TOXICOLOGICAL PROFILE FOR CHLORPYRIFOS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A Toxicological Profile for chlorpyrifos was released in August 1995 for public comment. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed in response to the Super-fund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfkd). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on April 29, 1996 (61 FR 18744). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,199O (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for chlorpyrifos. The panel consisted of the following members:

1 . Dr. William Buck, Professor of Toxicology, University of Illinois, Tolono, IL 61880;

2 . Dr. Joel Coats, Professor, Department of Entomology, Iowa State University, Ames, IA 50011; and

3 . Dr. Frederick Oehme, Professor, Comparative Toxicology Laboratories, Kansas State University, Manhattan, KS 66506-5606

These experts collectively have knowledge of chlorpyrifos' physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be addressed in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about chlorpyrifos and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup. Chlorpyrifos has been found in at least 7 of the 1,428 current or former NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance. As more sites are evaluated, the sites with chlorpyrifos may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to chlorpyrifos, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS CHLORPYRIFOS?

Chlorpyrifos is an organophosphorus insecticide that has been widely used in the home and on the farm. In the home, chlorpyrifos has been used to control cockroaches, fleas, and termites; it has also been an active ingredient in some pet flea and tick collars. On the farm, it is used to control ticks on cattle and as a spray to control crop pests. In 1997, chlorpyrifos was voluntarily withdrawn from most indoor and pet uses by the manufacturer, DowElanco.

1. PUBLIC HEALTH STATEMENT

Chlorpyrifos is a white crystal-like solid with a strong odor. It does not mix well with water, so it is usually mixed with oily liquids before it is applied to crops or animals. It may also be applied to crops in a microencapsulated form. Chlorpyrifos is the active ingredient of various commercial insecticides including Dursban® and Lorsban®. See Chapter 3 for more information on the chemical and physical properties of chlorpyrifos. See Chapter 4 for more information on the production and use of chlorpyrifos.

1.2 WHAT HAPPENS TO CHLORPYRIFOS WHEN IT ENTERS THE ENVIRONMENT?

Chlorpyrifos enters the environment through direct application to crops, lawns, domesticated animals, and in the home and workplace. Chlorpyrifos may also enter the environment through volatilization, spills, and the disposal of chlorpyrifos waste. Chlorpyrifos that has been applied to the soil generally stays in the area where it has been applied because it sticks tightly to soil particles. Because of this, there is a low chance that chlorpyrifos will be washed off the soil and enter local water systems. Also, since it does not mix well with water, if it does get into the natural waters, it will be in small amounts and will remain on or near the surface and will evaporate. Volatilization is the major way in which chlorpyrifos disperses after it has been applied. Once in the environment (soil, air, or water), chlorpyrifos is broken down by sunlight, bacteria, or other chemical processes. Please refer to Chapters 4 and 5 for more information.

1.3 HOW MIGHT I BE EXPOSED TO CHLORPYRIFOS?

You can be exposed to chlorpyrifos in many places because of its wide range of uses. You can be exposed to it in your home or office if chlorpyrifos has recently been used to control household pests such as fleas or cockroaches. Exposure can also occur outside your home if chlorpyrifos has been applied to the ground around the foundation to control termites. Chlorpyrifos degrades rapidly in the environment; however, low levels may persist for long

periods of time after it has been applied either inside or outside the home. Opening windows before and after chlorpyrifos spraying rapidly lowers airborne levels in a house.

You can also be exposed to chlorpyrifos in a farm setting. The greatest risk occurs soon after a crop has been sprayed, because that is when its levels will be the highest. However, chlorpyrifos rapidly degrades and becomes bound to plants and the ground. The EPA recommends a 24-hour waiting period before entering fields where chlorpyrifos has been applied. In addition, there is the risk of exposure to chlorpyrifos when it is being prepared for use. Care should be taken to ensure that only a licensed applicator sprays chlorpyrifos, and that unnecessary or unprotected individuals remain away from the site of application during the spraying.

Chlorpyrifos can also be found at some waste disposal sites, so exposure to higher levels than what is commonly found after home or commercial use may occur there.

1.4 HOW CAN CHLORPYRIFOS ENTER AND LEAVE MY BODY?

Chlorpyrifos can enter your body through your mouth, lungs, and skin. After being eaten or drunk, chlorpyrifos quickly passes from the intestines to the bloodstream, where it is distributed to the rest of the body. It can also enter the body through the lungs by breathing chlorpyrifos sprays or dust. When chlorpyrifos enters the body this way, it passes quickly into the blood. It may also enter your body through the skin, but the chances of being exposed to harmful levels of chlorpyrifos this way are not as great as with inhalation and oral exposure, because the amount that gets through the skin is relatively small (less than 3% of what was put on the skin). Dermal exposure of infants represents a greater health risk than with adults because of the texture of infant skin and because infants laying or crawling on an area sprayed with chlorpyrifos may have a greater amount of their skin exposed to chlorpyrifos. Infants crawling on areas recently sprayed with chlorpyrifos may also be exposed to greater amounts of chlorpyrifos through inhalation of its vapors. For more information, please refer to Chapter 2.

1.5 HOW CAN CHLORPYRIFOS AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical can harm people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

In people, short-term oral exposure (one day) to low (milligrams) levels of chlorpyrifos can cause dizziness, fatigue, runny nose or eyes, salivation, nausea, intestinal discomfort, sweating, and changes in heart rate. Short-term oral exposure to much higher (grams) levels of chlorpyrifos may cause paralysis, seizures, loss of consciousness, and death. Reports in people also show that short-term exposure to chlorpyrifos may cause muscle weakness weeks after the original symptoms have disappeared. Other effects of exposure to chlorpyrifos include changes in behavior or sleeping pattern, mood changes, and effects on the nerves and/or muscles in the limbs (which may appear as odd sensations such as numbness or tingling, or as muscle weakness). The EPA has not classified chlorpyrifos for carcinogenicity (Class D). For more information, please refer to Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CHLORPYRIFOS?

There is a general test that can be performed to determine if you have been exposed to carbamate or organophosphate insecticides. Those types of pesticides inhibit the activity of acetylcholinesterase, the enzyme responsible for inactivating acetylcholine, the compound ultimately responsible for most of the

toxic symptoms seen with chlorpyrifos. The test measures the activity of the enzyme acetylcholinesterase in the blood or a similar enzyme, pseudocholinesterase, in the plasma, or both. If enzyme activity is inhibited, then exposure to an organophosphate or carbamate pesticide is suspected. There is also a biochemical test that can determine if you have been specifically exposed to chlorpyrifos. After chlorpyrifos enters the body, it is changed by the liver into other forms of the compound that may or may not be less toxic than the original material. The major nontoxic chlorpyrifos metabolic product formed by the liver is 3,5,6-trichloro-2-pyridinol, or TCP. TCP is primarily eliminated from the body in the urine and can be detected in the urine using readily available laboratory equipment. The extent of the exposure, length of time after exposure, and the amount of water in the body will affect the level of TCP in the urine. Typically, TCP can be found in the urine for several days after exposure to chlorpyrifos. In addition to chlorpyrifos, TCP is a metabolite of methyl chlorpyrifos and triclopyr. TCP may also be found in the environment, but it is unlikely that urinary levels of TCP result from environmental-TCP exposure. Direct exposure to chlorpyrifos or chlorpyrifos-like compounds is the most likely cause. For more information, please refer to Chapter 2.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations, on the other hand, provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then the levels are adjusted to help protect people.

because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for chlorpyrifos include the following:

- Chlorpyrifos is one of a list of chemicals regulated under "The Emergency Planning and Community Right-to-Know Act of 1986" (EPCRA). This requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report their release of those chemicals to any environmental media annually.

- Chlorpyrifos is designated a hazardous substance and subject to regulations in the Federal Water Pollution Act and the Clean Water Act.

- EPA has established tolerances for chlorpyrifos in raw agricultural commodities, foods, and animal feeds.

See Chapter 7 for specific regulatory values for chlorpyrifos.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: (404) 639-6000
Fax: (404) 639-63 15 or 6324

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles. contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22 161
Phone: (800) 553-6847 or (703) 487-4650

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 exposureinhalation, 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 lowestobserved-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 dys-function. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt

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

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (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.

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 LD_{50} (lethal dose, 50% kill) studies were available.

The LD_{50} for acute-duration inhalation exposure to chlorpyrifos aerosol has been determined for mice and female rats (Berteau and Deen 1978). In mice, an LD_{50} of 94 mg/kg (milligrams per killogram of body weight) was determined after whole-body inhalation exposure to 6,700-7,900 mg/m^3 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/m^3 chlorpyrifos in 65% xylene, and an acute-exposure inhalation LD_{50} 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 LD_{50} 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/m^3 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/m^3 of Pyrenone-Dursban® W.B. Pressurized Spray for 4 hours (Dow 1984).

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-l and Figure 2-l.

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-l 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/m^3. 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

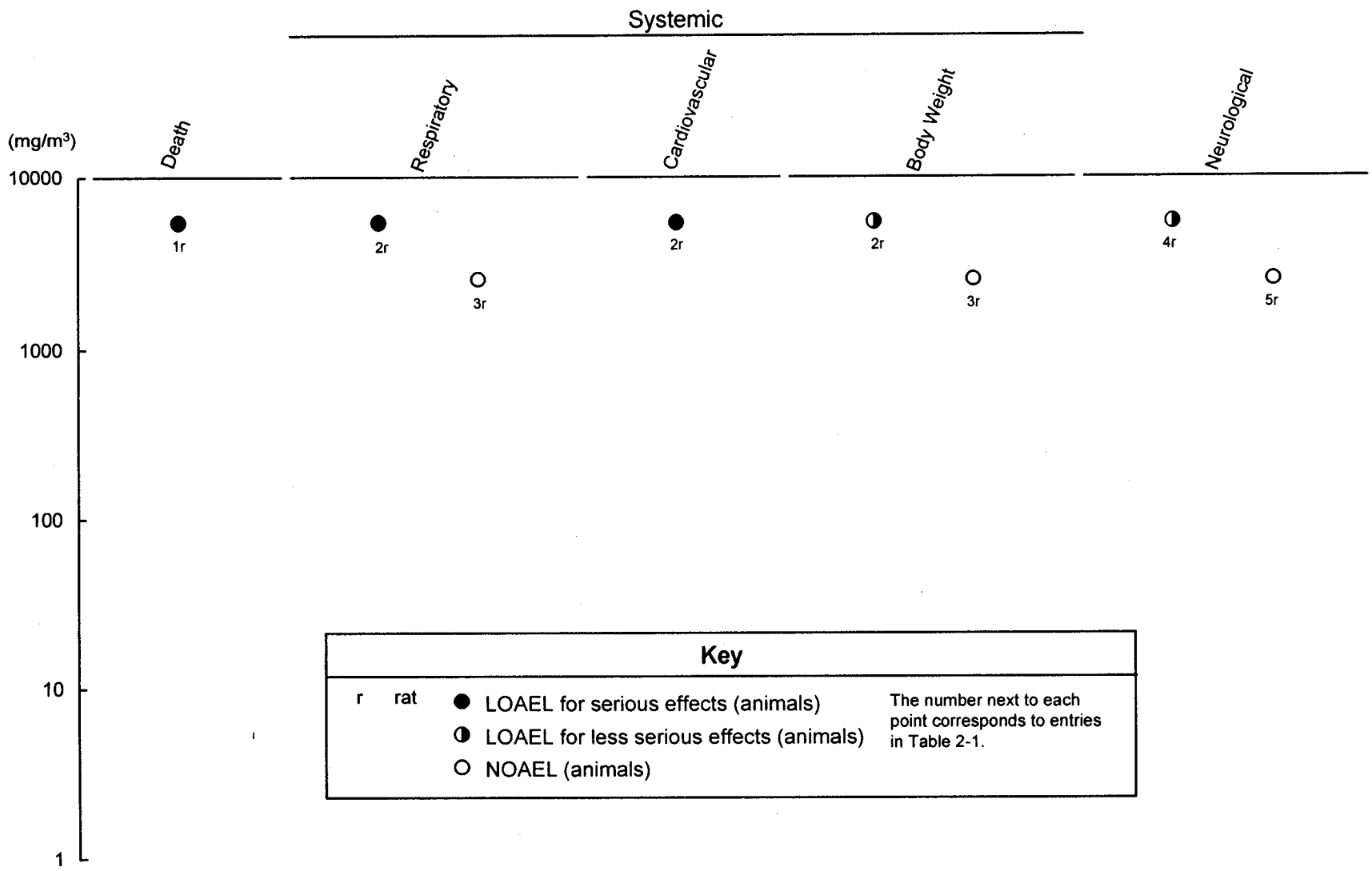
Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)		LOAEL Serious (mg/m3)		Reference
	ACUTE EXPOSURE								
	Death								
1	Rat (Sprague-Dawley)	4 hr					5300	(80% mortality in males, 20% mortality in females)	Dow 1983a
	Systemic								
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

[a]The 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)



exposed to an atmosphere containing 2,500 mg/m^3 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/m^3 chlorpyrifos for 6 hours a day, 5 days a week for 13 weeks. Histopathological evaluation of lungs from the control and 0.295 mg/m^3 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/m^3. 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 lectrocardio gram 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.

