifos) was assessed using the *Drosophila* wing mosaic and sex-linked recessive lethal tests (Patnaik and Tripathy 1992). In the wing mosaic test, second- and third-instar larvae that were trans-heterozygous for the recessive marker mutations multiple wing hair (mwh) and flare-3 (flr3) were obtained from a cross of mwh females and flr3/TM3 Ser males. They were exposed to various concentrations of Durmet[®], and the frequency of the mutant mosaic spot induction on the wings noted. The Basc technique was used to evaluate the

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induction of sex-linked lethals. Because of an increase in the frequency of induction of mosaic wing spots and sex-linked recessive lethals, Durmet[®] was considered to be genotoxic to *Drosophila* somatic and germ cells.

Intermediate-duration oral exposure to chlorpyrifos (as Dursban[®]) has been shown to increase the incidence of erythroblast chromosomal aberrations (Amer and Fahmy 1982). In that study, mice received rat chow containing either 0, 80, or 240 ppm Dursban[®] for 24 hours, 7 days, 14 days, or 14 days with a 7-day recovery period. Doses of 1.39 or 4.18 mg/kg/day Dursban[®] were estimated from those concentrations. Dursban[®] at 4.18 mg/kg/day caused a statistically significant increase in the percentage of polychromatic erythrocytes (PE) and PE with micronuclei after 24 hours (70 and 176% increases, respectively) and 7 days (25 and 257% increases, respectively) of exposure. PE with micronuclei were also significantly increased at 14 days of treatment with 4.18 mg/kg/day (458% increase). These increases were transient, and percentages of PE and PE with micronuclei were normal seven days after the end of the dosing period. These results indicate that during exposure, chlorpyrifos increased the incidence of erythroblast chromosomal aberrations. Similar transient increases in PE and PE with micronuclei were found after mice were dose-fed 2.09 mg/kg/day Dursban[®] for 10 weeks (Amer and Fahmy 1982). No data were located for genotoxic effects in animals following chronic-duration oral exposure to chlorpyrifos. Genotoxicity studies are also discussed in Section 2.5.

2.2.2.8 Cancer

No information was located concerning carcinogenic effects of chlorpyrifos in humans following oral acute-, intermediate-, or chronic-duration exposures.

No studies were located concerning carcinogenic effects of chlorpyrifos in animals following acute- or intermediate-duration exposure. Chronic-duration exposure studies have shown no carcinogenicity. Male and female Sherman rats and Beagle dogs exposed to up to 3 mg/kg/day chlorpyrifos in feed for 1-2 years had no increased incidence of tumors compared to controls (McCollister et al. 1974).

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2.2.3 Dermal Exposure**2.2.3.1 Death**

No information was found concerning death in humans following acute-, intermediate-, or chronic-duration dermal exposure to chlorpyrifos.

Acute-duration dermal exposure LD_{50} for chlorpyrifos was determined to be 202 mg/kg in Sherman rats (Gaines 1969). Survival times of 46 hours to 13 days were reported. Acute-duration dermal exposure of 185 young (9-52 months of age) bulls to an undetermined dose of Dursban 44[®] to control lice killed 7 of the animals (Everett 1982). Additionally, age-related death was observed in newborn piglets sprayed with an undetermined amount of chlorpyrifos at various times after birth (Long et al. 1986). Mortality was 4 of 4 in piglets treated 0-3 hours after birth, 3 of 3 in piglets treated 1-3 hours after birth, 3 of 5 in piglets treated 24-30 hours after birth, and 0 of 3 in piglets treated 30-36 hours after birth. The results indicate that newborn piglets are more susceptible to the chlorpyrifos toxicity. In hens, intermediate-duration dermal exposure to 20 mg/kg/day killed 2 of 3 hens after 30 and 38 days of exposure, respectively (Francis et al. 1985). No data were located concerning death in animals following chronic-duration dermal exposure to chlorpyrifos.

The LD_{50} value for mortality in rats is shown in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located concerning the potential cardiovascular, endocrine, body weight, or metabolic effects of chlorpyrifos in humans or animals following acute-, intermediate-, or chronic-duration dermal exposure to chlorpyrifos.

Respiratory Effects. No information was found concerning respiratory effects in humans following intermediate-duration dermal exposure to chlorpyrifos.

The effects of presumed acute-duration dermal exposure to chlorpyrifos were reported for 12 persons exposed to chlorpyrifos primarily in the home or workplace following professional application of the pesticide (Thrasher et al. 1993). The route of exposure was not reported; however, dermal in addition

Table 2-3. Levels of Significant Exposure to Chlorpyrifos - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE						
Death						
Rat (Sherman)	once				202 M (LD ₅₀)	Gaines 1969

LOAEL = lowest-observable-adverse-effect level; LD₅₀ = lowest dose, 50% kill; M = male; NOAEL = no-observable-adverse-effect level; NS = not specified; wk = week(s)

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to inhalation exposure was likely. The approximate dose received and the length of time between exposure and the onset of symptoms was not known for any of the patients. The pesticide-exposed persons reported an increase in flu-like symptoms and upper and lower respiratory problems when compared to 60 (28 male and 32 female) control subjects. In a chronic-duration exposure study by Brenner et al. (1984) the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. There were no statistically significant differences in the prevalence of respiratory illness or other respiratory symptoms in the exposed groups compared to matched controls. Exposure was assumed to be via both inhalation and dermal routes.

Piglets acutely exposed (by spraying) to an undetermined amount of chlorpyrifos at 0-3, 1-3, 24-30, or 30-36 hours after birth were observed for clinical signs of toxicity, and various tissues were taken for histopathological evaluations (Long et al. 1986). Mortality was 4 of 4, 3 of 3, 3 of 5, and 0 of 3 in piglets treated 0-3, 1-3, 24-30, and 30-36 hours after birth, respectively. Dyspnea, resulting from cholinergic over-stimulation, was observed in the pigs that eventually died. However, microscopic evaluation of the lung tissues from the treated piglets did not reveal any abnormalities. No data were located for respiratory effects in animals following intermediate- or chronic-duration dermal exposure to chlorpyrifos.

Gastrointestinal Effects. Gastrointestinal effects have been observed in humans following acute-, intermediate-, and chronic-duration exposures (Kaplan et al. 1993; Thrasher et al. 1993). Nonspecific gastrointestinal disturbances were reported by individuals acutely exposed to unknown quantities of chlorpyrifos. The exact number of individuals experiencing gastrointestinal disturbances, however, was not reported. Additionally, the approximate dose received and the length of time between exposure and the onset of symptoms was not known for any of the patients (Thrasher et al. 1993). Intermediate-duration exposure to chlorpyrifos also causes gastrointestinal distress in humans. Diarrhea developed in a 40-year-old male exterminator who was repeatedly exposed to an unknown concentration of Dursban[®] in a closed environment over a 6-month interval (Kaplan et al. 1993). Exposure -was assumed to be via both inhalation and dermal routes. Erythrocyte cholinesterase levels determined at the onset of symptoms were reported to be initially low (value not given). The diarrhea probably resulted from stimulation of parasympathetic nervous system-dependent physiological

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processes as a consequence of cholinesterase inhibition. Stimulation of the parasympathetic nervous system increases gastrointestinal motility, thereby decreasing food transit times. The net result is that there is less time for water to be absorbed by the intestinal system and diarrhea results. In a chronic-duration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. There were no statistically significant differences in the prevalence of digestive system illnesses or symptoms between the exposed groups and matched controls. Exposure was assumed to be via both inhalation and dermal routes.

Piglets acutely exposed by spraying an undetermined amount of chlorpyrifos at 0-3, 1-3, 24-30, or 30-36 hours after birth were observed for clinical signs of toxicosis, and various tissues were taken for histopathological evaluations (Long et al. 1986). Mortality was 4 of 4, 3 of 3, 3 of 5, and 0 of 3 in piglets treated 0-3, 1-3, 24-30, and 30-36 hours after birth. Diarrhea resulting from cholinergic overstimulation was observed in the pigs that eventually died. Necropsy of the piglets revealed increased fluid in the intestines of some, but only in those piglets exposed 1-3 hours after birth. Two of 4 bulls treated with 1 g testosterone for 86 days, then dermally exposed to 0.33 mL/kg of a chlorpyrifos solution (equivalent to approximately 0.04 mg/kg) 28 and 58 days after the start of the testosterone treatment, had to be killed because of severe diarrhea (Haas et al. 1983). No data were located for gastrointestinal effects in animals following intermediate- or chronic-duration dermal exposure to chlorpyrifos.

Hematological Effects. No hematological effects were observed in a 40-year-old male exterminator who was repeatedly exposed to an unknown concentration of Dursban[®] in a closed environment over a 6-month interval (Kaplan et al. 1993). Exposure was assumed to be via inhalation and dermal routes. No information was found concerning hematological effects in humans following acute- or intermediate-duration dermal exposure to chlorpyrifos.

Acute-duration dermal exposure to 0.33 mL/kg of a chlorpyrifos solution (equivalent to approximately 0.04 mg/kg) caused no hematological effects in groups of 4 Holstein bulls and steers (Haas et al. 1983). No information was found concerning hematological effects in animals following intermediate or chronic-duration dermal exposure to chlorpyrifos.

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Musculoskeletal Effects. Musculoskeletal effects have been observed in humans following acute and intermediate-duration exposure to chlorpyrifos (Brenner et al. 1984; Kaplan et al. 1993; Thrasher et al. 1993). In humans, acute-duration exposure to undetermined amounts of chlorpyrifos was reported to produce unspecified muscle pain (Thrasher et al. 1993) and muscle cramps (Kaplan et al. 1993). A family became ill and complained of muscle cramps after their house was sprayed with Dursban[®] (Kaplan et al. 1993). The time from exposure to the onset of symptoms and exposure-level data were not reported. Intermediate-duration exposure to chlorpyrifos also causes musculoskeletal effects in humans. Muscle twitching was reported by a 40-year-old exterminator exposed to unspecified amounts of chlorpyrifos over a 6-month period (Kaplan et al. 1993). In the Kaplan et al. (1993) case reports, exposure was assumed to be via inhalation and dermal routes. It should be noted that in the Kaplan et al. (1993) and Thrasher et al. (1993) studies, chlorpyrifos exposure could not be conclusively determined for each case report. Also, in the Thrasher et al. (1993) study, the approximate dose received and the length of time between exposure and the onset of symptoms was not known for any of the patients.

In a chronic-duration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. There were no statistically significant differences in the prevalence of musculoskeletal illnesses or symptoms between the exposed groups and matched controls. Exposure was assumed to be via both inhalation and dermal routes.

In animals, musculoskeletal effects have been observed following intermediate-duration exposure (Jaggy and Oliver 1992). Creatine kinase activity increased an undetermined amount in a female cat exposed to an unspecified amount of chlorpyrifos during apartment spraying every third day for 18 days (Jaggy and Oliver 1992). It was assumed that some of the exposure was dermal. No information was found concerning musculoskeletal effects in animals following acute- or chronic-duration dermal exposure to chlorpyrifos.

Hepatic Effects. In a chronic-duration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals.

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Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. There were no statistically significant differences in the prevalence of hepatic illnesses or symptoms between the exposed groups and matched controls. Exposure was assumed to be via both inhalation and dermal routes. No information was found concerning hepatic effects in humans following acute- or intermediate-duration dermal exposure to chlorpyrifos.

In animals, hepatic effects have been observed following intermediate-duration exposure (Jaggy and Oliver 1992). Increased serum total protein and albumin levels were observed in a female domestic short-hair cat exposed to an unspecified amount of chlorpyrifos in an apartment that was sprayed with chlorpyrifos every third day for 18 days (Jaggy and Oliver 1992). It is assumed that some of the exposure was via the oral route as a result of grooming. No information was found concerning hepatic effects in animals following acute- or chronic-duration dermal exposure to chlorpyrifos.

Renal Effects. No information was found concerning renal effects in humans following acute duration dermal exposure to chlorpyrifos.