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.

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/m^3 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 organophosphorns 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 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/m^3 chlorpyrifos for 6 hours a day, 5 days a week for 13 weeks. Histopathological evaluation of livers from the control and 0.295 mg/m^3 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 chronicduration 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/m^3 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.

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.

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 chronicduration 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® weight were investigated in male and female Sprague-Dawley rats exposed for 4 hours to an atmosphere containing 5,300 mg/m^3 (Dow 1983a). Male rats that survived 2 days postexposure lost 9-l1% 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/m^3 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

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 shortterm 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

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/m^3 (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/m^3 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/m^3 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.

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

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/m^3 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 melunogaster* males (Woodruff et al. 1983). Initial attempts were made to identify an approximate LD_{50} (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 F_1 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 0.717 mg/m^3 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 chronicduration oral exposure.

Acute oral LD_{50} 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 LD_{50} of 82 mg/kg for female Sherman rats and an LD_{50} of 155 mg/kg for males. Similarly, McCollister et al. (1974) reported an LD_{50} of 135 mg/kg for female Dow-Wistar rats and an LD_{50} of 163 mg/kg for males. However, in contrast to this apparent sex effect suggested by Gaines' (1969) data, an LD_{50} of 155 mg/kg was reported for female Sherman rats while the male LD_{50} was 118 mg/kg (McCollister et al. 1974). An LD_{50} of 60 mg/kg has been determined for mice (unspecified gender) (El-Sebae et al. 1978). In male guinea pigs, an oral LD_{50} 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, LD_{50} 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

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 LD_{50} 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	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	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	3 F	15 F (porphyrin deposits)		Breslin et al. 1996
			Bd Wt	3 F		15 F (44% decreased body weight gain on Gd 12-16)	
7	Rat (Long- Evans)	once (GO)	Bd Wt	50 M	100 M (13.3% decreased body weight)		Moser 1995
			Metab	20 M	50 M (hypothermia)		
8	Mouse (CF-1)	Gd 6-15 1x/d (GO)	Hepatic	25 F			Deacon et al. 1980
			Bd Wt	10 F	25 F (14% mean body weight gain decrease Gd 6-17)		

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 Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
9	Mouse (CF-1)	Gd 6-15 1x/d (GO)	Hepatic	10 F			Deacon et al. 1980
			Bd Wt	10 F			
	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)			20 M (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 Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
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 Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	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 Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
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 Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
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 Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	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 Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
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)		0.1 M	1.0 M (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	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
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

[a]The number corresponds to entries in Figure 2-2.

[b]Used 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.

[c]Used to derive an intermediate oral MRL of 0.003 mg/kg/day; dose divided by an uncertainty factor of 10 for human variability.

[d]Used 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; LD_{50} = 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)

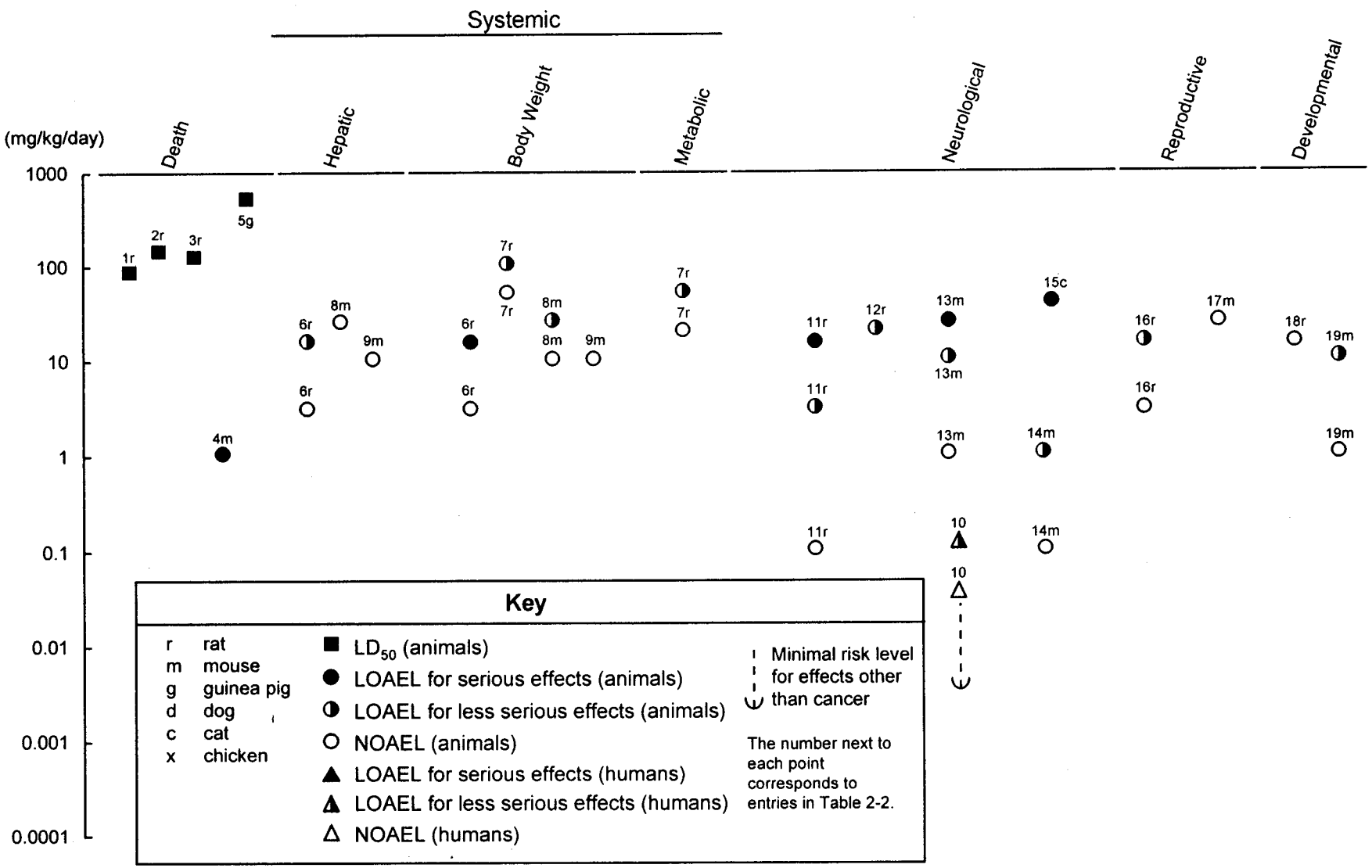


Figure 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (cont.)

Intermediate (15-364 days)

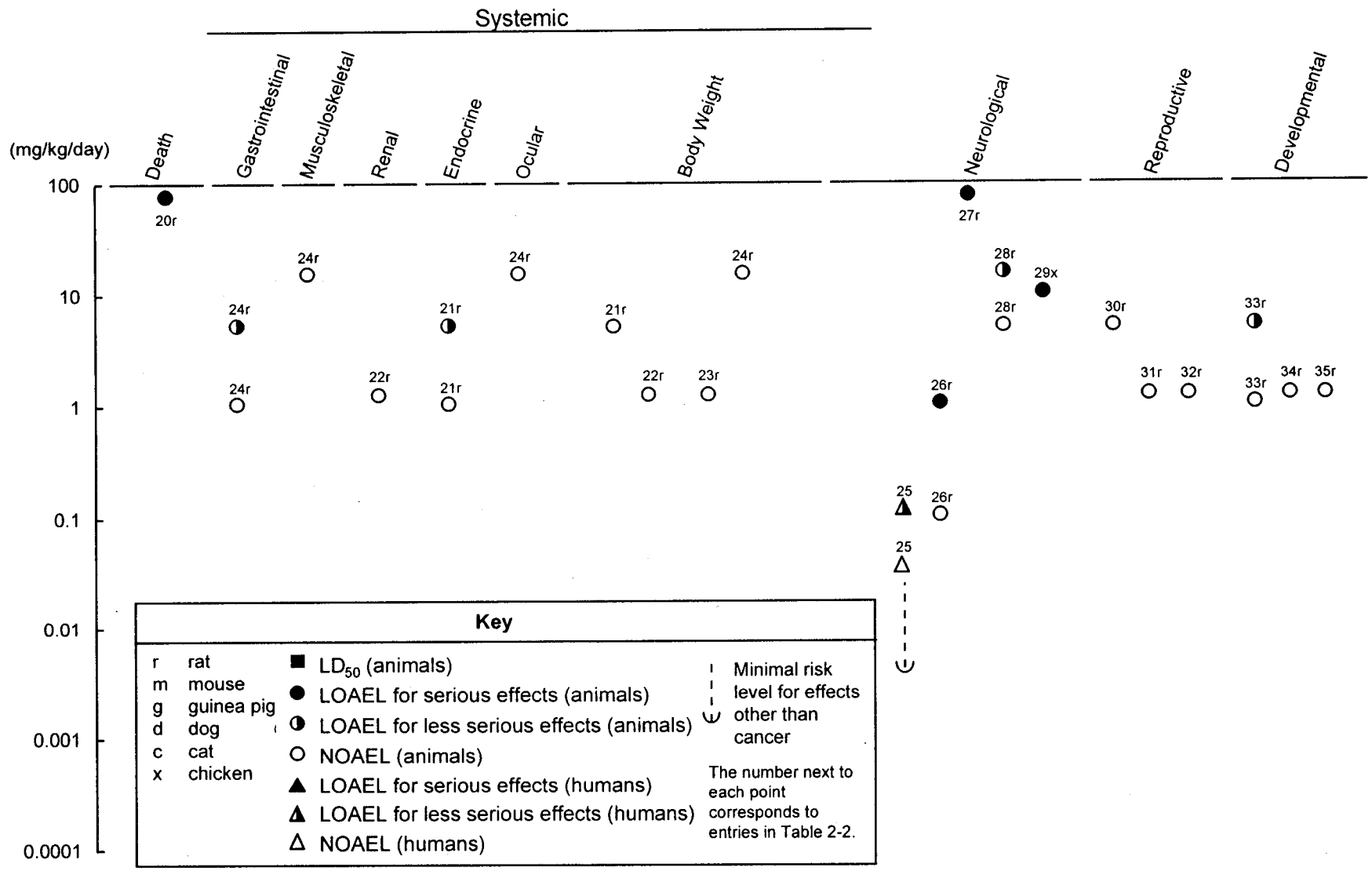
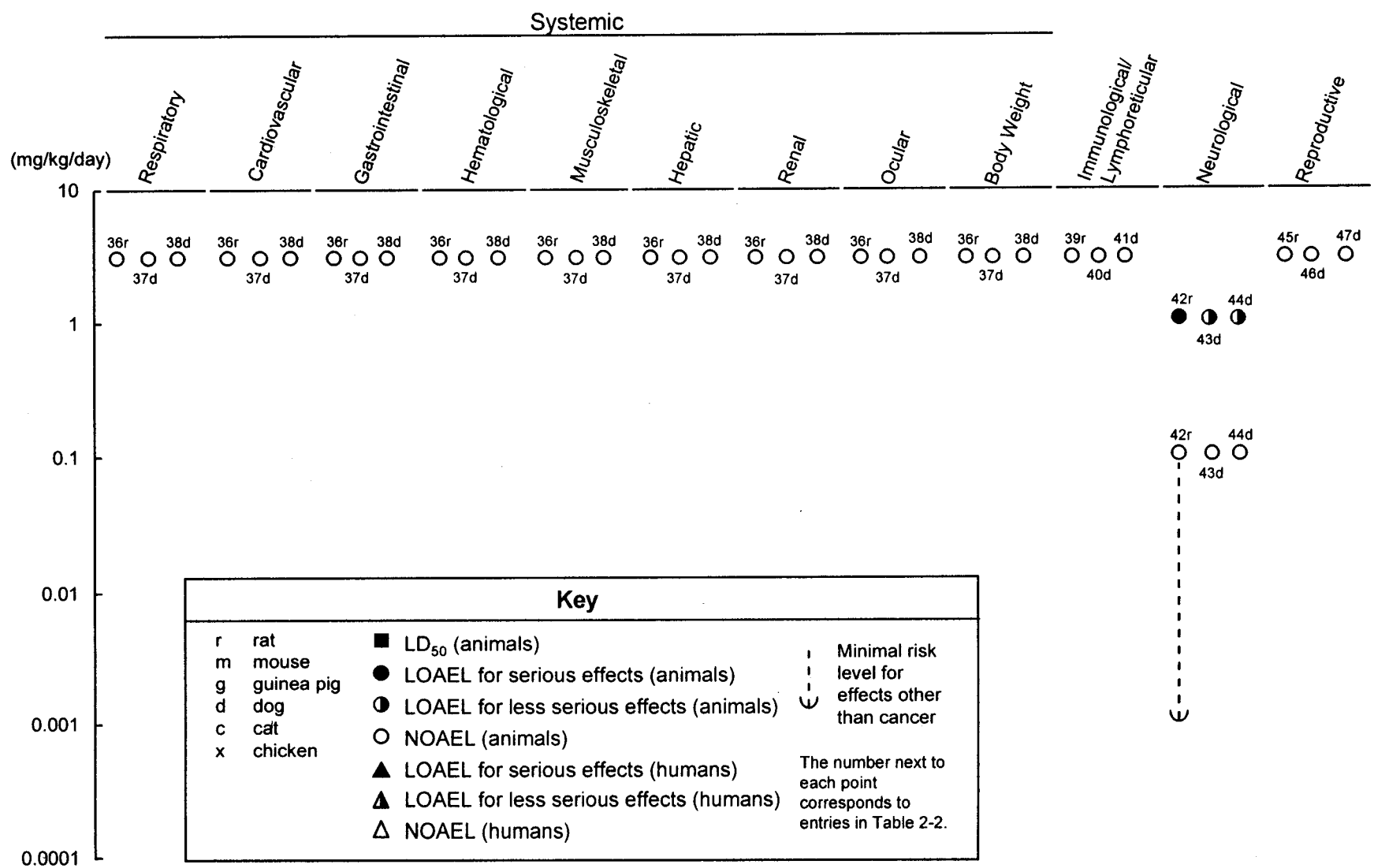


Figure 2-2. Levels of Significant Exposure to Chlorpyrifos - Oral (cont.)

Chronic (≥365 days)



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 chronicduration 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

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 l-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

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).

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 l-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 fasiculata 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

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 mgikg/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 lo-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).

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). I n 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 mgtkglday 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 l-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)

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 treatmentrelated histopathological changes in thymus, spleen, mesenteric lymph node, or bone marrow in any of the F_0 or F_1 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 l-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, acuteduration oral exposure to undetermined amounts of chlorpyrifos has been reported to inhibit both erythrocyte and plasma cholinester ase 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 chronicduration 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

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 4344%. 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 un-determined 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

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.

(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. 19931 and a 5-year-old girl [Selden and Curry 19871) 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). Chronicduration 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 mgfkglday 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.

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 lo-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 l-2 years (McCollister et al. 1974).

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 softtissue 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 stemebrae (2.1-fold increase), and unfused stemebrae (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

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-l1% 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 LD_{30} 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 F_1 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

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 l-2 years had no increased incidence of tumors compared to controls (McCollister et al. 1974).

2.2.3 Dermal Exposure

2.2.3.1 Death

No information was found concerning death in humans following acute-, intermediate-, or chronicduration 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 l-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 in 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; LD_{50} = lowest dose, 50% kill; M = male; NOAEL = no-observable-adverse-effect level; NS = not specified; wk = week(s)

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

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 chronicduration 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 l-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 intermediateor chronic-duration dermal exposure to chlorpyrifos.

Musculoskeletal Effects. Musculoskeletal effects have been observed in humans following acuteand 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 chronicduration 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.

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.

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 acuteduration 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 acuteor chronic-duration dermal exposure to chlorpyrifos.

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

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 erythematous 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

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 chronicduration 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

l-3 hours after births showed a 55--67% inhibition in activity. Blood acetylcholinesterase activity determined in piglets 12-17 hours after exposure displayed 8l-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 chlorpyrifes in humans or animals following acute-, intermediate-, or chronic-duration dermal exposure.

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

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

(Bakke et al. 1976; Smith et al. 1967) and mice (Ahdaya et al. 19Sl), nearly 90% of the administered dose of ^{14}C-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 dosedependent, 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.

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 l0-16 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 (<0.0l-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 (Clabom 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

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).

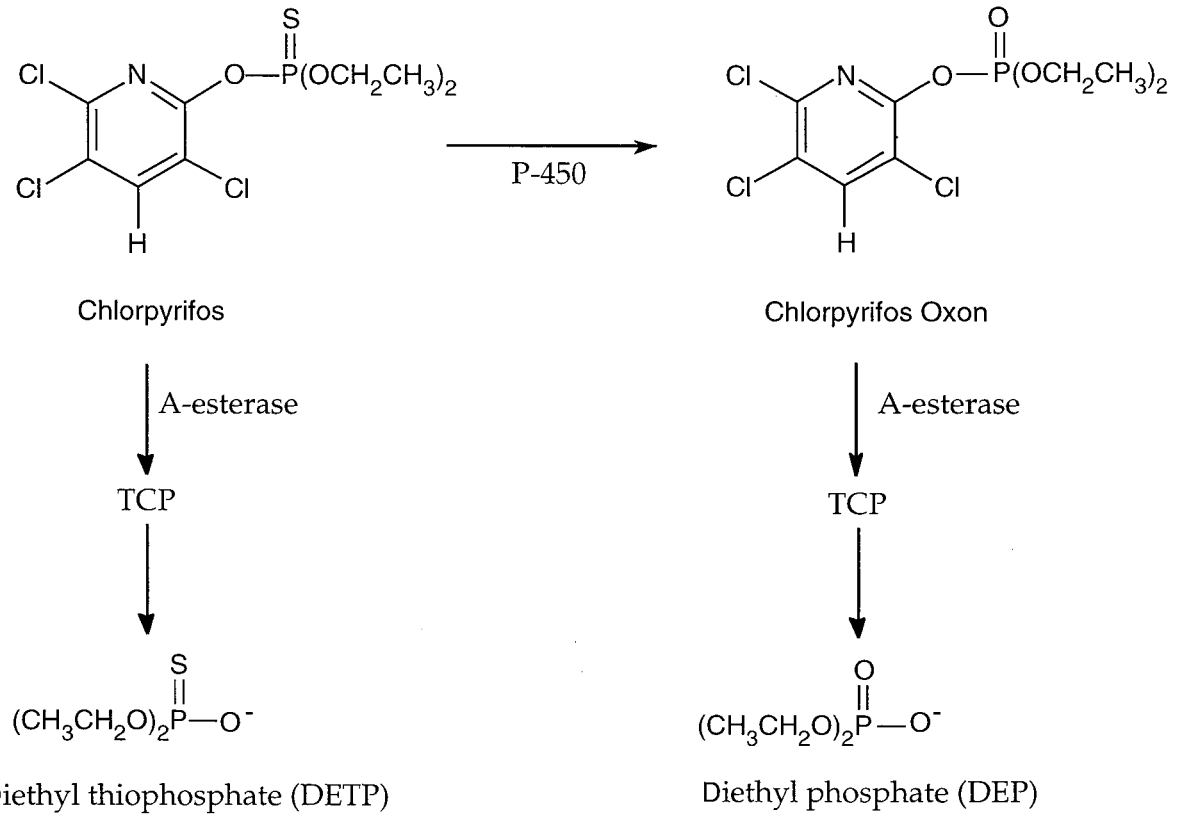
2.3.3 Metabolism

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.

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



Adapted from Drevenkar et al. 1993

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 ^{14}C-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 (halflife 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

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 t he chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these

differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

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

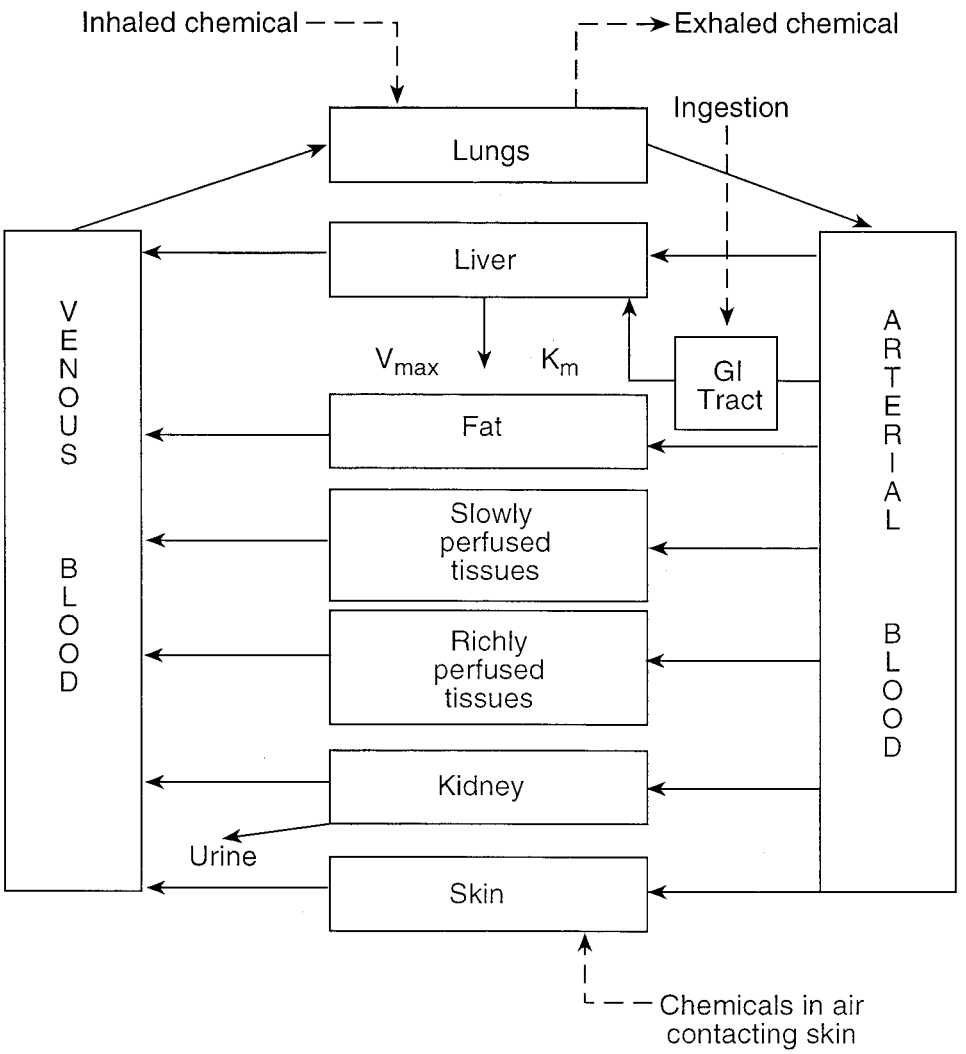
No PBPK information was found for chlorpyrifos.

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.

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.

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 Marts 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 Marts 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.

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 acuteduration, 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

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 intermediateduration 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

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.

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

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 CO_2), 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 stemebrae, and unfused stemebrae 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

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 stemebrae and an decreased incidence of fused stemebrae 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 LD_{50} for acute-duration inhalation exposure to chlorpyrifos was determined for mice and female rats (Berteau and Deen 1978). In mice, an LD_{50} of 94 mg/kg was determined after whole-

body inhalation exposure to 6,700-7,900 mg/m^3 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/m^3 chlorpyrifos in 65% xylene, and an acuteduration exposure inhalation LD_{50} of 78 mg/kg was determined by varying the exposure duration from 48 to 61 minutes. The acute-duration oral exposure LD_{50} 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 LD_{50} 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.

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 lo-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.

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-l ,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

in which the symptoms arose l-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 erythematous 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 acuteduration 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 acuteduration oral exposure to chlorpyrifos during pregnancy (Deacon et al. 1980). However, decreased

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 stemebrae (2.1-fold increase), and unfused stemebrae (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 chlorpyrifosinduced 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 *(Drosophila melanogaster)* germ cells	Complete chromosome loss	+	Woodruff et al. 1983
Fly *(Drosophila melanogaster)* germ cells	Partial chromosome loss	–	Woodruff et al. 1983
Fly *(Drosophila)* somatic and germ cells	Induction of mosaic wing spots	+	Patnaik and Tripathy 1992
Fly *(Drosophila)* 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

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 metabolitets), 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

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.