The effects of intermediate-duration exposure to undetermined amounts of chlorpyrifos in humans were assessed in a survey of pesticide applicators working in a variety of settings (Ames et al. 1989). Exposure was assumed to be via inhalation and dermal routes. Those applicators reported an unspecified decrease in urinary frequency. This information is also presented in Section 2.2.1 of this profile because the route of exposure is not specified in the Ames et al. (1989) report, and it is probable that exposure occurred by multiple routes. In a chronic-duration exposure study by Brenner et al. (1984) the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. There were no statistically significant differences in the prevalence of renal illnesses or symptoms between the exposed groups and matched controls. Exposure was assumed to be via both inhalation and dermal routes. No information was found concerning renal effects in humans following acute- or intermediate-duration dermal exposure to chlorpyrifos. Exposure was assumed to be via inhalation and dermal routes.

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In animals, renal effects have been observed following intermediate-duration exposure (Jaggy and Oliver 1992). Urea nitrogen, alkaline phosphatase, and alanine aminotransferase levels increased in a female cat exposed to an unspecified amount of chlorpyrifos during apartment spraying every third day for 18 days (Jaggy and Oliver 1992). It was assumed that at least some of the exposure was dermal. No information was found concerning hepatic effects in animals following acute- or chronic-duration dermal exposure to chlorpyrifos. No data were located for renal effects in animals following acute- or chronic-duration dermal exposure to chlorpyrifos.

Dermal Effects. No information was found concerning dermal effects in humans following acute duration dermal exposure to chlorpyrifos.

The effects of intermediate-duration exposure to undetermined amounts of chlorpyrifos in humans were assessed in a survey of pesticide applicators working in a variety of settings (Ames et al. 1989). Exposure was assumed to be via inhalation and dermal routes. Those applicators reported an unspecified increase in skin flushing. This effect may be related to a disruption of autonomic function. This information is also presented in Section 2.2.1 of this profile, because the route of exposure is not specified in the Ames et al. (1989) report, and it is probable that exposure occurred by multiple routes. Additionally, prolonged dermal contact with chlorpyrifos may produce irritation; dermal sensitization may also occur (HSDB 1995). In a chronic-duration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. There were no statistically significant differences in the prevalence of dermal illnesses or symptoms between the exposed groups and matched controls. Exposure was assumed to be via both inhalation and dermal routes. No information was found concerning dermal effects in humans following acute- or intermediate-duration dermal exposure to chlorpyrifos. Exposure was assumed to be via inhalation and dermal routes.

No data were located for dermal effects in animals following acute-, intermediate-, or chronic-duration dermal exposure to chlorpyrifos.

Ocular Effects. No information was found concerning ocular effects in humans following acute or chronic-duration dermal exposure to chlorpyrifos.

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Intermediate-duration exposure to an undetermined amount of chlorpyrifos caused an unspecified increase in tearing in a 40-year-old male exterminator repeatedly exposed to Dursban[®] over a 6-month period (Kaplan et al. 1993). Exposure was assumed to be via inhalation and dermal routes. Additionally, the effects of intermediate-duration exposure to undetermined amounts of chlorpyrifos in humans were assessed in a survey of pesticide applicators working in a variety of settings (Ames et al. 1989). Exposure was assumed to be via inhalation and dermal routes. Those applicators reported an unspecified increase in blurred vision. This information is also presented in Section 2.2.1 of this profile, because the route of exposure is not specified in the Ames et al. (1989) report, and it is probable that exposure occurred by multiple routes.

No data were located for ocular effects in other animals following acute-, intermediate-, or chronic-duration dermal exposure to chlorpyrifos.

2.2.3.3 Immunological and Lymphoreticular Effects

No information was located concerning the potential immunological and lymphoreticular effects of chlorpyrifos in humans following intermediate- or chronic-duration dermal exposure, or in other animals following acute-, intermediate-, or chronic-duration dermal exposure.

The effects of acute-duration dermal exposure to chlorpyrifos were reported for 12 persons exposed to chlorpyrifos primarily in the home or work place following professional application of the pesticide (Thrasher et al. 1993). The route of exposure for any of the exposed persons was not given. The approximate dose received and the length of time following exposure were not known for any of the patients. It is assumed that exposure occurred primarily by inhalation, but dermal exposure was also possible. Examination of blood taken from the chlorpyrifos-exposed persons indicated that there were changes in some lymphocyte subtypes when compared to 60 (28 male and 32 female) control subjects. The presence of autoantibodies to smooth muscle, parietal cells, intestinal brush border, mitochondria, or nuclei was also determined. Analysis of the blood revealed a 300% increase in the mean absolute counts of CD26 cells and a decrease in the relative percentages of CD5 (11%) and CD4 (7%) lymphocytes. Additionally, 83% of the chlorpyrifos-exposed individuals had increased levels (300-1,200%) of circulating autoantibodies to at least one of the cell types or organelles (except mitochondria) listed above, and 25% of the chlorpyrifos-exposed patients had elevated autoantibodies to three or more of the cell types or organelles, compared to 0-3.7% in the control group. The authors

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suggested that the increase in autoantibodies was due to chlorpyrifos-induced tissue damage (Thrasher et al. 1993). However, the causality of these effects must be interpreted with caution. This study was a retrospective case study where the symptoms arose 14.5 years post-exposure to chlorpyrifos. No exposure data were presented and there were no objective data or methods for ruling out confounding chemical exposures. Ten of the patients had a history of some type of atopy or drug sensitivity, while one patient had been diagnosed with systemic lupus erythematosus and another had a lupus-like syndrome. From the results of this study, it may be concluded that the patients had some immunological abnormalities, but it is difficult to attribute the effects to chlorpyrifos exposure (Richardson 1995). Additionally, although CD26 is a surface marker whose expression is increased on the surface of activated T cells, it has not been validated as a diagnostic indicator of immunotoxicity in either animal or human studies. Of primary importance is the fact that the following are not known: how the expression of the CD26 marker varies in a normal human population; what kinds of conditions can cause changes in the expression of CD26, especially regarding studies of potential drug/chemical-induced changes in its expression; the functional significance of changes in CD26 expression; and how much the expression of CD26 must change to be causally associated with changes in immune function. Finally, although it is true that elevations in autoantibodies to a number of self-antigens can be caused by exposure to a variety of drugs and chemicals, the presence of autoantibodies can also be measured in normal healthy human populations. Thus, the biological significance of these findings is unclear.

In spite of the widespread use of insecticides containing chlorpyrifos, there are no definitive reports that it sensitizes human skin. A study, which assessed a number of pesticides via patch tests in California nursery workers, reported no positive responses with chlorpyrifos in 38 out of the 39 exposed workers who were tested (O'Malley et al. 1995). The duration of exposure to any of the 6 pesticide formulations to which exposure occurred was not specified in this paper. Although none of the 21 control subjects were positive for chlorpyrifos, there were positive responses to other pesticides noted in the controls. Therefore, the biological significance of the positive response to chlorpyrifos in the single exposed worker could not be determined.

2.2.3.4 Neurological Effects

The accidental application of an unspecified amount chlorpyrifos into the eye of a 42-year-old woman caused unilateral miosis presenting as anisocoria (Flach and Donahue 1994). Unilateral effects were

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probably due to the unilateral application of the pesticide. In a review of the physical, neurotoxic, and respiratory problems suffered by 41 people exposed to organophosphate pesticidal products, symptoms of moderate to severe organophosphate poisoning were reported. In men and women exposed to unspecified amounts of only chlorpyrifos at home or at work, these symptoms included: seizures; peripheral and central nervous system disturbances; headaches; dizziness; nausea/vomiting; chest problems; heart problems; ear, nose, and throat problems; eye problems; skin problems; diarrhea; incoordination of the bowel/bladder; multiple chemical sensitivity; arthritis; fatigue; bladder symptoms; nightmares; sleep disturbances; joint problems; abnormal limbic system responses; thyroid problems; and weakness (Sherman 1995). However, in the Sherman (1995) report, no exposure-level data were presented. Additionally, the effects were reported by patients in uncontrolled studies. The cognitive complaints were nonspecific, nonquantitative, and could be attributable to a wide variety of possible causes.

Intermediate-duration dermal exposure to chlorpyrifos has been associated with neurological effects (Kaplan et al. 1993). Memory impairment and sensory loss were observed in a 42-year-old female exposed to Dursban[®] that had been applied in her basement 8 times over 3 weeks (Kaplan et al. 1993). Muscle twitching, paresthesia, numbness, sensory loss, mild distal weakness, areflexia of lower extremities, and nerve conduction and quantitative sensory threshold abnormalities were observed in a 40-year-old male exterminator repeatedly exposed to Dursban[®] over a 6-month period (Kaplan et al. 1993). Exposure in this study was assumed to be via inhalation and dermal routes. In a chronic-duration exposure study by Brenner et al. (1984), the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos was compared with 335 matched controls with no history of exposure to organophosphorus chemicals were. Employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and airmonitoring data. There were no statistically significant differences in the prevalence of central and peripheral nervous system illnesses or symptoms between the exposed groups and matched controls. Exposure was assumed to be via both inhalation and dermal routes.

Piglets acutely exposed by spraying an undetermined amount of chlorpyrifos at 0-3, 1-3, 24-30, or 30-36 hours after birth were observed for clinical signs of toxicity (Long et al. 1986). Mortality was 4 of 4, 3 of 3, 3 of 5, and 0 of 3 in piglets treated 0-3, 1-3, 24-30, and 30-36 hours, respectively, after birth. Weakness, trembling, ataxia, miosis, and lateral recumbency were observed in the piglets that eventually died. Additionally, determinations of brain cholinesterase activity in piglets exposed

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1-3 hours after births showed a 55--67% inhibition in activity. Blood acetylcholinesterase activity determined in piglets 12-17 hours after exposure displayed 81-99% decreases in activity in piglets exposed up to 30 hours after birth. Intermediate-duration dermal exposure to 20 mg/kg/day chlorpyrifos applied to the ventral wing surface at the humerus for at least 28 days produced debilitation and paralysis in 2 of 3 exposed hens after 20-28 days of dosing (Francis et al. 1985). No data were located for neurological effects in animals following chronic-duration dermal exposure to chlorpyrifos.

2.2.3.5 Reproductive Effects

No information was found concerning reproductive effects in humans following acute-, intermediate-, or chronic-duration dermal exposure to chlorpyrifos.

An unspecified amount of Dursban 44[®] was applied once to 185 young bulls (9-52 months of age) for lice control. Semen output was analyzed from historical samples collected from 583 control animals to establish normal production (Everett 1982). Following exposure, semen production and sperm viability were determined in frozen samples. The bulls were divided into 2 post-exposure groups (6-month and 7-12-month) in order to assess the short- and long-term effects of the treatment, respectively. Six months post-exposure, the treated bulls were reported to have an unspecified increase in nonmotile sperm upon thawing of samples. Sperm motility and ejaculate volume were decreased, and the number of post-thaw nonmotile sperm increased in those bulls that became ill after treatment and required veterinary interventions. No adverse effects on bull sperm were observed 7-12 months postexposure. No data were located for reproductive effects in animals following intermediate- or chronic-duration dermal exposure to chlorpyrifos.

2.2.3.6 Developmental Effects

No information was located concerning the potential developmental effects of chlorpyrifos in humans or animals following acute-, intermediate-, or chronic-duration dermal exposure.

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2.2.3.7 Genotoxic Effects

No information was located concerning the potential genotoxic effects of chlorpyrifos in humans following acute-, intermediate-, or chronic-duration dermal exposure.

The effect of intermediate-duration dermal exposure to chlorpyrifos was assessed in Swiss mice (Amer and Fahmy 1982). Dursban® (99 mg/kg) was applied as a solution in 0.1 mL dimethyl sulfoxide (DMSO) to the backs of mice for 24 hours, 7 days, or 14 days, and the percentage of polychromatic erythrocytes (PE) determined. The applications were performed twice weekly for the 7- and 14-day exposures. Additionally, some animals exposed for 14 days were allowed to recover 1 or 2 weeks before having the percentage of PE determined. Controls received DMSO only. After 1 and 14 days of exposure, the percentage of PE increased 17 and 82%, respectively. However, no effect on PE was observed for the 7-day-exposure group. As a result, the authors concluded that the effect seen after one day of exposure was probably spurious. The percentage of PE was still elevated in the 14-day exposure group 7 days after termination of exposure. However, normal percentages of PE were found in the 14-day-exposure group after 14 days of recovery. Additionally, there was no induction of micronuclei in any of the treatment groups. The results indicate that chlorpyrifos has the potential to cause transient increases in the incidence of erythroblast chromosomal aberrations. No data were located for genotoxic effects in animals following acute- or chronic-duration dermal exposure to chlorpyrifos.