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

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 bronchochronstriction 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

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-l 18.
- 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-l 119.
- 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

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

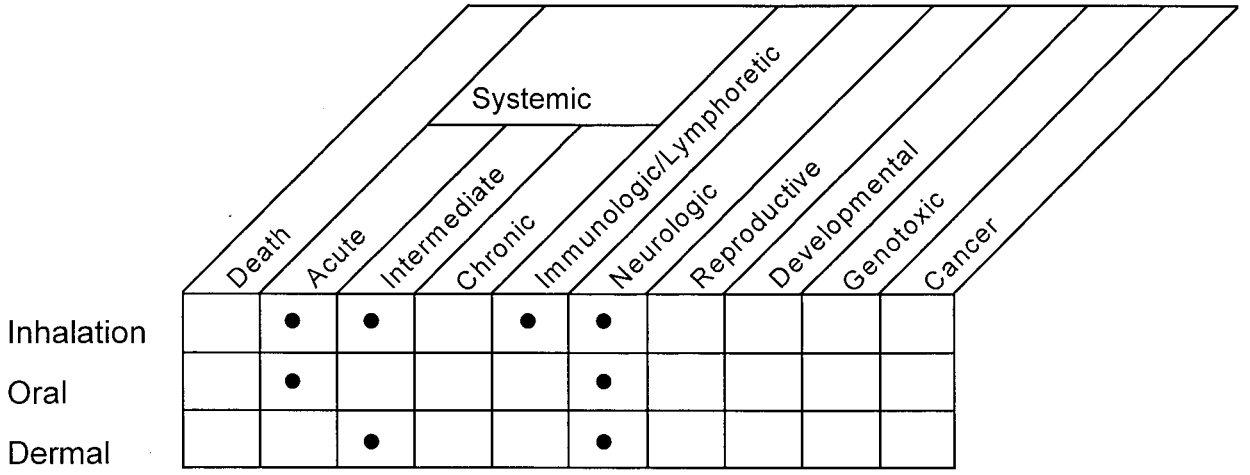
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chlorpyrifos is available. Where adequate information is not 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.

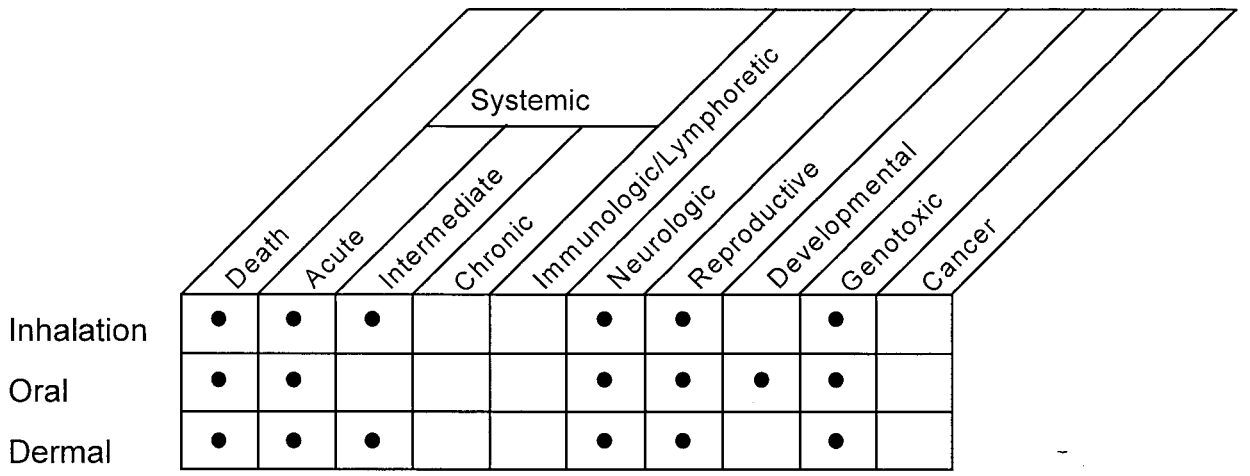
2.10.1 Existing Information on Health Effects of Chlorpyrifos

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



Human



Animal

- ● Existing Studies

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

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 intermediateduration 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 recessivelethals 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

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 615 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

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

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 form 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.

3. CHEMICAL AND PHYSICAL INFORMATION

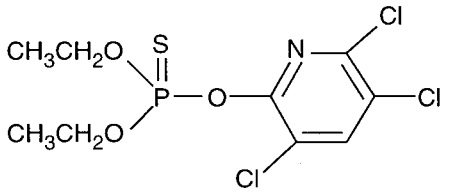
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of chlorpyrifos is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of chlorpyrifos is located in Table 3-2.

Table 3-1. Chemical Identity of Chlorpyrifos

Characteristic	Information	Reference
Chemical name	O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate	Merck 1989
Synonym(s)	Phosphorothioic acid O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl) ester; chlorpyrifos-ethyl; chlorpyriphos	Merck 1989
Registered trade name(s)	Dowco 179; ENT 27311; Dursban; Lorsban; Pyrinex; DMS-0971	Merck 1989
Chemical formula	$C_9H_{11}Cl_3NO_3PS$	Merck 1989
Chemical structure		Merck 1989
Identification numbers:		
CAS Registry	2921–88–2	Merck 1989
NIOSH RTECS	TF6300000	HSDB 1994
EPA Hazardous Waste	059101	HSDB 1994
OHM/TADS	7800025	HSDB 1994
DOT/UN/NA/IMCO	NA 2783 Chlorpyrifos	HSDB 1994
HSDB	389	HSDB 1994
NCI	No data	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-2. Physical and Chemical Properties of Chlorpyrifos

Property	Information	Reference
Molecular weight	350.57	Merck 1989
Color	White granular crystals White to tan Amber solid cake with amber oil Colorless crystals	Merck 1989 EPA 1988 Verschueren 1983 Worthing 1987
Physical state	Crystalline solid	EPA 1988
Melting point	41–42 °C	Merck 1989
Boiling point	Decomposes at approximately 160 °C	Verschueren 1983
Density at 43.5 °C	1.398 g/cm^3	Verschueren 1983
Odor	Mild mercaptan	EPA 1988
Odor threshold: Water Air	 No data No data	
Solubility: Water at 20 °C Water at 25 °C	 0.7 mg/L 2 mg/L	 Bowman 1983 Merck 1989
Organic solvent(s)	79% w/w in isooctane 43% w/w in methanol Readily soluble in other organic solvents	Merck 1989
Partition coefficients: Log K_{ow} Log K_{oc}	 4.82 3.73	 McCall et al. 1980
Vapor pressure at 20 °C Vapor pressure at 25 °C	1.87x10^{-5} mm Hg 1.87x10^{-5} mm Hg	Verschueren 1983 Merck 1989
Henry's law constant: at 25 °C	1.23x10^{-5} atm-m^3/mol	HSDB 1995
Autoignition temperature	No data	
Flashpoint	None	EPA 1988b
Flammability limits at 25 °C	No data	
Conversion factors (25 °C)	1 ppm=14.3 mg/m^3 1 mg/m^3=0.070 ppm	
Explosive limits	No data	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Chlorpyrifos is prepared commercially by several methods (Rigterink 1966). In a preferred method, the final step in the synthesis is reacting 3,5,6-trichloro-2-pyridinol (TCP) and O,O-diethylphosphorochloridothioate under basic conditions in dimethylformamide (Sittig 1985). Chlorpyrifos was introduced in 1965 by Dow Chemical Company under the protection of U.S. Patent 3,244,586. It is produced under many trade names including Brodan®, Detmol UA®Dowco 179®, Dursban®, Empire®, Equity®, Eradex®, Lentrek®, Lock-On®, Lorsbanv®, Pageant®, Piridane®, and Stipend® Producers of chlorpyrifos in the United States are DowElanco in Midland, Michigan and Lafayette, Indiana, and SureCo, Inc. in Fort Valley, Georgia (SRI 1994). Production volumes have not been located.

No information is available in the Toxics Release Inventory (TRI) database on total environmental releases of chlorpyrifos from production facilities, because chlorpyrifos is not included under SARA, Title III, and, therefore, is not one of the chemicals that facilities are required to report (EPA 1993c).

4.2 IMPORT/EXPORT

Information on import/export volumes was not located.

4.3 USE

Chlorpyrifos is a broad spectrum organophosphate insecticide/acaricide which is used to control a variety of insects. First introduced into the non-crop specialty market, it was marketed in the late 1960s to control pests in turfgrass and omamentals, and to control indoor pests. Chlorpyrifos was first registered for termiticide use in the United States in 1980 (Racke 1993). Products are available for both professional pest control workers and homeowners. Agricultural commercial products were introduced in the mid-1970s. As a foliar pesticide for alfalfa and cotton, it is used to control aphids, armyworms, pillbugs, chinch bugs, common stalk borers, corn borers, corn earworm, corn rootworm adults, cutworms, flea beetle adults, grasshoppers, and lesser cornstalk borers. It also controls peach tree borer and overwinter scale on dormant fruit trees and is used as a slurry seed treatment for seed

corn maggot. It has additional uses as a foliar and soil applicant on sorghum, soybeans, sugarbeets, and sunflowers, and as a soil applicant for peanuts. Dursban® is used to control fire ants, ornamental plant insects, stored-product insects, and turf- and wood-destroying insects. Lorsban® is used as a soil insecticide for pillbugs, corn rootworms, cutworms, flea beetle larvae, grubs, lesser cornstalk. borer, seed corn beetle, seed corn maggot, symphylan, and wireworm on corn (Farm Chemicals Handbook 1994). At one time, it was used to kill mosquitoes in the immature, larval stage of development, a use that involved application of formulated product directly to bodies of water, but hlorpyrifos is no longer registered for this purpose (EPA 1986). Other discontinued uses are spray-dip or pour-on applications of chlorpyrifos for cattle and sheep (Racke 1993).

Formulations for chlorpyrifos include emulsifiable concentrate, dust, flowable, granular wettable powder, microcapsule, pellet, and spray. Chlorpyrifos acts on pests primarily as a contact poison, with some action as a stomach poison. It is a nonsystemic contact chemical, meaning that it acts only where it comes into direct contact with plant tissues, and is not transported to other plant parts. It interferes with the activity of acetylcholinesterase, an enzyme that is essential for the proper working of the nervous systems of both humans and insects.

There is currently no federal requirement to report sales or use of pesticides; consequently, the only figures available are estimates (Felsot 1991). From data collected from usage surveys conducted by USDA, EPA, and the Department of Food and Agriculture of the State of California, the usage of chlorpyrifos is estimated to be 7,023,190 pounds active ingredient per year (Gianessi 1986). Agricultural uses account for most of its applications. In 1982, total agricultural use of chlorpyrifos was estimated at 2.2-3.2 million kg (4.8-7.0 million pounds), and industrial uses ranged between 0.68 and 1.04 million kg (1.5-2.3 million pounds) (EPA 1982). The State of Ohio Agricultural Extension Service estimates that 36.33 metric tons (80,093 pounds) of chlorpyrifos were used in the Lake Erie Basin in 1986 (Baker and Richards 1988). In 1984, about 0.15 million kg (0.33 million pounds) of chlorpyrifos was applied to about 600,000 hectares (1.48 million acres) of wetlands in the United States for mosquito control (Odenkirchen and Eisler 1988); this use has since been discontinued.

Chlorpyrifos is used significantly in urban settings, where it has replaced chlordane and other chlorinated cyclodiene termiticides. Therefore, its use can be estimated based on former chlordane use; the annual application of chlorpyrifos for termite control is estimated at approximately 1.7 million

pounds of active ingredient (Cink and Coats 1993). Each year, the pesticides used to control structural pests account for about 15% of California's nonagricultural use of conventional pesticides. Structural pest control encompasses treatment of private residences, office buildings, schools, hotels, hospitals, restaurants, and other publicly used buildings. In 1990, 604,713 pounds of chlorpyrifos were used as structural pesticides in California, and 693,354 pounds were used in 1991 (Robinson et al. 1994). Pesticides for commercial landscape maintenance account for about 2% of nonagricultural use in California. The landscaping use figures for chlorpyrifos in 1990 and 1991 were 45,267 pounds and 32,118 pounds, respectively. Nationally, chlorpyrifos is ranked twelfth in frequency of indoor pesticide applications and fifth in frequency of outdoor pesticide applications (Robinson et al. 1994).