Other genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No information was located concerning the potential carcinogenic effects of chlorpyrifos in humans or other animals following acute-, intermediate-, or chronic-duration dermal exposure.

2.3 TOXICOKINETICS

Most of the toxicokinetic data on chlorpyrifos were collected following oral or dermal administration. Limited inhalation exposure data are available. Studies in humans and other animals indicate that orally administered chlorpyrifos is well absorbed, with 70-90% of the administered dose being

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absorbed within 48 hours after exposure. In humans, only 3% of a the dermally applied dose is absorbed. In animals, the skin did not appear to provide an effective barrier to absorption. This seems unexpected based on the human data. However, those animal studies are confounded by the fact that dermal irritation, which may have decreased skin integrity, accompanied the dermal dosing, thereby increasing absorption. Animal studies indicate that orally and dermally administered chlorpyrifos rapidly distributes to all the major organs. Chlorpyrifos metabolism is similar in both humans and other animals. Chlorpyrifos is bioactivated to chlorpyrifos oxon in the liver via cytochrome P-450-dependent desulfuration. The oxon is hydrolyzed by A-esterase to diethylphosphate and 3,5,6-trichloro-2-pyridinol (TCP), the major metabolite detected in humans and other animals. The tissue elimination of chlorpyrifos is organ-dependent, with the slowest elimination occurring from fat (half-life 62 hours). Chlorpyrifos is primarily excreted in the urine in the form of TCP conjugates.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

The absorption of chlorpyrifos following acute-duration inhalation exposure has been demonstrated in humans (Aprea et al. 1994). Determination of chlorpyrifos metabolites in the urine from 1 man and 11 women exposed to chlorpyrifos in an orchard previously sprayed with chlorpyrifos indicated that significantly higher levels of urinary excretion of alkylphosphates were found in all exposure groups than in unexposed controls. There was a high correlation between quantities of the active ingredients on the hands and urinary excretion of total dimethylated alkylphosphates and of dimethylthiophosphates and dimethylphosphate. Respiratory absorption appears to have been significant in view of the difference in urinary excretion of dimethylated alkylphosphates found between subjects with and without face masks. No toxicokinetic information was located concerning the absorption of chlorpyrifos following inhalation exposure in other animals.

2.3.1.2 Oral Exposure

The absorption of chlorpyrifos following acute-duration oral exposure has been investigated in humans and other animals. In humans, determination of chlorpyrifos metabolites in the urine from 6 adult males orally exposed to chlorpyrifos administered orally in dipropylene glycol methyl ether indicated an average of 70% of the administered dose was absorbed within 48 hours (Nolan et al. 1984). In rats

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(Bakke et al. 1976; Smith et al. 1967) and mice (Ahdaya et al. 1981), nearly 90% of the administered dose of ¹⁴C-labeled chlorpyrifos in an acute-duration oral exposure was absorbed 48-60 hours after dosing, as assessed by the amount of radioactivity recovered in the feces and urine.

2.3.1.3 Dermal Exposure

The absorption of chlorpyrifos following dermal exposure has been investigated in humans and other animals. In humans, determination of chlorpyrifos metabolites in the urine from 6 adult males dermally exposed to chlorpyrifos indicated that an average of 3% of a dose administered in dipropylene glycol methyl ether was absorbed within 48 hours, compared to 70% of an oral dose (Nolan et al. 1984). In goats, 80-96% of a 22 mg/kg dermal dose (vehicle not specified) was absorbed 12-16 hours after dosing (Cheng et al. 1989). In female Fischer 344 rats, the percentage of chlorpyrifos dissolved in acetone absorbed through the skin during a 72-hour period was dose-dependent, with relatively more absorption occurring at higher doses (Shah et al. 1987). In that study, approximately 99% of a 21.03 mg/kg dose was absorbed, compared with 46% of a 4.21 mg/kg dose. However, considerably more irritation and blistering accompanied the high dose, compromising the integrity of the skin and increasing the possibility of absorption. Thus, the dose-dependent absorption of chlorpyrifos may have been enhanced by the destruction of the epidermis. In that same study, Shah et al. (1987) also assessed the effect of age on dermal penetration of chlorpyrifos. On average, 23% more chlorpyrifos was absorbed by young (33-day-old) than by adult (82-day-old) rats. The possible age-dependence of the dermal absorption of chlorpyrifos was also investigated in a study in which piglets of varying ages were sprayed with a solution containing an unspecified concentration of chlorpyrifos (Long et al. 1986). In that study, the toxicity of chlorpyrifos decreased with increasing time following birth.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No toxicokinetic information was located concerning the distribution of chlorpyrifos following inhalation exposure in humans or other animals.

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2.3.2.2 Oral Exposure

The distribution of ^{14}C -labeled chlorpyrifos following oral exposure has been investigated using male Wistar rats (Smith et al. 1967) and Hereford crossbred heifers (Dishburger et al. 1977). The results of the Smith et al. (1967) study indicate that a single dose of 50 mg/kg chlorpyrifos administered via gavage readily distributes to all organs of the body, but that it accumulates in the fat and is liberated slowly ($t_{1/2}$, 62 hours) compared to elimination from other tissues ($t_{1/2}$, for elimination from liver, kidney, and heart is about 10-16 hours). Similar distribution was seen in Hereford crossbred heifers exposed to 0, 3, 10, 30, or 100 ppm chlorpyrifos for 30 days (Dishburger et al. 1977). In keeping with the results of the Smith et al. (1967) study, chlorpyrifos residues were found predominantly in fatty tissues and averaged 0.02 (<0.01-0.05 ppm) and 3.28 ppm (2.28-4.7 ppm) in the fat of cattle fed 3 and 100 ppm chlorpyrifos, respectively, for 30 days with no withdrawal.

2.3.2.3 Dermal Exposure

The distribution of dermally applied ^{14}C -labeled chlorpyrifos has been investigated using goats (Cheng et al. 1989), mice (Shah et al. 1981), and bovines (Claborn et al. 1968; Ivey et al. 1972). The results from those studies indicate that chlorpyrifos readily distributes to all organs of the body, with relatively higher concentrations being found in the blood, liver, and fat than in other organs (e.g., heart, gastrointestinal tract, skeletal muscle). Radioanalysis of the blood and selected tissues (liver, kidney, heart, fat and muscle) of 2 male weanling goats receiving a single dose of 22 mg/kg radiolabeled chlorpyrifos indicated very low tissue radioactivity levels equivalent to 0.04 ppm (chlorpyrifos equivalents) in muscle to 0.90 ppm in omental fat (Cheng et al. 1989). Eight hours after a single dermal application of 1 mg/kg radiolabeled chlorpyrifos to female ICR mice, the amount of radioactivity recovered was highest in the excretory products (38.4%) followed by the carcass (24.1%); blood (2.7%); intestine (1.9%); liver (1.8%); kidney (0.8%); stomach and ear (0.5% each); lungs, brain, bladder, and fat (0.2% each); heart, bone marrow, and muscle (0.1% each); and spleen (<0.1%). In 11 Hereford cattle dipped once in a 0.05% emulsion of Dursban® and in 1 Holstein-cross calf sprayed with 8.75 mL/kg of a 25% emulsion of Dursban®, chlorpyrifos residues were highest in fat (Claborn et al. 1968). Similarly, in 57 beef cattle dipped up to 6 times in a 0.023-0.027% solution of chlorpyrifos, the residues of chlorpyrifos were found mostly in the fatty tissues. The low residues found in other tissues (muscle, kidneys, and liver) could be attributed to the small amount of fat present in those tissues. The highest residues in fat occurred 1 week after the second and third

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dippings (0.726-1.24 and 0.937-2.01 ppm, respectively), and were eliminated at 10 weeks or reduced to an insignificant level (Ivey et al. 1972).

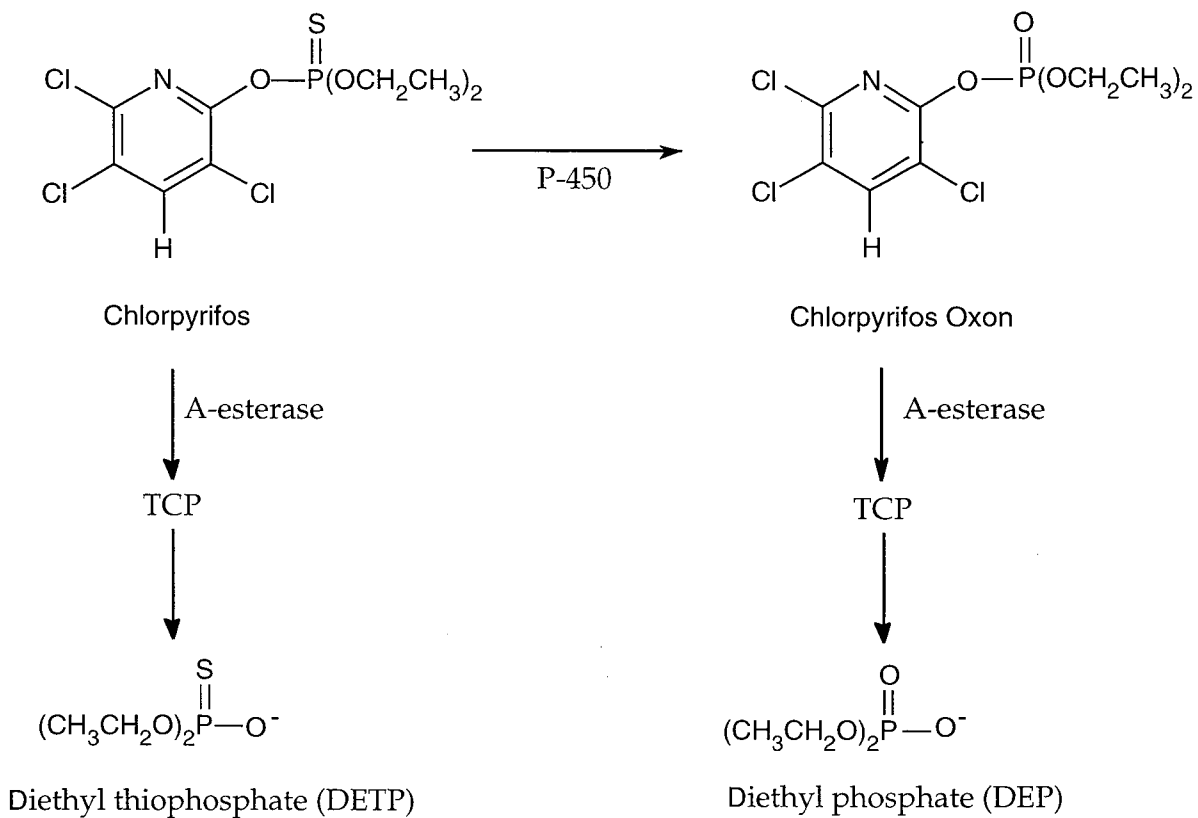
2.3.3 Metabolism

An adaptation of the scheme for the metabolism of organophosphate compounds analyzed in serum and urine of persons poisoned by chlorpyrifos (Drevenkar et al. 1993) is presented in Figure 2-3.

In the rat and mouse, chlorpyrifos is bioactivated in the liver to chlorpyrifos oxon via cytochrome P-450-dependent desulfuration (Ma and Chambers 1994; Sultatos and Murphy 1983a). The oxon is rapidly hydrolyzed to TCP, probably by A-esterase (Sultatos and Murphy 1983a, 1983b). Studies using liver perfusion have shown that both bioactivation and detoxification of chlorpyrifos occur very rapidly, since only TCP can be detected in the hepatic effluent once steady-state conditions are reached (Sultatos and Murphy 1983a, 1983b). Hydrolysis of the chlorpyrifos oxon by A-esterase is probably the more common route of detoxification, since TCP or a conjugate of TCP is the major metabolite of chlorpyrifos in humans (Nolan et al. 1984) and rodents (Bakke et al. 1976; Smith et al. 1967; Sultatos and Murphy 1983a, 1983b; Sultatos et al. 1985).

The relative rates of desulfuration and detoxification are gender-dependent and may account for the increased toxicity of chlorpyrifos in female rats (Chambers and Chambers 1989; Sultatos 1991). The results of the above studies indicate that although the rates of bioactivation (desulfuration) and detoxification (dearylation) are higher in males than females, the ratio of the rates of bioactivation to detoxification is 2-3-fold higher for females. Those studies suggest that females may be at increased risk to chlorpyrifos-induced toxicity. However, bulls with high levels of testosterone were more sensitive than steers (castrated bulls) to the toxic effects of chlorpyrifos (Haas et al. 1983). Although no metabolism data were present in that study, it suggests that for bovines, the male may be more susceptible than the female.

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Figure 2-3. Organophosphorus Compounds in Serum and Urine of Persons Poisoned by Chlorpyrifos

Adapted from Drevenkar et al. 1993

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2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Examination of urine samples from pesticide applicators presumably exposed to chlorpyrifos by inhalation revealed the presence of TCP (Jitsunari et al. 1989). Examination of urine samples from 1 man and 11 women exposed to chlorpyrifos in an orchard previously sprayed with chlorpyrifos indicated that significantly higher levels of urinary excretion of alkylphosphates were found in all exposure groups than in unexposed controls. There was a high correlation between quantities of the active ingredients on the hands and urinary excretion of total dimethylated alkylphosphates and of dimethylthiophosphates and dimethylphosphate. Respiratory absorption appears significant in view of the difference in urinary excretion of dimethylated alkylphosphates found between subjects with and without face masks (Aprea et al. 1994).

2.3.4.2 Oral Exposure

Male rats exposed to ¹⁴C-labeled chlorpyrifos had their urine and feces collected every 12 hours for 48 hours (Bakke et al. 1976). The combined urine from all 4 samples contained approximately 88% of the administered radiolabel, and it separated into at least 6 chlorpyrifos metabolites. Three of these metabolites were identified as the glucuronide of TCP, a glycoside of TCP, and TCP, comprising 80, 4, and 12% of the total metabolites, respectively. In a similar study, 90% of the radiolabel was found in the urine, and 10% was recovered in the feces (Smith et al. 1967). Additionally, the elimination half-life was estimated for several compartments. Chlorpyrifos was eliminated slowly from fat (half-life 62 hours) and relatively rapidly from liver, heart, and kidney (half-life 10-16 hours) (Smith et al. 1967). In humans, an elimination half-life of 27 hours has been estimated following oral or dermal exposure (Nolan et al. 1984).

2.3.4.3 Dermal Exposure

A half-life of 21 hours has been estimated for the urinary elimination and fecal excretion of chlorpyrifos following dermal exposure in mice (Shah et al. 1981). For humans, an elimination half-life of 27 hours has been estimated following oral or dermal exposure (Nolan et al. 1984). As with

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oral exposure, the majority of dermally absorbed chlorpyrifos is eliminated in the urine, based upon the quantity of radioactivity in the urine (Shah et al. 1981).

2.3.5 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 and Krishnan 1994; Andersen et al. 1987). 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

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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 2-4 shows a conceptualized representation of a PBPK model.

If PBPK models for chlorpyrifos exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

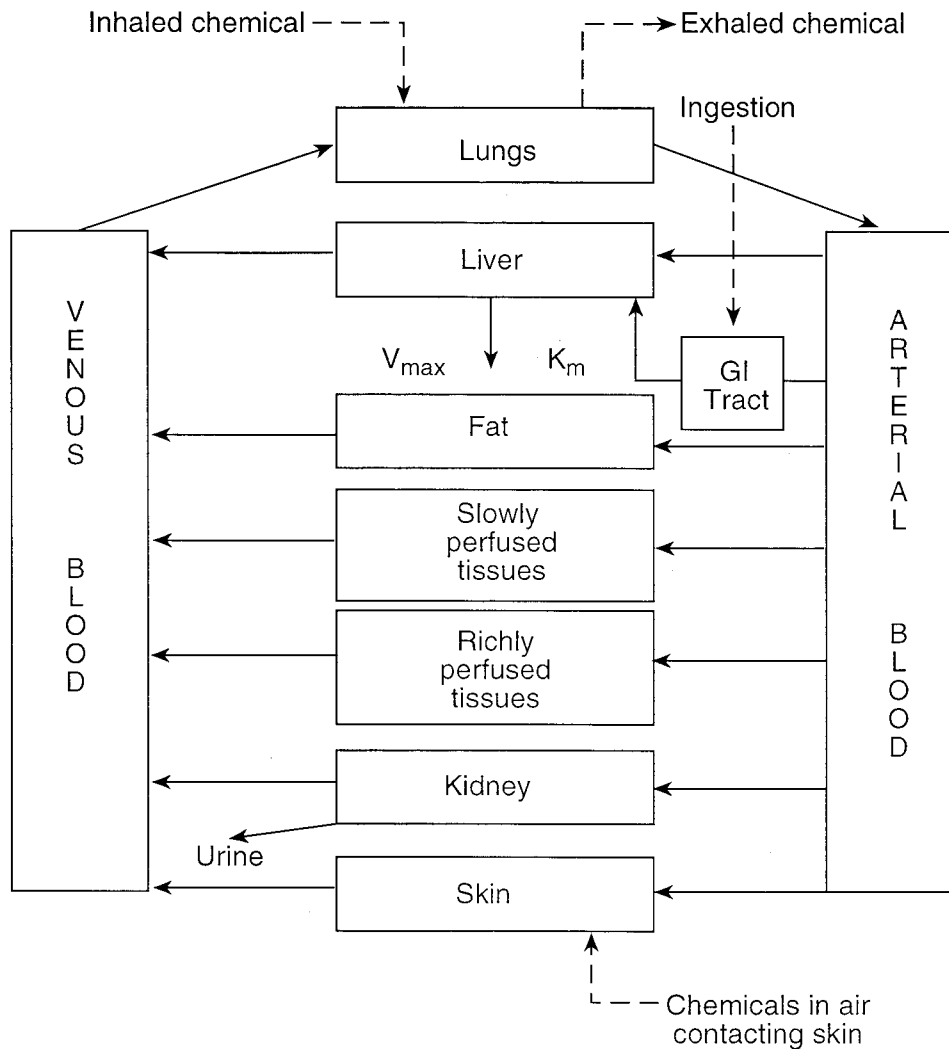
No PBPK information was found for chlorpyrifos.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Chlorpyrifos is well absorbed through the gut and lungs, but dermal absorption is considerably less effective. The skin presents a reasonably effective barrier to penetration, unless the pesticide is mixed with a carrier or the skin is compromised. However, since all commercial chlorpyrifos products, with the exception of granular forms, contain solvents or emulsifiers, human exposure to chlorpyrifos that is not mixed with a carrier is unlikely. Oral and dermal absorption of chlorpyrifos was assessed in six adult male humans (Nolan et al. 1984). On average, 70% of the oral dose was absorbed, compared to

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1992

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.

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only 3% of the dermal dose. Once chlorpyrifos has been absorbed, it rapidly distributes to all organs (Shah et al. 1981; Smith et al. 1967). The half-life for elimination of chlorpyrifos from the various organs in rats is comparable (10-16 hours), except for elimination from fat, which was estimated to be 62 hours (Smith et al. 1967). The elimination half-life in humans has been estimated to be 27 hours (Nolan et al. 1984).

The major site of chlorpyrifos metabolism is the liver, where it is rapidly bioactivated (desulfurated) by a P-450-dependent monooxygenase to chlorpyrifos oxon (Ma and Chambers 1994; Sultatos and Murphy 1983a). The oxon is 300-400 times more potent at inhibiting rat brain acetylcholinesterase than the parent compound (Huff et al. 1994). The rate of detoxification of the oxon is also rapid (Sultatos and Murphy 1983a, 1983b). Thus, it is rare to find either the parent compound or the oxon in body fluid samples (Nolan et al. 1984; Sultatos and Murphy 1983a), except in very high exposures. What is found in the general circulation is the major oxon metabolite TCP (Bakke et al. 1976; Nolan et al. 1984; Smith et al. 1967). TCP is a relatively unique metabolite of chlorpyrifos, and it (or one of its conjugates) is almost exclusively (90%) excreted in the urine (Bakke et al. 1976; Smith et al. 1967). Kinetic studies using rats indicate that following a single-dose exposure, most (>90%) of the chlorpyrifos is eliminated within 48 hours (Bakke et al. 1976; Smith et al. 1967). Thus, urine TCP can be used as a qualitative biomarker for chlorpyrifos exposure, provided the testing is performed within 48 hours after exposure. It should be noted that the relative rate of detoxification of chlorpyrifos is lower in female rats (i.e., ratio of bioactivation to detoxification), and it is postulated that this may account for the increased toxicity of chlorpyrifos in those animals (Chambers and Chambers 1989; Chambers et al. 1994; Sultatos 1991).

The dose of chlorpyrifos is important in predicting the potential toxicity. Further, factors such as age, health, and possibly gender may significantly lower the threshold for toxic effects. While acuteduration, high-dose intoxication has been demonstrated in a variety of species, including humans, the effects of longer-term, low-level exposure are less clear. Small-scale attempts to quantify chlorpyrifos related toxicity in pesticide applicators suggest that intermediate-duration exposure to low levels of chlorpyrifos may adversely affect health (Ames et al. 1989); but whether the effects may be related to cumulative direct target insult or simply to cholinesterase inhibition is less clear. Low levels of exposure are assumed for that study, because pesticide applicators are usually presumed to wear protective clothing and respirators when spraying the pesticide. However, neither the dose nor the length of exposure could be estimated.

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2.4.2 Mechanisms of Toxicity

Chlorpyrifos-induced toxicity results almost entirely from inhibition of neural acetylcholinesterase by chlorpyrifos and its bioactivation product, chlorpyrifos oxon (Namba et al. 1971). Acetylcholinesterase (true cholinesterase) belongs to a class of choline ester hydrolases which includes butyrylcholinesterase, or pseudocholinesterase (Ballantyne and Marrs 1992). Acetylcholinesterase is found postsynaptically in central and peripheral cholinergic synapses, including the preganglionic autonomic synapses and postganglionic parasympathetic synapses (Palmer 1980). It is also found at the motor end plate in the neuromuscular junction and is further associated with erythrocytes (red blood cells) (Ballantyne and Marrs 1992). Butyrylcholinesterase can be found in the plasma, and also in nonneuronal tissues such as the liver and fat (Ballantyne and Marrs 1992). Butyrylcholinesterase levels can be affected by health, age, genetic factors, and gender, with or without exposure to cholinesterase inhibiting substance (Ballantyne and Marrs 1992). Inhibition of butyrylcholinesterase can be used as an indicator of exposure to cholinesterase-inhibiting substances, but is not, in and of itself, considered to constitute an adverse health effect.

Organophosphorus insecticides, such as chlorpyrifos and its oxon, may cause irreversible cholinesterase inhibition by forming a stable covalent bond at the active site (Goodman et al. 1990). Stability of the bond is further enhanced by a process called aging, which occurs when one of the alkyl groups of the diethylester is lost (Goodman et al. 1990). Aging of the cholinesterase enzyme is an important factor in determining the effectiveness of oximes, such as pyridine-2-aldoxime methyl chloride (2-PAM or pralidoxime), to reactivate the enzyme through nucleophilic attack on the phosphorus. Once aging has occurred, 2-PAM can no longer reactivate the enzyme. Thus, in the absence of oximes, recovery of enzyme activity often depends heavily on the synthesis of new cholinesterase enzyme. The result of cholinesterase inhibition is cholinergic overstimulation. The resulting effects can be reversed by administration of the cholinergic blocking agent, atropine.

2.4.3 Animal-to-Human Extrapolations

Extrapolating from laboratory animals to humans may be done in the case of chlorpyrifos because the mechanism of action of the pesticide is the same in all species examined, and the metabolism and excretion of the pesticide are similar, if not identical, in humans and common laboratory animals.