4.4 DISPOSAL

The recommended treatment and disposal methods for chlorpyrifos are incineration, adsorption, and landfilling (IRPTC 1989). For small amounts, the recommended disposal is adsorption onto materials such as sand and burying in locations away from domestic water supplies. For the decontamination of containers, the triple rinse and drain procedure is recommended. The use of a caustic soda-methanol or caustic soda-detergent rinse solution is also effective in decontaminating the container, but the rinse solutions must be disposed of either by incineration or burial in an area away from water supplies (IRPTC 1989).

Small-scale farm operators have a pressing need for methods to dispose of unused concentrated and dilute formulated chlorpyrifos suspensions or solutions such as rinsate. The use of solid state fermentation techniques to dispose of pesticide waste may be a viable alternative to other disposalmethods that are either too expensive or technically too sophisticated. Chlorpyrifos was evaluated in bioreactors by Berry et al. (1993), who reported that chlorpyrifos levels were reduced to 0.6% (by solvent extraction) in 290 days in wheat straw/horse manure reactors, and that leachability studies showed that of the 28 µg chlorpyrifos in the soil column, only 72 ng leached.

While not strictly a disposal method, it is worth pointing out that NaOH-methanol and sodium hypochlorite can be used to degrade (but not necessarily detoxify) chlorpyrifos. For example, on exposed surfaces, the use of caustic soda-methanol or caustic soda-detergent rinse solution can also be effective in decontaminating containers used to store chlorpyrifos, but these rinse solutions must be

disposed of either by incineration or proper burial (Dillon 1981). A full discussion of regulations regarding disposal of chlorpyrifos is given in Chapter 7.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chlorpyrifos enters the environment as the result of its use as a broad spectrum insecticide/acaricide for treatment of crops, lawns, ornamental plants, domestic animals, and a variety of building structures. Unintentional releases to the environment include improper indoor application, redeposition of air residues, spills, and the disposal of chlorpyrifos wastes. Indoor use by unlicensed or untrained applicators has occasionally resulted in excessive human exposure. EPA (1997) reported that most of the more serious chlorpyrifos poisonings appear to involve either the misuse or inappropriate use of the pesticide by pest control operators.

The important physical and chemical characteristics which influence the fate and transport of chlorpyrifos in the environment are its low solubility, volatility, and strong affinity for colloidal matter. Abiotic hydrolysis, photodegradation, and biodegradation are all important processes for the transformation and degradation of chlorpyrifos. Chlorpyrifos bioconcentrates to only a limited extent, and has little mobility in most soils. Chlorpyrifos exists in the atmosphere primarily in the vapor phase, but can partition to particulates. Chlorpyrifos is not persistent in water, due to volatilization and strong adsorption to particulate matter.

Indoor air, food, and soil are the environmental media with the highest degree of chlorpyrifos contamination; ambient air, groundwater, and surface water have lesser degrees of contamination. Although a large amount of chlorpyrifos is used in various environments (see Chapter 4), levels of general exposure are mediated by its limited mobility and persistence, and by environmental degradation processes.

Several subpopulations are at higher risk of exposure: workers in industries that manufacture and formulate chlorpyrifos, those who apply the insecticide, and farm workers who enter treated fields after the insecticide has been applied. Among the general population, people who use the insecticide in homes and gardens and people who ingest food exposed to chlorpyrifos are at higher risks of exposure.

Chlorpyrifos has been identified in at least 7 of the 1,428 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1996). However, the number of sites evaluated for chlorpyrifos is not known. The frequency of these sites within the United States can be seen in Figure 5- 1.

5.2 RELEASES TO THE ENVIRONMENT

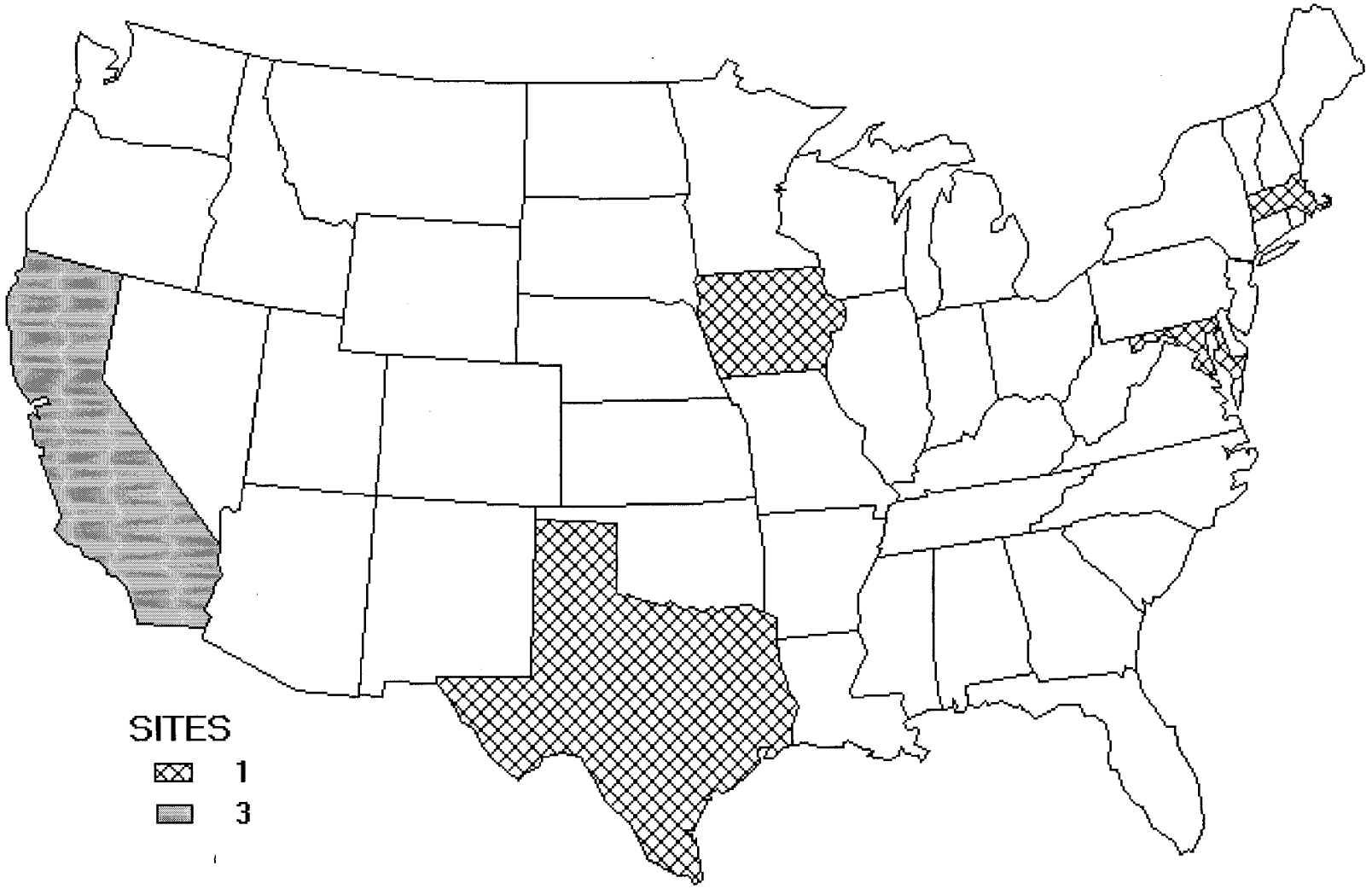
5.2.1 Air

Chlorpyrifos enters the atmosphere as a result of its use as an insecticide/acaricide. Chlorpyrifos is released to the atmosphere by volatilization during foliage or soil application by ground or air broadcast equipment (Racke 1993). Air emissions from chlorpyrifos production have been reported to be 0.5 kg per 1,000 kg (one metric ton) produced (Sittig 1980). The Toxics Release Inventory in 1992 did not require reporting of chlorpyrifos releases to air (EPA 1993c). No information was found on detections of chlorpyrifos in air at NPL hazardous waste sites (HazDat 199).

5.2.2 Water

Chlorpyrifos is released to water during foliage or soil application as an insecticide/acaricide by ground or air broadcast equipment and during subsequent runoff or leaching (Racke 1993). Leaching and runoff from treated fields, pesticide disposal pits, or hazardous waste sites may inadvertently contaminate both groundwater and surface water with chlorpyrifos. Entry into water can also occur from accidental spills, redeposition of atmospheric chlorpyrifos, and discharge of waste water from chlorpyrifos manufacturing, formulation, and packaging facilities (HSDB 1996; Racke 1993). In the past, chlorpyrifos was aerially applied to water over swamps for mosquito abatement; however, it is no longer registered for this use. No other uses are known which result in direct application to water (EPA 1986). The Toxics Release Inventory in 1992 did not require reporting of chlorpyrifos releases to water (EPA 1993c). There is also a potential for release of chlorpyrifos to water from hazardous waste sites. Chlorpyrifos has been detected in surface water samples collected at 4 of the 7 NPL sites and in groundwater samples collected at 1 of the 7 NPL sites where chlorpyrifos has been detected in some environmental medium (HazDat 1996). The HazDat information used includes data from NPL sites only.

Figure 5-1. Frequency of NPL Sites with Chlorpyrifos Contamination



Derived from HazDat 1996

5.2.3 Soil

Chlorpyrifos is released in agricultural, home, and garden soil during direct soil or foliar treatment, and from disposal of chlorpyrifos-containing wastes in hazardous waste sites (HSDB 1994). Much of the chlorpyrifos (or its metabolites) applied to foliage eventually reaches soil (Racke 1993). Soil in waste disposal sites may include manufacturing wastes containing chlorpyrifos. A primary method for disposing of liquid pesticide wastes has been the dumping of liquid materials into soil evaporation pits, ditches, and ponds. Topsoil from such discharge areas is expected to be contaminated with pesticides; the soil from one discharge pit contained chlorpyrifos at concentrations of 1,012-3,193 mg/L in the top 7.5 cm (Winterlin et al. 1989). Soil from tail water pits used for collecting irrigation runoff may also be a source of chlorpyrifos if the soil is treated with this insecticide (Kadoum and Mock 1978). Chlorpyrifos may also enter soil by redeposition of atmospheric chlorpyrifos (Racke 1992). Entry may also occur from spills during storage, transport, or equipment loading and cleaning, although the sophistication of contemporary management practices limits this amount. The Toxics Release Inventory in 1992 did not require reporting of chlorpyrifos releases to soils (EPA 1993c). Chlorpyrifos also can be released to soils and sediments from hazardous waste sites. Chlorpyrifos has been detected in soil samples collected at 3 of the 7 NPL sites and in sediment samples collected at 1 of the 7 NPL sites where chlorpyrifos has been detected in some environmental medium (HazDat 1996). The HazDat information used includes data from NPL sites only.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The vapor pressure of chlorpyrifos is 1.9×10^{-5} mm Hg at 25 °C (2.5×10^{-8} atm) (Racke 1993). This suggests that while chlorpyrifos is in the atmosphere, it will exist primarily in the vapor phase but will also partition to available airborne particulate (Eisenreich et al. 1981). Experimental evidence during fog events (Glotfelty et al. 1990) supports this hypothesis. The removal rate by dry deposition is low for such compounds (Schroeder and Lane 1988); therefore, depending on its reactivity characteristics and the amount of available airborne particulate, chlorpyrifos may travel long distances in the air. The low solubility of chlorpyrifos at 1.12 mg/L at 24 °C (Felsot and Dahm 1979) indicates that dry deposition is a more important process than wet deposition.

The transport of chlorpyrifos from water to air can occur due to volatilization. Compounds with a Henry's law constant (H) of $<10^{-5}$ atm-m^3/mol may volatilize slowly from water (Lyman et al. 1990). Therefore, chlorpyrifos, with an H value of $6.6x10^{-6}$ atm-m3/mol at 25 °C (Downey 1987) may volatilize slowly from water. The dimensionless Henry's law constant (H′) or air/water partition coefficient for chlorpyrifos, as calculated from vapor pressure and solubility data, has been reported to be $5x10^{-4}$ (Glotfelty et al. 1987), $7.3x10^{-4}$ (Suntio et al. 1987), and $1.7 \pm 0.3x10^{-4}$ (Fendinger and Glotfelty 1990). Using these data, the estimated volatilization half-life from a river 1 meter deep flowing 1 m/set with a wind velocity of 3 m/sec is estimated to be 9 days (Lyman et al. 1982).