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2.5 RELEVANCE TO PUBLIC HEALTH**Overview**

The most likely mode of exposure to chlorpyrifos at a hazardous waste site is through the skin. The most significant effect of acute-duration exposure to chlorpyrifos is cholinergic over-stimulation resulting from cholinesterase inhibition. Clinical signs associated with parasympathetic stimulation include headache, diaphoresis, nausea, vomiting, diarrhea, epigastric cramping, bradycardia, blurred vision, miosis, bronchoconstriction and excess mucous secretions, pulmonary edema, dyspnea, muscle fasciculations, salivation, lacrimation, and urination (Ballantyne and Marrs 1992). Exposure to high doses can also produce a profound tachycardia, pulmonary edema, loss of bowel control, convulsions, coma, and death.

The actual symptoms seen in patients poisoned with cholinesterase-inhibiting pesticides result from actions at both nerve synapses and neuromuscular junctions. Cholinesterase inhibition in skeletal muscle can cause muscle weakness, fasciculations, and tremors. Central nervous system effects may include anxiety, headaches, drowsiness, confusion, tremor, ataxia, abnormal gait, hypotension, respiratory depression, convulsions, and coma (Ballantyne and Marrs 1992). Reversible peripheral neuropathies and polyneuritis have also been observed in humans and other animals following acute-duration, high-dose exposures.

Transient memory impairment following acute-duration exposure to chlorpyrifos has been observed in humans. Acute-duration exposure to high levels of chlorpyrifos in laboratory animals has been shown to cause long-term down-regulation of central muscarinic receptors (Bushnell et al. 1993). Chlorpyrifos has not been shown to affect reproduction in laboratory animals, but sperm production was decreased in bulls dermally exposed to chlorpyrifos. Limited information for rodents suggests that in utero exposure to chlorpyrifos may increase the incidence of skeletal variations and be developmentally neurotoxic to offspring. Additionally, data collected from mice and *Drosophila* indicate that chlorpyrifos may be genotoxic.

Following acute-duration exposure in humans or animals, chlorpyrifos is rapidly eliminated from the body; only trace amounts of chlorpyrifos metabolites can usually be found in the blood or urine 48 hours after a single exposure. However, in humans (Lotti et al. 1986), bulls (Haas et al. 1983), and

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cats (Jaggy and Oliver 1992), clinical signs of toxicity may be evident for weeks following exposure, long after the chlorpyrifos should have been eliminated. There is no evidence to suggest that chlorpyrifos is bioaccumulated. Little information is available concerning the effects of intermediate duration exposure of humans or animals to chlorpyrifos, and no information was located regarding the effects of chronic-duration exposure.

Measurement of erythrocyte and plasma cholinesterase activity is usually performed if organophosphate poisoning is suspected. However, erythrocyte cholinesterase inhibition by itself is not always associated with the presence of cholinergic symptoms, and plasma (pseudo-) cholinesterase inhibition is generally considered only an index of exposure. Brain acetylcholinesterase inhibition, where available, and erythrocyte acetylcholinesterase inhibition are commonly used to correlate cholinesterase inhibition with a threshold for toxic manifestations associated with inhibition of the cholinesterase enzyme. In the case of chlorpyrifos, this particular insecticide is considered a selective pseudocholinesterase inhibitor (HSDB 1995). The course of inhibition of the respective acetyl- and butyrylcholinesterase enzymes have different times of onset after a single exposure, with acetylcholinesterase inhibition following the drop in butyrylcholinesterase activity (Ballantyne and Marrs 1992). Thus, both plasma and erythrocyte cholinesterase activities should be measured if chlorpyrifos exposure is suspected. It should be noted that the degree of erythrocyte cholinesterase inhibition does not always correlate with toxicity; this is especially true in children. In some cases, children have been highly symptomatic after chlorpyrifos exposure at a time when only plasma cholinesterase levels have been reduced, or when all cholinesterase levels were within normal ranges. Thus, measuring cholinesterase activity in children may have little practical value except to confirm exposure to chlorpyrifos.

There are many populations at potentially greater risk to chlorpyrifos-induced toxicity. Populations at risk include the elderly, persons with pre-existing medical conditions, infants and children, and women (especially pregnant women). The elderly are considered at risk for increased toxicity because of the general decline in health that accompanies aging. Persons with chronic respiratory ailments such as asthma, emphysema, and bronchitis would be at greater risk for respiratory distress following chlorpyrifos exposure. Additionally, approximately 5% of the population are succinylcholine (diacetylcholine) sensitive and would be at greater risk following chlorpyrifos exposure because they have a genetically based deficiency in pseudocholinesterase. Research using rats indicates that females are more susceptible to the toxic effects of chlorpyrifos, possibly because they detoxify chlorpyrifos at

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a slower rate than males. However, in bovines, bulls have been shown to be at increased risk to some aspects of chlorpyrifos toxicosis. It is not known if gender differences in chlorpyrifos metabolism or susceptibility exist in humans. Additionally, the doses of chlorpyrifos needed to cause death in pregnant mice are approximately six times lower than those need to cause death in nonpregnant mice, suggesting that pregnancy may increase the risk of chlorpyrifos-induced toxicity.

It is difficult to determine whether the increased susceptibility of children to chlorpyrifos toxicity is due to physiological or behavioral characteristics. Results from an animal study conducted in piglets suggest that chlorpyrifos more easily penetrates the skin of young animals, compared to adults. Very young children and infants also have a decreased metabolic capacity to eliminate toxicants and are more susceptible to central nervous system toxicants, thus lowering the exposure levels needed to cause chlorpyrifos toxicity in that population. Chlorpyrifos may also affect neurological development after birth. Studies in rat neonates indicate that 2 mg/kg chlorpyrifos inhibits brain DNA synthesis (Whitney et al. 1995). However, studies in pregnant rats suggest that high levels of chlorpyrifos exposure during gestation are needed to adversely affect offspring mortality, reduce birth weight, and alter offspring behavior (Breslin et al. 1996; Deacon et al. 1980), and studies in preweanling rats found that the neurobehavioral toxicity of chlorpyrifos was less severe and of shorter duration than in adult rats (Stanton et al. 1994).

Minimal Risk Levels for Chlorpyrifos

Inhalation MRLs

No MRLs have been derived for this route of exposure because of the lack of suitable information for any exposure durations.

Oral MRLs

- An MRL of 0.003 mg/kg/day has been derived for both acute (14 days or less) and intermediate (15-364 days) oral exposure to chlorpyrifos. The combination of the length of exposure period and the critical effect in this study enable it to be used for the derivation of both acute- and intermediate-duration oral exposure MRLs.

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These MRLs are based upon a study by Coulston et al. (1972) in which 16 human adult male volunteers (4 per dose group) were administered chlorpyrifos in doses of 0, 0.014, 0.03, or 0.1 mg/kg once daily in a tablet with breakfast for up to 28 days. The low- and mid-dose groups were dosed for 28 and 21 days, respectively, but the high-dose treatment was discontinued after 9 days due to one individual in this group experiencing a runny nose, blurred vision, and a feeling of faintness. Twice each week, blood samples were obtained from each volunteer for determination of cholinesterase activity. Mean plasma and RBC cholinesterase levels were ascertained for all groups and compared with pretreatment values, and comparison was also made between treated and control groups. At weekly intervals, additional blood samples were obtained for hematology and routine serum chemistry determinations. Urinalyses were also performed on a weekly basis. Throughout the course of the experiment, no treatment-related effects were found among any of the parameters examined in the urinalyses, hematological, or serum chemistry tests. In the high-dose group, mean plasma cholinesterase (ChE) was depressed by 66% of average baseline levels after 9 days of treatment. In the group receiving 0.03 mg/kg/day, plasma ChE levels were reduced by an average of 30% from baseline levels; however, when compared with control group levels on a day-to-day basis, plasma ChE was reduced by only 13% of concurrent control values. Statistical analysis of this treatment group revealed the decrease was not different from controls. There was no statistically significant effect on plasma ChE activity during the four-week experiment in the low-dose group. No effect on RBC ChE activity was apparent at any dose, and the plasma ChE levels in all high-dose volunteers had returned to baseline levels within four weeks.

Although the authors of the Coulston et al. (1972) study indicated that the individual with the runny nose, blurred vision, and faint feeling was treated for a cold and was asymptomatic by the end of the day (day 9), they neither provided further comment indicating that the symptoms were unrelated to treatment nor explained why the high-dose treatments were discontinued after 9 days. Therefore, the highest dose that can be unequivocally stated to be a NOAEL in this study is the 0.03 mg/kg/day dosage. While plasma cholinesterase activity was depressed by approximately 65% in the high-dose group, plasma (pseudo-) cholinesterase activity is considered by ATSDR to be only an indicator of exposure to a cholinesterase-inhibiting substance or substances, and does not, in and of itself, constitute an adverse health effect.

The MRLs derived from the Coulston et al. (1972) study are closely supported by the Deacon et al. (1980) study, in which pregnant adult CF-1 mice (40-47 per group) were bred and administered daily

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gavage chlorpyrifos dosages of 1, 10, or 25 mg/kg/day in cottonseed oil on Gd 6-15. A group of 51 female control animals was given an equivalent volume of cottonseed oil without the test material. Since the high dose resulted in severe maternal toxicity, additional mice (35-41 per dosage group) were bred and administered chlorpyrifos at doses of 0.1, 1, or 10 mg/kg/day on Gd 6-15, inclusively, to further evaluate the teratogenic potential of chlorpyrifos. Animals were observed daily (from day 6 on) for signs of toxicity. Maternal body weights were recorded for Gd 6-15. Maternal body weight, liver weight, and weight of the gravid uterus (including ovaries) were recorded at the time of cesarean section on Gd 18. After sacrifice (with CO₂), the number and position of live, dead, and resorbed fetuses were noted. Fetuses were weighed, their crown-rump length measured, and then examined for external alterations and cleft palate. In addition, 1 in 3 of the fetuses from each litter were examined for evidence of soft-tissue alterations by dissections under a stereomicroscope. To determine the degree of plasma and erythrocyte cholinesterase depression, groups of 4-10 bred mice were given 0, 1, 10, or 25 mg/kg/day on Gd 6, Gd 6-10, or Gd 6-15. Subsequently, groups of 5-15 mice were given 0.1, 1, or 10 mg/kg/day of chlorpyrifos concurrently with the animals for the teratologic study on Gd 6, Gd 6-10, or Gd 6-15. Five hours after the final dosing for each period, blood was obtained by cardiac puncture. A homogenate of fetuses from the litters of mice sacrificed on Gd 15 was prepared to measure total fetal cholinesterase levels.

In the 25 mg/kg/day group, severe maternal toxicity (4 deaths; clinical symptoms indicating "severe cholinesterase inhibition") was observed in 32 of 47 mice. Cholinergic symptoms included excessive salivation, tremors, urine-soaked coat, ataxia, and lethargy. Mean body weight was significantly decreased in this group on day 16, and the mean value for total body weight gain was also significantly decreased, as were food and water consumption at this dosage. Plasma and RBC ChE levels were significantly decreased from controls at Gd 6, Gd 6-10, and Gd 6-15, and fetal homogenate ChE levels were also significantly decreased. While there was no significant effect on the incidence of pregnancy, average number of implantations, live fetuses, or resorptions (at this or any experimental dosage), there was a significant decrease in fetal body weight and crown-rump length at the high dose. There were also significant increases in the occurrence of several minor skeletal variants, including delayed ossification of the skull bones, delayed ossification of the sternalbrae, and unfused sternalbrae at 25 mg/kg/day. By contrast, the 10 mg/kg/day groups showed only occasional mild to moderate symptoms of ChE inhibition in 9 of 44 treated animals, with both plasma and RBC ChE levels significantly decreased from controls at Gd 6, Gd 6-10, and Gd 6-15; fetal ChE levels significantly decreased in this group as well. In the 1 mg/kg/day groups, only a single animal showed

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any cholinergic symptom (excess salivation on day 7). In the two 1 mg/kg/day treatment groups, plasma (but not RBC) levels were significantly reduced from controls at Gd 6 and Gd 6-15; both plasma and RBC levels were significantly reduced in mice treated from Gd 6 through 10 in the primary study; and both plasma and RBC ChE levels were significantly decreased on days 6-10 and 6-15 in the second (concurrent) phase of this study. There was also a significantly increased incidence of exencephaly at this dosage, but this effect was not seen at either of the higher dosages, making this finding questionable and of indeterminable significance. An increase in the incidence of unfused stembrae and a decreased incidence of fused stembrae were also observed at this treatment level. The 0.1 mg/kg/day dosage is considered to be the NOAEL for both fetotoxicity and acetylcholinesterase inhibition for this study.