The amount of chlorpyrifos available to be volatilized from surface water is reduced by sediment adsorption. Chlorpyrifos has a strong affinity for soil colloids, as evidenced by its measured range of organic carbon-adjusted soil sorption coefficient (K_{oc}) of 973-31,000 (Felsot and Dahm 1979; Kenaga 1980; McCall et al. 1980; Racke 1993). This suggests that chlorpyrifos in natural water ecosystems adsorbs strongly to suspended solids and sediments, and that this process may transport considerable amounts of chlorpyrifos from water to particulate matter. Several studies have reported very low concentrations of chlorpyrifos in surface waters (see Section 5.4.2).

In macrophyte-dominated freshwater model ecosystems, *Elodea nutalli* vegetation adsorbed a large proportion of the dose of chlorpyrifos applied and hampered mixing of the insecticide in the water column (Brock et al. 1992). Only a relatively small proportion of the applied dose became incorporated in the sediment. In open-water model ecosystems, however, mixing was rapid and the sediment compartment, particularly its upper layer, was a sink for chlorpyrifos.

Aquatic bioconcentration factors (BCF) ranging from 1 to 5,100 for chlorpyrifos and metabolites have been determined extensively from laboratory and field studies (ASTER 1996; Cid Montafies et al. 1995; Macek et al. 1972; Mulla et al. 1973; Odenkirchen and Eisler 1988; Racke 1993). These studies suggest that chlorpyrifos bioconcentrates to varying degrees in different organisms, and with different doses and durations of exposure. It has been suggested that the BCF values determined-during short duration single-dose exposure studies may not be indicative of long-term exposure due to nonattainment of equilibrium conditions (Racke 1993). It has been observed that 5-9 days are necessary for steady-state conditions (Hedlund 1973; Welling and deVries 1992).

5. POTENTIAL FOR HUMAN EXPOSURE

The transport processes that may move chlorpyrifos from soil to other media are volatilization, leaching, runoff, and biotransfer by plants. Post-application volatilization of chlorpyrifos applied as an agricultural insecticide and subsequent atmospheric transport is thought to be a primary means by which chlorpyrifos is dispersed throughout the environment. Volatilization is affected by soil cultivation practices. Cumulative losses of chlorpyrifos by volatilization from no-till (NT) and from conventionally tilled (CT) plots were measured by Whang et al. (1993). The NT/CT flux ratio increased from a factor of about 3 on days 1 and 2 to a factor of 12 by day 26. Soil dryness did not often limit volatilization, and differences in soil moisture resulting from different tillage practices were not usually a major reason for differences between fluxes.

Volatilization rates, which result from the complex interplay between chlorpyrifos sorbed to soil, dissolved in the soil pore water, and present in the soil air spaces, can be quite variable. Chlorpyrifos (applied to the soil at 11 $\mu g/cm^2$) was captured from 3 moist soils (0.3 bar soil moisture tension, 25 °C) by blowing an airstream of 1 km/hour over the soils. The calculated flux rate ranged from 80-290 g/hectare/day during the first 3 days, with 62-89% of applied chlorpyrifos remaining after 36 hours (McCall et al. 1985). Racke et al. (1991) observed significantly less volatility over a longer exposure period with ranges of 3-39 g/hectare/day, and >90% of the applied chlorpyrifos remaining after 30 days. When applied as a foliar spray, chlorpyrifos volatilized from corn leaves rapidly. In the laboratory, 80% volatilized within 48 hours at 30 °C with a simulated wind speed of 0.8 km/hour (McCall et al. 1985). A field study confirmed the fairly rapid rate of volatilization, with an observed half-life of about 1.5 days on corn and soybean foliage (McCall et al. 1984).

Leaching studies have shown chlorpyrifos to have little mobility in soil. Laboratory leaching studies revealed that all the surface-applied residues of chlorpyrifos were confined to the upper 5 cm of several soils after elution with 20 cm of water (Harris et al. 1988; McCall et al. 1985). Field studies have confirmed this lack of mobility, with chlorpyrifos residues being confined to the upper 12 inches of soils in several trials (Fontaine and Teeter 1987; Oliver et al. 1987). The leaching and dissipation of the applied ^{14}C-chlorpyrifos in sandy soil under simulated field precipitation, drainage and temperature was less than 0.2% (Fermanich and Daniel 1991). Amounts of chlorpyrifos lethal to termites moved to a depth of at least 30 cm in decomposed granite soil from the Santa Ana River bed in Colton, California, after it was applied at 500 ppm to the top 7.62 cm of soil in a long column of 34 mm diameter and ≈130 mL of water was dripped through (Smith and Rust 1992).

Studies indicate that runoff of chlorpyrifos is of minor environmental significance. In a study conducted in an Iowa cornfield, approximately 0.003% of 3 applications of chlorpyrifos was transported via runoff to a pond within the watershed (McCall et al. 1984). Information from irrigated environments (e.g., turf) indicates that because of the lack of erosion of soil particles, strongly sorbed chlorpyrifos is not transported via runoff (Watschke and Mumma 1989). Even during a simulated l00-year rainfall event (13.6 cm) occurring less than a week after application, only between 0.10 and 0.29% of the applied chlorpyrifos was present in runoff. In another study of runoff from turfgrass treated at 1.12 kg/hectare with irrigation applied at 150 mm/hour, no residue of chlorpyrifos was detected at 5 μg/L (minimum detection level) (Harrison et al. 1992). The movement of chlorpyrifos was studied from 1985 to 1987 in a small agricultural Saskatchewan watershed (Waite et al. 1992). In 1985-86, 3-4 million hectares of farmland were treated with insecticides at application rates as high as 1 kg/hectare to control grasshopper infestations. The frequency of occurrence and concentrations of chlorpyrifos in groundwater, surface water and runoff from spring snow melt were measured. No chlorpyrifos was found in any of the samples at detection limits of 1 ppb in 1985 and 0.1 ppb in 1986.

Spills are an important way that chlorpyrifos enters surface waters. A spill of chlorpyrifos into a marine bay resulted in initial water concentrations of up to 300 μg/L, but because of sediment sorption, dissipation, and dilution, the concentration had dropped to below detectable levels within 17 days (Cowgill et al. 1991).

Some research has shown that only very small levels of chlorpyrifos are taken up by plant roots, translocated, or metabolized by plant tissues (Kenaga et al. 1965; Smith et al. 1967). Cranberry bean plants were hydroponically grown in nutrient solutions containing 50 ppm of chlorpyrifos emulsifiable concentration. After 72 hours, only 0.07-0.1% of the radioactivity present, composed of TCP and other degradation products, had been translocated to the plant tops. In another experiment (Smith et al. 1967), one leaf of the cranberry bean plant was treated foliarly with 1 mg of chlorpyrifos. After 7 days, <1% of the chlorpyrifos applied was found in nontreated areas of the plant.

However, other researchers have found that soil-applied doses of chlorpyrifos are transported to foliage (Rouchaud et al. 1991). Cauliflower and brussels sprouts were treated with chlorpyrifos by pouring it onto soil around the stem of the plant for protection against the root fly. During plant growth, chlorpyrifos and its soil metabolites were transported from soil into the plant foliage, where it could give a secondary plant protection against the foliage insects. The foliage concentrations of the

nonsystemic chlorpyrifos was ≥1 mg/kg fresh weight during a period of about 44 days after soil treatment in brussels sprouts crops and a period of 3.5 days in cauliflower crops.

5.3.2 Transformation and Degradation

Chlorpyrifos undergoes a number of different transformation and degradation reactions in the environment as discussed in the following sections. The resulting environmental transformation products are shown in Figure 5-2.

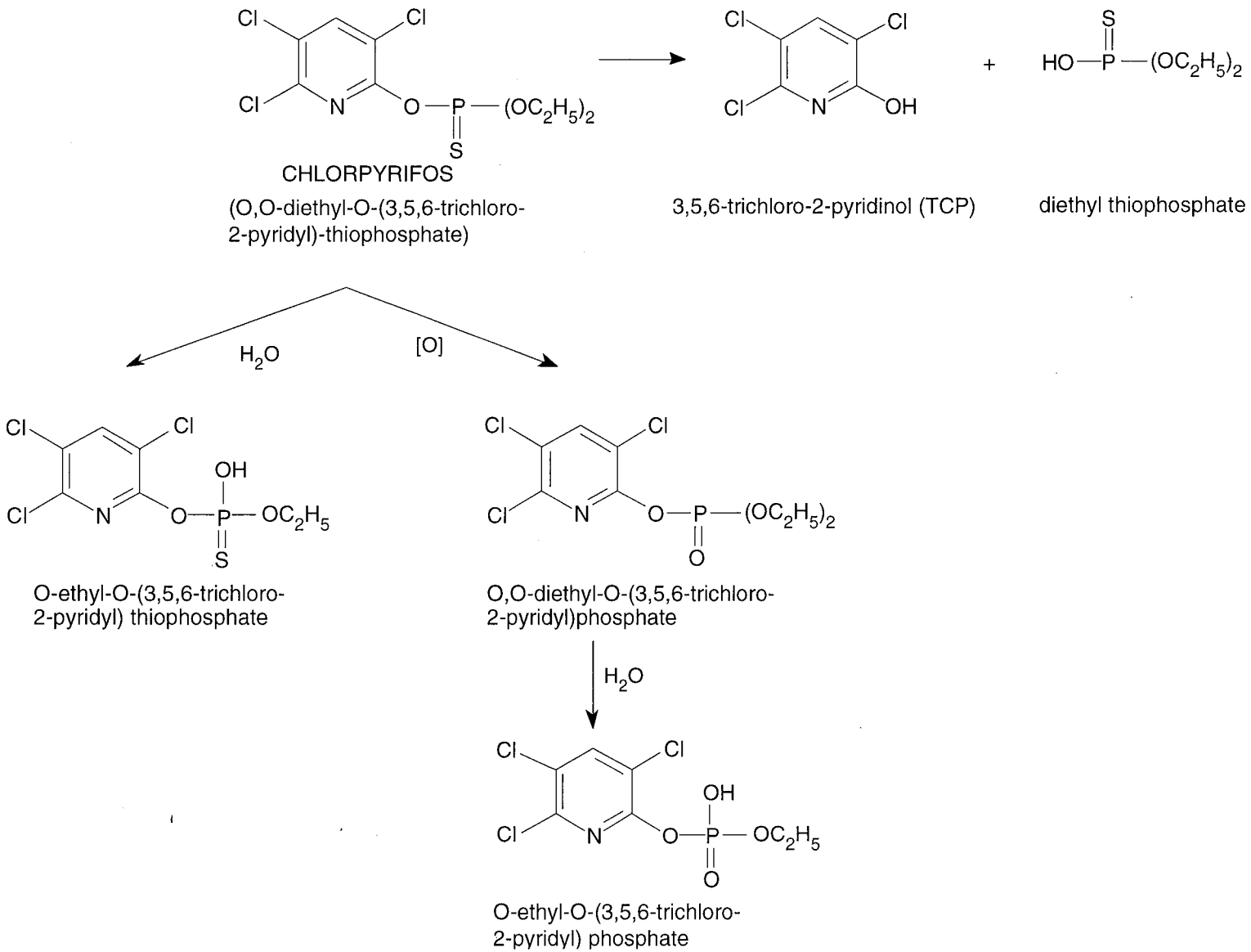
5.3.2. 1 Air

Both chlorpyrifos and its degradation product, TCP, have ultraviolet (UV) absorbencies above 295 nm, indicating their susceptibility to photodegradation by sunlight. The photodegradation half-life of chlorpyrifos in the laboratory is approximately 2.6 days (Fontaine and Teeter 1987). While in the atmosphere, chlorpyrifos will react with photochemically induced hydroxyl radicals. Its estimated halflife is 6.34 hours (Atkinson 1987).

5.3.2.2 Water

The processes primarily responsible for the transformation and degradation of chlorpyrifos in water are abiotic hydrolysis and photosensitized oxidation. Neutral hydrolysis is favored below pH 9, whereas alkaline hydrolysis dominates above pH 9 (Macalady and Wolfe 1983). Thus, both the disappearance half-life and the products are pH-dependent. Neutral hydrolysis yields O-ethyl-O-3,5,6-trichloro-2-pyridyl phosphorothioate, while alkaline hydrolysis occurs by base-catalyzed cleavage at the phosphate ester linkage to produce TCP and phosphorthioic acid. Neutral hydrolysis is pseudo-first-order kinetics, while alkaline hydrolysis is second-order kinetics (Wolfe 1988). Keeping the temperature at 25 °C, the half-life of chlorpyrifos in distilled water was 89.14 days at pH 1, and 0.01 days at pH 12.9 (Macalady and Wolfe 1983). At 20 °C, it has a half-life of 120 days at pH 6.1 and 53 days at pH 7.4 (Freed et al. 1979). The activation energy for the hydrolysis of chlorpyrifos at pH 7.4 is 14 kcal/mol, indicating its sensitivity to temperature change. Laboratory studies on the interaction of chlorpyrifos with Cu^{2+} have demonstrated metal-catalyzed hydrolysis and have provided rate constants for this pathway (Blanchet and St. George 1982).