With the application of appropriate uncertainty factors to account for extrapolation of animal experimental data to humans and for intraspecies variability (100 total uncertainty factor), an acute MRL of 0.001 mg/kg/day could be calculated from this study alone. However, the human data from the Coulston et al. (1972) study is considered to be more appropriate for use in MRL derivation, and the calculated MRL of 0.003 mg/kg/day is considered adequate to afford protection from all adverse health effects that have been associated experimentally as well as clinically with acute- and intermediate-duration exposure to chlorpyrifos.

- An MRL of 0.001 mg/kg/day has been derived for chronic (365 days or more) oral exposure to chlorpyrifos.

The chronic-duration exposure MRL was derived from a study by McCollister et al. (1974). In that study, Sherman rats were fed chlorpyrifos at levels corresponding to 0, 0.01, 0.03, 0.1, 1, or 3 mg/kg/day for 2 years, beginning at 7 weeks of age. Additional groups of 5-7 rats of each sex at each dose level were set up to provide interim pathological examination and acetylcholinesterase (AChE) determinations. Red blood cell AChE activity was depressed in both male and female rats dosed with diets containing 1 and 3 mg/kg/day chlorpyrifos. Doses of 0.1 mg/kg/day and below had no effect on RBC ChE. Based on the NOAEL of 0.1 mg/kg/day for cholinesterase inhibition, an MRL of 0.001 mg/kg/day was calculated, using uncertainty factors of 10 for interspecies extrapolation and 10 for intraspecies variability in susceptibility.

Death. The LD₅₀ for acute-duration inhalation exposure to chlorpyrifos was determined for mice and female rats (Berteau and Deen 1978). In mice, an LD₅₀ of 94 mg/kg was determined after whole-

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body inhalation exposure to 6,700-7,900 mg/m³ chlorpyrifos in 65% xylene. In that study, the dose range was achieved by varying the length of exposure from 27 to 50 minutes. Virgin female Sprague-Dawley rats were similarly exposed to 5,900-7,500 mg/m³ chlorpyrifos in 65% xylene, and an acuteduration exposure inhalation LD₅₀ of 78 mg/kg was determined by varying the exposure duration from 48 to 61 minutes. The acute-duration oral exposure LD₅₀ in female rats ranges between 82 mg/kg (Gaines 1969) to 135 mg/kg (McCollister et al. 1974) and 122 mg/kg (Gaines 1969) to 163 mg/kg (McCollister) for male rats. Approximately 9% mortality was seen in pregnant mice orally dosed with 25 mg/kg/day chlorpyrifos on Gd 6-15 (Deacon et al. 1980). The LD₅₀ for male Leghorn chicken has been reported by Miyazaki and Hodgson (1972) and McCollister et al. (1974) to be 34.8 and 32 mg/kg chlorpyrifos, respectively.

Systemic Effects

Respiratory Effects. Acute-duration exposure to chlorpyrifos in humans has been shown to cause respiratory distress, probably due to acetylcholinesterase inhibition (Aiuto et al. 1993; Lotti et al. 1986; Selden and Curry 1987). In piglets, acute-duration dermal exposure to chlorpyrifos causes dyspnea, also a result of acetylcholinesterase inhibition (Long et al. 1986).

Cardiovascular Effects. In humans, acute-duration oral exposure to chlorpyrifos initially causes bradycardia, then tachycardia (Aiuto et al. 1993; Selden and Curry 1987). However, the progression to tachycardia is a dose-dependent effect.

Gastrointestinal Effects. Gastrointestinal distress, including nausea and diarrhea, has been observed in humans following acute- (Kaplan et al. 1993) or intermediate-duration (Kaplan et al. 1993) inhalation exposure or acute-duration dermal exposure (Thrasher et al. 1993) to chlorpyrifos. In bulls, acuteduration dermal exposure caused severe diarrhea and rumen atony (Haas et al. 1983).

Hematological Effects. Acute-duration inhalation exposure to chlorpyrifos in humans has not been shown to affect blood chemistry (Kaplan et al. 1993).

Musculoskeletal Effects. In humans, muscle pain (Thrasher et al. 1993) and muscle cramps (Kaplan et al. 1993) have been reported following acute-duration dermal and inhalation exposure, respectively, to chlorpyrifos. Increased muscle tone (Joubert et al. 1984) and vocal cord paralysis (Aiuto et al.

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1993) were observed in humans following acute-duration oral exposure. Muscle twitching and fasciculations, hyper- or hyporeflexia, and coreo-athetotic motions have also been observed following acute-duration chlorpyrifos exposure (Aiuto et al. 1993; Joubert et al. 1984; Lotti et al. 1986; Selden and Curry 1987).

Hepatic Effects. In pregnant mice, acute-duration oral exposure to 25 mg/kg/day chlorpyrifos did not affect absolute or relative liver weight (Deacon et al. 1980).

Endocrine Effects. No information was found associating endocrine effects with chlorpyrifos exposure in humans or animals.

Renal Effects. An increase in urinary frequency was observed in adult male humans acutely exposed by inhalation to chlorpyrifos (Kaplan et al. 1993). However, unspecified decreases in urinary frequency were observed in humans following intermediate-duration inhalation or dermal exposure to undetermined amounts of chlorpyrifos (Ames et al. 1989).

Dermal Effects. In humans, intermediate-duration (3 months) inhalation or dermal exposure to undetermined amounts of chlorpyrifos resulted in an unspecified increase in skin flushing (Ames et al. 1989).

Ocular Effects. Acute-duration exposure in children (Aiuto et al. 1993; Selden and Curry 1987) and adults (Joubert et al. 1984) can cause miosis. In humans, intermediate-duration (3 months) inhalation or dermal exposure to undetermined amounts of chlorpyrifos resulted in an unspecified increase in blurred vision (Ames et al. 1989).

Body Weight Effects. The effects of Dursban[®] on body weight and body weight gain were assessed in pregnant mice following acute-duration oral exposure to doses as high as 25 mg/kg/day chlorpyrifos from Gd 6-15 (Deacon et al. 1980). A statistically significant decrease in mean body weight gain for Gd 10-15 (33.3%) and overall (Gd 6-17, 14%) was observed in animals exposed to 25 mg/kg/day chlorpyrifos. In the same study, the body weight gains of dams exposed to 1 or 10 mg/kg/day chlorpyrifos were comparable to controls. Additionally, body weights determined on Gd 18 for all the treatment groups were similar to control values.

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Immunological and Lymphoreticular Effects. A study by Brenner et al. (1984) compared the prevalence of selected illnesses and symptoms in 175 employees involved in the production of chlorpyrifos and 335 matched controls with no history of exposure to organophosphorus chemicals. The employees were further subdivided for dose-response testing into three exposure intensity groups on the basis of job title and air-monitoring data. There were no statistically significant differences in illness or prevalence of symptoms between the exposed and unexposed groups, or among the three exposure subgroups. Exposure was assumed to be via inhalation and dermal routes. Although the objective of this study was not to specifically address whether exposure to chlorpyrifos causes any changes in immune function in humans, the results offered no evidence to suggest that chlorpyrifos suppresses human immunocompetence.

In spite of the widespread use of insecticides containing chlorpyrifos, there are no definitive reports that it sensitizes human skin. A study, which assessed a number of pesticides via patch tests in California nursery workers, observed no positive responses to chlorpyrifos in 38 out of the 39 exposed workers who were tested (O'Malley et al. 1995). The duration of exposure to any of the pesticides was not specified in this paper. Although none of the 21 control subjects were positive for chlorpyrifos, positive responses to other pesticides were noted in the controls.

The effects of acute-duration dermal exposure to chlorpyrifos were reported for 12 persons exposed to chlorpyrifos primarily in the home or workplace following professional application of the pesticide (Thrasher et al. 1993). The approximate dose received and the length of time following exposure were not known for any of the patients. Examination of blood taken from the chlorpyrifos-exposed persons indicated that there were changes in some lymphocyte subtypes when compared to 60 (28 male and 32 female) control subjects.

Analysis of the blood revealed a 300% increase in the mean absolute counts of CD26 cells and a decrease in the relative percentages of CD5 (11%) and CD4 (7%) lymphocytes. Additionally, 83% of the chlorpyrifos-exposed individuals had increased levels (300-1,200%) of circulating autoantibodies to at least one of the following cell types or organelles: smooth muscle, parietal cells, brush boarder, and nuclei. Twenty-five percent of the chlorpyrifos-exposed patients had elevated autoantibodies to 3 or more of the cell types or organelles compared to 0-3.7% in the control group. The authors suggested that the increase in auto antibodies was due to chlorpyrifos-induced tissue damage. However, the causality of these effects must be interpreted with caution. This study was a retrospective case study

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in which the symptoms arose 1-4.5 years post-exposure to chlorpyrifos. No exposure data were presented and there were no objective data or methods for ruling out confounding chemical exposures. Ten of the patients had a history of some type of atopy or drug sensitivity while one patient had been diagnosed with systemic lupus erythematosus and another had a lupus-like syndrome. From the results of this study, it may be concluded that the patients had some immunological abnormalities, but it is difficult to attribute the effects to chlorpyrifos exposure (Richardson 1995).

Neurological Effects. The most common effect in humans and other animals following acute-duration chlorpyrifos exposure is inhibition of cholinesterase activity (Berteau and Deen 1978; Deacon et al. 1980; Hooser et al. 1988; Joubert et al. 1984; Kaplan et al. 1993; Long et al. 1986; Selden and Curry 1987). In humans, acute-duration exposure to unspecified amounts of chlorpyrifos is associated with a variety of symptoms, including headache, excessive salivation, lacrimation, diaphoresis, bradycardia, tachycardia, excessive respiratory tract secretions, bronchoconstriction, paresthesia, lightheadedness, memory impairment, stupor (Joubert et al. 1984), seizure-like motor activity, and coma (Aiuto et al. 1993; Kaplan et al. 1993; Lotti et al. 1986; Selden and Curry 1987). Motor symptoms such as muscle twitching, fasciculations, and coreo-athetotic movements have also been observed following acute-duration oral exposure to chlorpyrifos (Aiuto et al. 1993; Joubert et al. 1984; Lotti et al. 1986; Selden and Curry 1987). Transient, delayed polyneuropathy has been noted in humans following acute- (Aiuto et al. 1993; Lotti et al. 1986) or intermediate-duration (Kaplan et al. 1993) exposure to chlorpyrifos.

Neurotoxic effects similar to the ones described above have also been observed in laboratory animals following acute-duration exposure (Capodicasa et al. 1991; Deacon et al. 1980; Hooser et al. 1988). In the Deacon et al. (1980) study, erythrocyte acetylcholinesterase activity was significantly inhibited at dosages of 10 and 1 mg/kg/day, but not at 0.1 mg/kg/day. Muscle weakness and abnormal gait were observed in hens orally dosed with 10 mg/kg/day chlorpyrifos for 90 days. The symptoms subsided by 60 days after the end of the dosing period. These symptoms differed from the classical OPIDN in the apparent reversibility of ataxia in the hens which survived (Francis et al. 1985). No-symptoms of classical OPIDN were observed in hens exposed to 10 mg/kg/day chlorpyrifos for 20 days (Richardson et al. 1993b).

Reproductive Effects. No effects on reproduction were observed in mice following acute-duration oral exposure to chlorpyrifos during pregnancy (Deacon et al. 1980). However, decreased

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sperm production was observed in bulls to which an undetermined amount of chlorpyrifos had been dermally applied (Everett 1982).