Figure 5-2. Environmental Degradation Pathways of Chlorpyrifos



Photodegradation in water is possible since chlorpyrifos absorbs in the UV region at >295 nm; however, its relative importance as a dissipative force in the environment is unclear. Laboratory studies from artificial light sources may not be very useful for predicting environmental photodegradation kinetics (Miller and Zepp 1983). For example, chlorpyrifos in natural waters is usually very strongly sorbed to suspended particulate and bottom sediment, and thus less readily available to photolytic forces than chlorpyrifos in clear distilled water in the laboratory.

Brock et al. (1992) performed experiments using macrophyte-dominated freshwater ecosystems and open-water model ecosystems. In both systems, 50% of the chlorpyrifos dose applied had disappeared on day 8 post-treatment. In the long run, loss of chlorpyrifos was more rapid in the macrophytedominated ecosystems than in the open-water ecosystems.

Under field conditions, chlorpyrifos exhibits very short persistence in the water compartment of aquatic ecosystems, and half-lives as short as several hours have been observed. This is due to its considerable volatility from water (arising from low solubility and moderate vapor pressure) and its high association with sediment. The rate of disappearance of chlorpyrifos from river and well waters in a pH range of 8-8.5 was studied in the laboratory at a range of temperatures and under conditions of light and dark (Frank et al. 1991). The half-life for the disappearance of chlorpyrifos was 4.8 days at 21 °C and 27 days at 4 °C, indicating that temperature plays a major role in the degradation of chlorpyrifos in water. The half-life for disappearance of chlorpyrifos was 56 days in the dark and 46 days in the light at 21 °C, indicating that sunlight photolysis is not a major route of chlorpyrifos degradation in water.

The persistence of chlorpyrifos in surface water was studied (Hughes et al. 1980) by application of 10 ppb chlorpyrifos to polyethylene-lined ponds and a single natural pond inoculated with leaf litter. In early post-treatment, there was rapid partitioning to adsorption on bottom sediments and polyethylene; 30-60% disappeared from the water within 24 hours. The time for the concentration of chlorpyrifos to decline to 0.01 ppb in the polyethylene-lined pond was estimated to be 40 to >200 days compared to 18 days for the natural pond. The desorption from sediments was considerably slower from organic matter than from polyethylene. Desorption from the polyethylene contributed to residual concentrations in the water of artificial ponds for up to 18 months. Similar results were noted in an artificial lake treated with chlorpyrifos: lake water concentrations peaked 1 day after treatment at 0.9 μg/L and leveled near 0.2 μg/L after 3 weeks (Mulla et al. 1973).

First-order degradation rate constants of chlorpyrifos were determined in estuarine water and sediment/water slurry systems (Walker et al. 1988). Half-lives of chlorpyrifos in sediment/slurry systems calculated from these rate constants ranged from 12 to 30 days for the non-sterile system, and 16-51 days for the sterile system. Half-lives for the seawater-only systems ranged from 13 to 41 days for the non-sterile systems and 3.5-24 days for the sterile systems. The half-life of chlorpyrifos in seawater was 24 days in a sediment-seawater slurry (Schimmel et al. 1983). These data indicate that abiotic processes predominate in estuarine systems.

5.3.2.3 Sediment and Soil

Chlorpyrifos may undergo degradation on the surface of soils by photo-induced reactions. Laboratory photodegradation of chlorpyrifos on soil surfaces with UV light (254 nm from mercury lamps) demonstrated that three different photochemical processes (hydrolysis, dechlorination, and oxidation) take place simultaneously (Walia et al. 1988). The oxidative and dehalogenated products formed during photo-irradiation of soil undergo further photolysis to form chloropyridinols and O,O-diethyl phosphorothioic acid. The oxon is unstable; it tends to hydrolyze more rapidly than chlorpyrifos and does not accumulate in the soil. With the passage of time, the percentage of chlorinated pyridinols also decreased, suggesting that these products are mineralized in the soil under UV-photo-irradiation conditions. Under simulated sunlight conditions, the rate of photodegradation of chlorpyrifos on a leaf surface was slow. Chlorpyrifos was stable up to 10 days; then the oxon (1.5%) and the hydrolytic product, TCP (2.5%), were detected. Dehalogenated analogs of chlorpyrifos could be detected only after 15 days of constant irradiation. Under these conditions, the photo-oxidation process was more predominant than the photohydrolytic or dehalogenation process. Formation of such photoproducts on an irradiated soil surface was very fast, but the rates in the laboratory will differ from those found under environmental conditions.

Chlorpyrifos undergoes transformation in soil by the processes of abiotic hydrolysis and microbial degradation. A few studies have attempted to separate abiotic chemical hydrolysis from-microbial processes and to determine their relative importance (Miles et al. 1979, 1983). The half-lives of chlorpyrifos in muck (48% organic matter [OM]) and loam (2.7% OM) were determined in sterilized and natural soils at 3 temperatures (3, 15, and 28 °C). The results indicate that in sterile soils, chlorpyrifos is progressively more degraded by abiotic hydrolysis as the temperature increases, and that it degrades faster in sandy loam than in muck (after 24 weeks, 38 versus 68% remaining at the

highest temperature). An explanation for the soil difference may lie in the pH. The sterile loam had a pH of 6.5, whereas the sterile muck had a pH of 5.9, indicating that increasing pH increases degradation. The degradation study of chlorpyrifos in natural soil gave the same progression for increasing temperature, and it continued to degrade faster in the loam than in the muck (half-lives of 16, 6, and 2.5 weeks versus >24, 15, and 6 weeks at the respective temperatures). All half-lives were shorter in the natural soils as opposed to the sterile soils, however, indicating microbial degradation in addition to abiotic chemical hydrolysis.

Some researchers have concluded that chlorpyrifos is not catabolized (Racke and Coats 1988, 1990) because it is resistant to enhanced degradation by microbes. When chlorpyrifos is applied to fields with a soil history of chlorpyrifos use, the breakdown of chlorpyrifos is not enhanced, and is often delayed (Racke and Coats 1988; Somasundaram et al. 1989). The biotic process at work is probably co-metabolism. Patterns of persistence were observed in a variety of agricultural soils after treatment with ^{14}C-chlorpyrifos and its hydrolysis product, TCP (Racke et al. 1988). In soils with no previous history of chlorpyrifos use, significant quantities of TCP and soil-bound residues were produced, but little $^{14}CO_2$. In soils with a history of chlorpyrifos use, neither TCP nor soil-bound residues accumulated, but large quantities of $^{14}C0_2$ were produced. Direct treatment of fresh samples of each of these soils with ^{14}C-TCP resulted in rapid mineralization of TCP to $^{14}CO_2$ only in those soils with a history of prior chlorpyrifos use. The rapid mineralization of TCP in these soils was microbially mediated. It is unclear if catabolic or co-metabolic processes are predominant (Racke and Robbins 1990) in the degradation of TCP. TCP exhibited sorption (K_d) coefficients of between 0.3 and 20.3 mL/g (mean of 3.1) and calculated mean Koc coefficients for the neutral and anionic forms of 3,344 and 54 mL/g, respectively.

In a study of persistence of chlorpyrifos in a silt loam soil, the disappearance rate was fast in the first 15 days, but slowed after that. The pseudo-first-order rate constants were 0.041 day^{-1} and 0.044 day^{-1}, for the band treatment at seeding, and 0.04 day^{-1} for the drench at seeding. The calculated half-lives ranged from 15.8 to 17.3 days (Szeto et al. 1988).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to chlorpyrifos depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. In

reviewing data on chlorpyrifos levels monitored in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

Chlorpyrifos has been detected in both outdoor and indoor air; of special concern are levels in fogwater and environments receiving broadcast pesticide application, and in selected indoor environments such as poorly ventilated and artificially lit environments and the infant breathing zone (25 cm above the carpet). Selected studies documenting chlorpyrifos concentration and persistence in these environments include Anderson and Hites (1988); Fenske et al. (1990); Jackson and Lewis (1981); Leidy et al. (1992); Lewis et al. (1988); Moye and Malagodi (1987); Vaccarro (1993); and Wright et al. (1991, 1994). Special issues in these environments are discussed below.

Substantially higher chlorpyrifos concentrations were measured in the infant breathing zone than in the adult breathing zone, implying a vertical gradient with the treated carpet serving as a source of volatilized chlorpyrifos (Fenske et al. 1990). All concentrations in the infant breathing zone exceeded the National Academy of Sciences interim guideline of 10 $\mu g/m^3$. This study also indicated that broadcast applications appear to produce average levels 5-10 times higher and peak levels l-2 orders of magnitude greater than other application procedures, with peak concentrations occurring 3-7 hours after application. Following treatment in the crawl spaces, significantly more chlorpyrifos was present in the air of houses built over sand than in the air of houses built over clay soils. However, no differences were found between rooms or construction types (slab, crawl, crawl-slab) (Wright et al.1988). The air of storage rooms in commercial pest control buildings was found to have a higher concentration (220 ng/m^3) of chlorpyrifos than office rooms (126 ng/m^3). The same study detected levels of chlorpyrifos from 20 to 1,488 ng/m^3 in the air of 6 food preparation serving areas following application of a 0.5% emulsion spray into cracks and crevices, although concentrations dropped considerably over 24 hours in all areas. Chlorpyrifos was detected in homes and pest control offices and vehicles, with residues ranging from 0.1 to 5 $\mu g/m^3$ (Leidy et al. 1992). Air concentrations in commercial pest control vehicles ranged from 9 to 221 ng/m^3 (Wright and Leidy 1980).

High fogwater concentrations (320-6,500 ng/L) were reported at Parlier, Corcoran, and Lodi, California, relative to air concentrations (0.6-14.7 ng/L), with enrichment factors of 160-260 (Plimmer

1992). Other researchers have found similar enrichment factors (Glotfelty et al. 1987, 1990). Enrichment was attributed to the effect of temperature correction, colloidal organic matter, and adsorption. The enrichment factor has also been correlated to hydrophobicity, as indicated by K_{ow} (Valsaraj et al. 1993).

There is less evidence of general contamination of ambient air, although residues have been detected. Ambient air monitoring at 10 U.S. locations in 1980 resulted in 14 detections from 123 samples, with a maximum of 100 ng/m^3 and an arithmetic mean of 2.1 ng/m^3 (Carey and Kutz 1985). This same study reported 2 detections of chlorpyrifos from 11 air samples in Pekin, Illinois, in 1980. Ambient air and wet-deposition monitoring of chlorpyrifos in California indicated that atmospheric transport is occurring from the Central Valley, where chlorpyrifos is used agronomically, to the Sierra Nevada Mountains; concentrations decrease with distance from the source area and elevation (Zabik and Seiber 1993). A maximum concentration of 6.5 ng/m^3 was recorded in the valley; the maximum value midslope was 0.083 ng/m^3. A loading rate of 0.8 μg/m^2 to Sierra National Park was calculated.

5.4.2 Water

Chlorpyrifos has been detected in groundwater and surface water, but only rarely, and generally well below levels of concern. Hallberg (1989) reported that chlorpyrifos was detected (concentrations unspecified) in 0.2% of 334 samples from groundwater used for public drinking water supply in Illinois, but was not detected in 15 Iowa samples. This same study detected chlorpyrifos in 45% of the wells in the vicinity of agrochemical dealers, and in 1.4% of farm water supply wells. In a survey of surface waters in southern Ontario from 1975-77, chlorpyrifos was detected in 3 of 949 samples from 11 agricultural watersheds (Braun and Frank 1980). Krill and Sonzogni (1986) reported no detections of chlorpyrifos in groundwater sampling of 358 wells in Wisconsin. In a study of 54 wells in California, Maddy et al. (1982) found no detectable levels of chlorpyrifos. Pionke et al. (1988) and Pionke and Glotfelty (1989) found no detectable levels of chlorpyrifos in a study of 21 wells and 2 springs (detection limit of 4 ng/L) in Pennsylvania. Maddy et al. (1982) found no detectable levels of chlorpyrifos in a study of 53 wells in California. In an intensive monitoring effort, Richards and Baker (1993) detected chlorpyrifos in 0-l .06% of 750 samples for each of 7 tributaries to Lake Erie from 1983 to 1991. A maximum chlorpyrifos concentration of 480 μg/kg in runoff from irrigated cropland in California was reported by Leonard (1990). Total seasonal losses as a percentage of application were 0.02-0.24, and were attributed to aerial application during irrigation. Chlorpyrifos

detections were not reported as part of the national surface water monitoring program for 1976-80 (Carey and Kutz 1985).