Developmental Effects. The potential for chlorpyrifos to be developmentally toxic was assessed in mice exposed to 0, 1, 10, or 25 mg/kg/day chlorpyrifos on Gd 6-15 (Deacon et al. 1980). On Gd 18, all fetuses were weighed, sexed, examined for external malformations and cleft palate, and had their crown-rump length determined. One-third of the fetuses of each litter were also examined for evidence of soft-tissue alterations. There was no biologically significant effect of treatment on the number of live fetuses per litter, the number of dead fetuses per litter, the number of resorptions per litter, the average fetal body weight, or average crown-rump length. However, significant increases in skeletal variations were observed in litters exposed to 25 mg/kg/day chlorpyrifos, a level also causing significant maternal toxicity. Increases were seen in the number of fetuses with delayed ossification of the skull bones (6.8-fold increase), delayed ossification of the sternalbrae (2.1-fold increase), and unfused sternalbrae (4-fold increase) at the same dosage. In the same study, total fetal homogenate cholinesterase levels were decreased by 19, 35, and 65% in the litters of mice given 1, 10, or 25 mg/kg/day chlorpyrifos, respectively, on Gd 6-15 (Deacon et al. 1980). The decreases in cholinesterase activity were significantly different from controls at the 10 and 25 mg/kg/day doses.

Genotoxic Effects. Results of studies conducted with rodent and insect cell lines suggest that chlorpyrifos may be genotoxic (Amer and Fahmy 1982; Patnaik and Tripathy 1992; Sobti et al. 1982; Woodruff et al. 1983). A dose-response effect of chlorpyrifos on the induction of micronuclei in bone marrow has been observed (Amer and Fahmy 1982). A dose-response relationship for chlorpyrifos-induced cytotoxic cytogenetic effects in human lymphoid cells has also been demonstrated. Chlorpyrifos has been shown to produce significant increases in sister chromatid exchanges (Sobti et al. 1982). It has also been reported that chlorpyrifos causes X chromosome loss (Woodruff et al. 1983). Spindle poisoning and induction of micronuclei and polyploidy have also been reported following chlorpyrifos exposure (Rao et al. 1988). Sex-linked recessive lethals have also been produced by chlorpyrifos exposure, indicating that chlorpyrifos is genotoxic to both somatic and germ cells (Patnaik and Tripathy 1992). Finally, chlorpyrifos at a concentration of 0.05 µg/mL caused induction of chromosomal aberrations and sister chromatid exchanges in spleen cells. Chromosomal aberrations included chromatic and chromosomal gaps and fragments. Additionally, some polyploid metaphases were observed (Amer and Aly 1992). The results of these studies are summarized in Tables 2-4 and 2-5.

Table 2-4. Genotoxicity of Chlorpyrifos *In Vivo*

Species (test system)	End point	Results	Reference
Fly (<i>Drosophila melanogaster</i>) germ cells	Complete chromosome loss	+	Woodruff et al. 1983
Fly (<i>Drosophila melanogaster</i>) germ cells	Partial chromosome loss	-	Woodruff et al. 1983
Fly (<i>Drosophila</i>) somatic and germ cells	Induction of mosaic wing spots	+	Patnaik and Tripathy 1992
Fly (<i>Drosophila</i>) somatic and germ cells	Induction of sex-linked recessive lethals	+	Patnaik and Tripathy 1992
Mouse (Swiss) bone marrow	Polychromatic erythrocytes (PE) and PE with micronuclei	+	Amer and Fahmy 1982

- = negative; + = positive

Table 2-5. Genotoxicity of Chlorpyrifos *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Human peripheral blood	Sister chromatid exchange		-	Nelson et al. 1990
Mouse (Swiss) bone marrow	Polychromatic erythrocytes (PE)		+	Amer and Fahmy 1982
Mouse (Swiss) bone marrow	Induction of micronuclei		-	Amer and Fahmy 1982
Mouse (Swiss) spleen cells	Cytotoxicity		+	Amer and Aly 1992
Mouse (Swiss) spleen cells	Chromosomal aberrations		+	Amer and Aly 1992

- = negative results; + = positive

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Cancer Effects. Research in rats and dogs (McCollister et al. 1974) found that chlorpyrifos did not increase the incidence of cancer, but the data from this study are not sufficient to assess any human cancer risk to chlorpyrifos exposure. The EPA has not classified chlorpyrifos for carcinogenicity (Class D).

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biological 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 metabolites, 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 chlorpyrifos are discussed in Section 2.6.1.

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

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be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by chlorpyrifos are discussed in Section 2.6.2.

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 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Chlorpyrifos

Measurement of erythrocyte or plasma cholinesterase activity is usually performed if organophosphate poisoning is suspected. Erythrocyte cholinesterase activity may be used as both an index of exposure and as a harbinger of potential toxicity. Butyrylcholinesterase activity may also be used as an indicator of exposure to a cholinesterase-inhibiting agent, but due to its lack of substrate specificity, it may not, by itself, be used as a reliable index of toxicity.

Chlorpyrifos is known to inhibit acetylcholinesterase activity, but the degree of inhibition does not correlate well with the onset of toxicity or the amount of exposure. Moreover, acetylcholinesterase inhibition may occur after exposure to a wide variety of organophosphate and carbamate pesticides. Thus, acetylcholinesterase activity is not a specific marker for chlorpyrifos exposure. However, unlike many pesticides, chlorpyrifos metabolism yields some relatively unique compounds. The major metabolite of chlorpyrifos is TCP. TCP can be found in the general circulation and in the urine, its principal route of excretion. Moreover, TCP levels correlate well with the degree of exposure to chlorpyrifos, and current analytic methods can detect TCP in the nanomolar range. The results of metabolism studies conducted in animals indicate that >90% of absorbed chlorpyrifos is eliminated from the body within 48 hours. Therefore, urine TCP can be used as a qualitative biomarker for chlorpyrifos exposure, providing the testing is performed within 48 hours after exposure. It should be noted that clinical signs of chlorpyrifos-induced toxicity may persist for several weeks after exposure, or longer in the case of extremely high exposures.

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2.6.2 Biomarkers Used to Characterize Effects Caused by Chlorpyrifos

There are no specific biomarkers that may be used to characterize the effects caused by chlorpyrifos. All the signs and symptoms (weakness, headache, dizziness, visual disturbances, increased salivation, increased lacrimation, nausea, vomiting, lack of appetite, stomachache, restlessness or increased excitement, myosis, bronchial spasms, diarrhea, miosis, sweating, bradycardia, hypertonia, facial muscle twitching, tremors, gait disturbances, feeling of fear, chest pain, difficult respiration, cyanosis of the mucous membrane, generalized convulsions, psychic disturbances, edema of lung, coma) of chlorpyrifos exposure relate directly to its inhibition of acetylcholinesterase, which may be caused by any organophosphate or carbamate insecticide.

For more information on biomarkers for renal and hepatic effects of chemicals, *see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage* (1990), and for information on biomarkers for neurological effects, *see* OTA (1990).

2.7 INTERACTIONS WITH OTHER CHEMICALS

The primary risk of interaction is with other compounds that also inhibit acetylcholinesterase. In those cases, the dose needed to produce chlorpyrifos-induced toxicity would be correspondingly lower. Additionally, it would be expected that concurrent exposure to other central nervous system toxicants such as solvents may exacerbate the chlorpyrifos-induced neurotoxicity or confound the diagnosis, depending on whether the toxicant has excitatory or depressant neurological effects. Additionally, chlorpyrifos toxicity in bovines appears to correlate with high circulating levels of testosterone, suggesting that sex steroids may lower the threshold for toxicity.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population may exhibit a different or enhanced response to chlorpyrifos than will most persons exposed to the same level of chlorpyrifos in the environment. Reasons may include genetic makeup, age, health and nutritional status, and concurrent exposure to some pharmaceuticals or other toxic substances. These parameters may result in reduced detoxification or excretion of chlorpyrifos, or compromised function of target organs affected by chlorpyrifos. Populations that are at greater risk

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due to their unusually high exposure to chlorpyrifos are discussed in Section 5.6, Populations With Potentially High Exposure.

There are many populations at potentially greater risk to chlorpyrifos-induced toxicity. Populations at risk include the elderly, persons with pre-existing medical conditions, infants and children, and pregnant women. The elderly are considered at risk for increased toxicity because of the general decline in health that accompanies aging. Persons with chronic respiratory ailments such as asthma, emphysema, and bronchitis would be at greater risk for respiratory distress following chlorpyrifos exposure due to the insecticide's ability to cause bronchoconstriction and increase mucous secretions in the airways. Persons suffering from heart disease may also represent a group at particular risk due to both direct cardiac effects and restriction in airway diameter. Research using rats indicates that females are more susceptible to the toxic effects of chlorpyrifos, possibly because they detoxify chlorpyrifos at a lower rate than males. However, in bovines, bulls have been shown to be at increased risk to chlorpyrifos toxicity. It is not known if gender differences in chlorpyrifos metabolism or susceptibility exist in humans. Additionally, the doses of chlorpyrifos needed to cause death in pregnant mice are approximately six times lower than those need to cause death in nonpregnant mice, suggesting that pregnancy may increase the risk of chlorpyrifos-induced toxicity.

Infants and children may also be at increased risk for toxicity. Results from animal studies suggest that chlorpyrifos more easily penetrates the skin of young animals, compared to adults. Children also have a decreased metabolic capacity to eliminate toxicants and are more susceptible to central nervous system toxicants, thus lowering the exposure levels considered protective against the potential toxicity of chlorpyrifos in that population. Chlorpyrifos may also be developmentally toxic. Studies of pregnant rats suggest that low levels of chlorpyrifos exposure during gestation have the potential to increase offspring mortality, reduce birth weight, and alter offspring behavior.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chlorpyrifos. 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 chlorpyrifos. When specific exposures have occurred, poison control centers and medical toxicologists should be

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consulted for medical advice. The following texts provide specific information about treatment following exposures to chlorpyrifos:

- Cholinesterase inhibitor pesticides, in Handbook of Poisoning, 1987, Appleton and Lang, Norwalk; R.H. Dreisbach, 110-118.
- Organophosphates and other insecticides, in Clinical Management of Poisoning and Drug Overdose, 2nd Edition, 1990, W.B. Saunders, Philadelphia; M. Haddad and J.F. Winchester, eds., 1105-1119.
- Insecticides: organophosphates and carbamates, in Goldfrank's Toxicologic Emergencies, 5th edition, 1994, Norwalk; C.K. Aaron and M.A. Howland, 1076-1087.

2.9.1 Reducing Peak Absorption Following Exposure

Gastric lavage may be used to reduce peak absorption following oral exposure to chlorpyrifos (Aiuto et al. 1993; Namba et al. 1971). Additionally, the oral administration of activated charcoal with a saline cathartic given repeatedly interrupts the enterohepatic circulation of chlorpyrifos and its metabolites by blocking intestinal absorption and reducing residency time in the intestine. For dermal exposure, gently washing the exposed area with soap and water would be recommended; however, rough cleansing may damage the skin, leading to increased absorption of the pesticide.

2.9.2 Reducing Body Burden

Repeated oral administration of activated charcoal interrupts enterohepatic circulation and reduces body burden via hepatic excretion into the gastrointestinal tract.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

There are two commonly used procedures (antidotes) to interfere with the mechanism of chlorpyrifos. One is to administer pralidoxime (2-PAM) intravenously to displace the chlorpyrifos or its oxon from the acetylcholinesterase enzyme and restore its activity (Namba et al. 1971). Since 2-PAM is itself a potent inhibitor of acetylcholinesterase, care should be taken not to use it in cases of concurrent exposure to carbamate insecticides, since this may exacerbate the toxicity of that group of pesticides. Additionally, 2-PAM cannot displace chlorpyrifos or its oxon from the aged form of the cholinesterase enzyme. However, 2-PAM may be given if clinical signs of toxicity are still observable. Since the

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percentage of aged acetylcholinesterase increases with time after exposure, 2-PAM treatment should be given as soon as chlorpyrifos exposure has been determined. Chlorpyrifos toxicosis can also be reduced using muscarinic cholinergic receptor blockers such as atropine. Atropine blocks the predominantly parasympathetic effects caused by chlorpyrifos (Aiuto et al. 1993; Goodman et al. 1990; Namba et al. 1971). Both atropine and 2-PAM are toxic and should be used with care. In addition to the above treatments, diazepam may be used to reduce muscle fasciculations and seizure activity (Ballantyne and Marrs 1992).

2.10 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 chlorpyrifos 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 chlorpyrifos.

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.

2.10.1 Existing Information on Health Effects of Chlorpyrifos

The existing data on health effects of inhalation, oral, and dermal exposure of humans and other animals to chlorpyrifos are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of chlorpyrifos. 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 (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments.

Figure 2-5. Existing Information on Health Effects of Chlorpyrifos

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		●	●		●	●				
Oral		●				●				
Dermal			●			●				

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●			●	●		●	
Oral	●	●				●	●	●	●	
Dermal	●	●	●			●	●		●	

Animal

● Existing Studies

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

2.10.2 Identification of Data Needs

Acute-Duration Exposure. In general, acute-duration toxicity of chlorpyrifos has been well characterized in humans and other animals. The most common effect in humans and other animals following acute-duration chlorpyrifos exposure is inhibition of cholinesterase activity (Berteau and Deen 1978; Deacon et al. 1980; Hooser et al. 1988; Joubert et al. 1984; Kaplan et al. 1993; Long et al. 1986; Selden and Curry 1987). In humans, acute-duration exposure to chlorpyrifos is associated with a variety of symptoms, including headache, excessive salivation and lacrimation, diaphoresis, bradycardia, tachycardia, excessive respiratory tract secretions, bronchoconstriction, paresthesia, lightheadedness, memory impairment, stupor (Joubert et al. 1984), seizure-like motor activity, and coma (Aiuto et al. 1993; Kaplan et al. 1993; Lotti et al. 1986; Selden and Curry 1987). Motor symptoms such as muscle twitching, fasciculations, and coreo-athetotic movements have also been observed following acute-duration oral exposure to chlorpyrifos (Aiuto et al. 1993; Joubert et al. 1984; Lotti et al. 1986; Selden and Curry 1987). Transient, delayed polyneuropathy has been noted in humans following acute- (Aiuto et al. 1993; Lotti et al. 1986) or intermediate-duration (Kaplan et al. 1993) exposure to chlorpyrifos. Neurotoxic effects similar to the ones described above have also been observed in laboratory animals following acute-duration exposure (Capodicasa et al. 1991; Deacon et al. 1980; Hooser et al. 1988). These data indicate that the database is adequate for this exposure duration and sufficient to derive an acute-duration exposure MRL. Although the symptoms associated with chlorpyrifos exposure are well characterized, the correlation between cholinesterase inhibition and the severity of the symptoms is not. Increased reporting in the biomedical literature of human chlorpyrifos exposures, and animal studies designed to examine the correlation between cholinesterase inhibition and toxicity are needed. Acute-duration exposure toxicity in bovines appears to be associated with high levels of testosterone. The nature of the chlorpyrifos-testosterone interaction needs to be evaluated to determine if gender-related susceptibility to chlorpyrifos toxicity exists.

Intermediate-Duration Exposure. The toxic effects of chlorpyrifos following intermediate-duration exposure are expected to be similar to the cholinergic effects seen after acute-duration exposure. For example, blurred vision and skin flushing have been reported following occupational exposure to chlorpyrifos by multiple routes (Ames et al. 1989). Sufficient oral exposure data exist to

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calculate an MRL for this exposure route. However, toxicological data for dermal and inhalation exposure are sparse. Since chlorpyrifos is rapidly absorbed through the lungs, inhalation exposure may represent a significant health risk. Limited attempts to identify chlorpyrifos-related toxicity in pesticide applicators suggest that intermediate-duration exposure to low levels of chlorpyrifos may adversely affect health (Ames et al. 1989); but whether the effects may be related to cumulative direct target insult or simply to cholinesterase inhibition is less clear. Low-level inhalation or dermal exposures are assumed for the Ames et al. (1989) study because pesticide applicators are usually presumed to wear protective clothing and respirators when spraying the pesticide. However, neither the dose nor the length of exposure could be estimated. Thus, toxicity-based dose-response information is needed following inhalation and dermal exposure to chlorpyrifos. Based on the Ames et al. (1989) study, it would be particularly relevant to assess the toxic effects of low-level intermediate-duration exposure on human health. Intermediate-duration exposure neurotoxicity studies conducted in animals are recommended. Better quantification of the toxicity caused by intermediate-duration occupational exposure would help in assessing the health risks posed by chlorpyrifos.

Chronic-Duration Exposure and Cancer. There is limited information regarding the potential toxic and carcinogenic effects of chronic, low-level exposure to chlorpyrifos (Brenner et al. 1984; McCollister et al. 1974; Miyazaki and Hodgson 1972). Of particular concern are the potential systemic effects of chronic-exposure to low levels of the pesticide by the oral, dermal, and inhalation routes, because of its widespread use in industry, the home, and agriculture.

Genotoxicity. Results of studies conducted with rodent and insect cell lines indicate that chlorpyrifos may be genotoxic (Amer and Fahmy 1982; Patnaik and Tripathy 1992; Sobti et al. 1982; Woodruff et al. 1983). A dose response effect of chlorpyrifos on the induction of micronuclei in bone marrow has been observed (Amer and Fahmy 1982). A dose response relationship of cytotoxic cytogenetic effects to chlorpyrifos exposure has also been demonstrated in human lymphoid cells. Chlorpyrifos has been shown to produce significant increases in sister chromatid exchanges, with the percentage of M3 metaphases showing a dose response decrease (Sobti et al. 1982). It has also been reported that chlorpyrifos causes X chromosome loss (Woodruff et al. 1983). Spindle poisoning and induction of micronuclei have also been reported following chlorpyrifos exposure (Rao et al. 1988). In addition, some polyploid metaphases were observed (Amer and Aly 1992). Sex-linked recessive lethals have also been produced by chlorpyrifos exposure, indicating that chlorpyrifos is genotoxic in both somatic and germ cells (Patnaik and Tripathy 1992). Finally, chlorpyrifos at concentrations of

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0.05 µg/rnL caused induction of chromosomal aberrations and sister chromatic exchanges in spleen cells. Chromosomal aberrations included chromatic and chromosomal gaps, and fragments. Thus, sufficient data exist to identify chlorpyrifos as genotoxic. Epidemiological studies are recommended to investigate whether the effects observed may also occur in humans.

Reproductive Toxicity. Chlorpyrifos administered orally at 25 mg/kg/day from Gd 6 to 15 caused severe maternal toxicity (Deacon et al. 1980). The toxicity was characterized by symptoms of profound cholinergic stimulation and death. Despite the maternal toxicity, the surviving dams gave birth to normal numbers of offspring. No effects on reproduction were observed in mice receiving lower doses of chlorpyrifos. Decreased sperm production was observed in bulls to which an undetermined amount of chlorpyrifos had been dermally applied (Everett 1982). The data are not sufficient to evaluate the reproductive health risk of chlorpyrifos, especially in light of its genotoxic potential. Since chlorpyrifos may affect sperm production and viability, and because the effects of intermediate or long-term exposure are not known, a two-generation reproductive toxicity assessment is recommended. This type of study would be useful because it would address the effects of chlorpyrifos on both male and female reproduction.

Developmental Toxicity. The acute oral administration of 25 mg/kg/day chlorpyrifos from Gd 6 to 15 decreased average fetal weight and crown-rump length (Deacon et al. 1980). Chlorpyrifos also inhibits fetal cholinesterase activity (Deacon et al. 1980). However, the fetal effects in that study occurred in tandem with severe maternal toxicity. Thus, it is not certain if the reduction in fetal growth was secondary to maternal toxicity. More information is needed in this area, especially as it relates to the effect of chlorpyrifos on the developing nervous system, because of the potential for chlorpyrifos to affect cholinergic systems. Developmental toxicity and neurotoxicity studies are recommended. Dosing in the neurotoxicity studies should extend from gestation through weaning in order to expose brain regions that develop primarily postnatally.

Immunotoxicity. Work by Brenner et al. (1984) failed to identify immunotoxicity in a comparison of 175 employees involved in the production of chlorpyrifos and 335 matched controls with no history of exposure to organophosphorus chemicals. Exposure in this study was assumed to be via inhalation and dermal routes. A study which assessed a number of pesticides via patch tests in California nursery workers observed no positive responses with chlorpyrifos in 38 out of the 39 exposed workers who were tested (O'Malley et al. 1995). In contrast, work by Thrasher et al. (1993) raises the

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possibility that certain aspects of human immune function may be altered by chlorpyrifos exposure. It should be noted that while the Thrasher et al. (1993) had several flaws, it nevertheless suggests that certain components of the immunological system may be affected by chlorpyrifos. Because of the lack of a definitive immunotoxicity study, this area must be considered a data gap. Thus, an assessment of a validated immune functional test battery following intermediate- and chronic-duration exposure by inhalation and dermal exposure to low levels (levels not causing overt toxicity) of chlorpyrifos is recommended.

Neurotoxicity. Acute-duration exposure to chlorpyrifos has been shown to cause transient delayed peripheral neuropathy in humans and hens. Limited epidemiological studies in humans failed to reveal motor effects of intermediate-duration chlorpyrifos exposure beyond those seen in acute-exposure scenarios. However, acute-duration oral exposure to chlorpyrifos in humans and other animals has been reported to cause transient memory impairment. Information is lacking regarding the potential for inhaled or dermally absorbed chlorpyrifos to cause similar cognitive deficits. Thus, data are needed regarding the potential development of neuropathies and neurobehavioral toxicity associated with intermediate- or chronic-duration oral, inhalation, and dermal exposure to chlorpyrifos. Epidemiological research is also needed to identify levels of cholinergic inhibition associated with the onset of cholinergic symptoms in people exposed to chlorpyrifos, and to determine if susceptible or sensitized individuals can be identified.

Epidemiological and Human Dosimetry Studies. Epidemiological/occupational studies are needed because of the large population that is potentially at risk to chlorpyrifos exposure, both in the work place and the home.

Biomarkers of Exposure and Effect. No additional information is needed in this area.

Chlorpyrifos has a unique metabolite, TCP, that has been well characterized and for which sensitive analytic methods exist.

Exposure. Although chlorpyrifos inhibits acetylcholinesterase, the degree of inhibition does not correlate well with toxicity or the amount of exposure. Moreover, acetylcholinesterase inhibition may occur after exposure to a wide variety of organophosphate and carbamate pesticides. Thus, acetylcholinesterase activity is not a specific marker for chlorpyrifos exposure, though total blood cholinesterase is a good indicator in animals. However, unlike many pesticides, chlorpyrifos

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metabolism yields some unique compounds. The major and unique metabolite of chlorpyrifos is TCP. TCP can be found in the general circulation and in the urine, its principal route of excretion. Moreover, TCP levels correlate well with the degree of exposure to chlorpyrifos, and analytic methods can detect TCP in the nanomolar range. Thus, TCP is a specific and sensitive marker for chlorpyrifos exposure.

Effect. There are no specific biomarkers that may be used to characterize the effects caused by chlorpyrifos. All clinical signs and symptoms of chlorpyrifos exposure relate directly to its inhibition of acetylcholinesterase, which may be caused by any organophosphate or carbamate insecticide.

Absorption, Distribution, Metabolism, and Excretion. In general, the absorption, distribution, metabolism, and excretion of chlorpyrifos have been well characterized in humans and other animals. However, female rats and bulls with high circulating testosterone levels appear to more susceptible to chlorpyrifos toxicity. Thus, toxicokinetic data is needed in rats and bovines to determine whether there are gender-related differences in chlorpyrifos metabolism which could be used to identify a specific population at risk. Additionally, clinical signs of chlorpyrifos toxicity may persist long after it has been eliminated from the body. Information is needed to determine if this is due to a metabolite or to long-term changes in organ responsiveness resulting from the exposure.

Comparative Toxicokinetics. Adequate data exist for this area.

Methods for Reducing Toxic Effects. The methods for reducing the toxic effects of chlorpyrifos are well established. Any improvements in management of organophosphate poisoning would be expected to be relevant to chlorpyrifos.

2.10.3 Ongoing Studies

No ongoing studies for chlorpyrifos were found.