5.4.3 Sediment and Soil

Limited data on chlorpyrifos residues in soils or sediments were located. At a detection limit of 0.01 mg/kg, chlorpyrifos was not detected in sediment samples collected from Lakes Superior and Huron, including Georgian Bay, in 1974 (Gloschenko et al. 1976). Chlorpyrifos detections were not reported in sediments as part of the national surface water monitoring program for 1976-80 (Carey and Kutz 1985). Soil evaporation pits, ditches, and ponds have been used to dispose of liquid pesticide wastes in California (Winterlin et al. 1989). A core soil sample taken from one such pit in northern California contained detectable levels of chlorpyrifos to a depth of 67.5 cm (Winterlin et al.1989).

5.4.4 Other Environmental Media

The Food and Drug Administration (FDA) identified chlorpyrifos in four grain samples and in four samples of animal feed in 1975 (Duggan et al. 1983). The FDA's pesticide residue monitoring program for domestic and imported food commodities detected chlorpyrifos 33 times in 1,044 samples in unspecified foods at unspecified concentrations during fiscal years 1978-82 and 295 times from 3,744 samples during fiscal years 1982-86 (Yess et al. 1991a, 1991b). From October 1, 1981, to September 30, 1986, the FDA Los Angeles District Laboratory detected chlorpyrifos in 1,969 of 19,851 samples of domestic and imported food and feed commodities (Luke et al. 1988). Chlorpyrifos was detected in 440 of 4,916 samples analyzed as part of the FDA Total Diet Study between 1986 and 1991. As part of the FDA's Pesticide Monitoring Program for domestic and imported foods, chlorpyrifos residues have been detected during 1988-89, 1989-90, 1990-91, and 1991-92 (FDA 1990, 1991, 1992, 1993). Chlorpyrifos was detected in domestic feed, lavender, lettuce, cantaloupe, peanuts, bell peppers, summer squash, and cherry tomatoes; and in imported apples, green beans, cabbage, coriander, cucumbers, eggplant, feijoa, kiwi, green leaf lettuce, cantaloupe, honeydew, nectarine, Chinese peas, peaches, peppers, spinach, squash, tomatillos, and tomatoes (Hundley et al. 1988). In the FDA's Revised Market Basket Study (FDA 1995), ready-to-eat foods were analyzed for pesticides and industrial chemicals repetitively for 10 years (1982-91). During that period, 37 market baskets, each containing 234 food items, were collected. Chlorpyrifos was detected in 121 of the food

items a total of 718 times; the average concentration found was 0.0036 μg/g (ppm). Gartrell et al.(1986) found chlorpyrifos in meat, fish and poultry, grain and cereal products, garden fruits, oils and fats, and sugar. Chlorpyrifos was detected in 121 different domestic foods (0.9% of samples) in 1988 and 128 domestic foods (1% of samples) in 1989 by state regulatory monitoring (Minyard et al. 1991). In a study of processed foods imported into Hawaii from western Pacific rim countries, chlorpyrifos was detected in oriental-style noodle soup and roasted peas at concentrations of 4.7 ppb and 10.95 ppb, respectively (Gans et al. 1994). In a pesticide residue screening program conducted in 1989-91 in San Antonio, Texas, on 6,970 produce samples, chlorpyrifos was detected in 41 produce samples (lemons, oranges, peppers, turnips), with a detection limit of 0.25 ppm (Schattenburg and Hsu 1992). In a study of pesticide residue contamination of processed milk-based and soy-based infant formula, chlorpyrifos was not detected (Gelardi and Mountford 1993). However, in a study of pesticide residues in cornposited milk, chlorpyrifos was found in 23 of 806 composite samples (Trotter and Dickerson 1992).

The EPA Office of Water has recommended that chlorpyrifos residues be monitored by states in their fish and shellfish contaminant monitoring programs in watersheds where this pesticide has been or is currently used extensively in agriculture (EPA 1993c. While no fish or shellfish consumption advisories are currently in effect for chlorpyrifos, this contaminant has not been widely monitored in state fish contaminant monitoring programs or the U.S. Fish and Wildlife Service National Contaminant Biomonitoring Program (EPA 1993c). In a national study, EPA (1992a) did detect chlorpyrifos in fish in 26% of 362 sites, with mean and maximum concentrations of 4.09 ng/g and 344 ng/g, respectively.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to chlorpyrifos primarily by inhaling indoor air and ingesting food containing chlorpyrifos, and through skin contact during or after pesticide application. Chlorpyrifos has been very infrequently detected in ambient air, and only at very low concentrations (see Section 5.4.1). It is not anticipated that the general population would experience substantial levels of exposure by inhaling ambient air. Chlorpyrifos has rarely been detected in drinking water (see Section 5.4.2), and consumption of chlorpyrifos-contaminated drinking water is not considered a significant exposure route for the general population.

Chlorpyrifos has been detected in some foods (see Section 5.4.4), so ingestion may be a route of exposure for the general population. The FDA has estimated daily food intakes of chlorpyrifos for different age/sex groups in the United States. The FDA estimated the dietary intake of chlorpyrifos for a 14-16-year-old male in the United States to be 3.4 ng/kg body weight/day, which is much lower than the Food and Agricultural Organization of the United Nations/World Health Organization's (FAO/WHO) acceptable daily intake (ADI) of 10 μg/kg body weight/day and ATSDR's intermediate oral MRL and EPA's RfD of 3 μg/kg body weight/day (FDA 1992; IRIS 1994).

Other than during home and garden insecticide application, exposure of the general public to chlorpyrifos through skin contact is not anticipated.

The Non-Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 on the number of workers and the number of facilities where workers could be potentially exposed to chlorpyrifos in the United States estimated that 911 janitors and cleaners in meat packing plants, and bread, cake, and related product industries; 10,452 pest control workers; and 41 groundskeepers and gardeners in the medical industry were potentially exposed (NOES 1994). The American Conference of Governmental Industrial Hygienists (ACGIH) (1993-94) recommends that workplace air levels of chlorpyrifos not exceed 0.2 mg/m^3 as a time-weighted average (TWA) for an 8-hour workday, 40-hour workweek and not exceed a 0.6 mg/m^3 short-term exposure limit (STEL). The STEL is a 15-minute TWA exposure which should not be exceeded during a workday, even if the 8-hour TWA is within the threshold limit value (TLV)-TWA; also exposure should not be >15 minutes and should occur not more than 4 times per day.

Workers involved in the manufacture, formulation, handling, or application of chlorpyrifos, or those involved in the disposal of chlorpyrifos-contaminated wastes are likely to be exposed to higher concentrations by dermal contact and inhalation than the general population. Persons working with plants that have been previously treated with these compounds also can be exposed by absorption through the respiratory system or skin (Aprea et al. 1994). A study of pet handlers responsible for flea control in California in 1987 indicated that chlorpyrifos was associated with increased frequency of blurred vision, flushing of skin, and a decrease in urination (Ames et al. 1989). In a study of airborne and surface concentrations of chlorpyrifos after application in offices, Currie et al. (1990) found airborne concentrations peaked 4 hours after application at 27 $\mu g/m^3$, and surface residue concentrations peaked at 5.9 ng/cm^2 48 hours after application. Airborne levels were found to be

lower in furnished offices than unfurnished offices. When granular chlorpyrifos at 0.75 active ingredient per acre was applied to a field by air, the estimated inhalation exposure to chlorpyrifos was 0.02 mg per 8-hour day for the pilot and 0.03 mg per 8-hour day for the ground staff (Myram and Forrest 1969). The estimated inhalation exposure to chlorpyrifos for workers using ground machines was 0.33 mg per 8-hour day (Myram and Forrest 1969).

Hodgson et al. (1986) reported symptoms of organophosphate intoxication among five office workers after chlorpyrifos treatment for termites. The duration of symptoms and erythrocyte cholinesterase levels over time suggested redistribution of the active ingredient after absorption to a second body compartment, with subsequent slow release into the bloodstream. Estimated potential dermal exposure (i.e., unprotected by clothing) of three greenhouse workers in Florida ranged from 17,500 to 24,000 μg/hour (Stamper et al. 1989), with highest exposure to applicators' legs. Tyvek® protective clothing afforded 89%, ±5% protection.

In a study of termiticide applicator exposure in eight North Carolina homes, exposures of 0.1-98 $\mu g/m^3$ were reported. Exposure levels were higher in houses constructed over a crawl-space (Wright et al. 1988). The NOES reported detectable levels of chlorpyrifos in indoor, outdoor, and personal air in Jacksonville, Florida, and in Springfield/Chicopee, Massachusetts (Whitmore et al.1994). Concentrations tended to be highest in summer, lower in spring, and lowest in winter. Indoor and personal air concentrations were generally higher than outdoor concentrations. Of 11 carpets sampled in the study, all had detectable levels of chlorpyrifos in carpet dust, (mean concentration of 5.8 μg/g), suggesting that infants and toddlers may be at higher risk of exposure. NAS/NRC (1982) recommends that air levels in houses not exceed 10 μg chlorpyrifos/m^3. Measurements of pesticides or their metabolites in human biological specimens, such as urine, are considered an appropriate way of approximating total pesticide exposure through all routes of entry into the body. As part of the National Health and Nutrition Examination Survey III (NHANES III), urine samples were collected from approximately 1,000 adults ranging in age from 20 to 59 years. These individuals represented a relatively board spectrum of the U. S. population, including individuals from both sexes-and different age groups, races/ethnicities, urban/rural residences, and regions of the country (Needham et al. 1995). Hill et al. (1995) examined the ranges of pesticide residues found in the urine of approximately 1,000 U.S. adults and found that 3,5,6-trichloro-2-pyridinol (TCP), considered a fairly specific metabolite and indicator of exposure to chlorpyrifos or chlorpyrifos-methyl, was present at detectable levels in 82% of the (993) individuals examined. Further, 31% of those subjects had urinary TCP concentrations of

5 μg/L or greater. This was consistent with the report of Bartele and Kastl (1992) that TCP was present in the pooled urine of unexposed control subjects at a concentration of 5 μg/L.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries that manufacture and formulate chlorpyrifos and applicators of the insecticide are at higher risk than the general population for chlorpyrifos exposure. Farm workers who enter treated fields after insecticide application may also be exposed to chlorpyrifos at higher levels than the general population. Those who use the insecticide for homes and gardens are also at higher risk of exposure to chlorpyiifos. Although no investigative evidence from the hazardous waste sites was located, it is likely that people who live near hazardous waste sites containing chlorpyrifos wastes are at higher risk of exposure to chlorpyrifos.

5.7 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 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.

5.7.1 Identification of Data Needs

Physidal and Chemical Properties. As seen in Table 3-2, the relevant physical and chemical properties of chlorpyrifos are known (HSDB 1994; Sanbom et al. 1977), and it is possible to predict

the environmental fate and transport of chlorpyrifos based on K_{ow} K_{oc} and H. Therefore, further data acquisition and research are not recommended as a high-priority activity.

Production, Import/Export, Use, Release, and Disposal. Knowledge of production and use data for a chemical is important in predicting its potential for environmental contamination and human exposure. Since chlorpyrifos is produced by two manufacturers (SRI 1994), to maintain confidentiality, its recent production volume is not known. Similarly, data concerning the import and export volumes for chlorpyrifos in recent years have not been located. There is currently no federal requirement to report the use of chlorpyrifos. The most recent estimates of its yearly use in the United States were published in 1986 (Gianessi 1986). Therefore, more current estimates of use and projected trends are needed. No information in the available literature was located that indicates the use of chlorpyrifos in any consumer products other than edible crops and vegetables during and after their planting. Although some information regarding the disposal of wastes containing chlorpyrifos is available, more detailed and recent information would be helpful. The standards promulgated by the EPA for the disposal of wastes containing chlorpyrifos are available (Berlow and Cunningham 1989).

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1992, became available in May of 1994. This database will be updated yearly and should provide a list of industrial facilities and emissions. However, no TRI data were located for chlorpyrifos because this chemical is not required to be reported. As with most pesticide agents, it is virtually impossible to make decent quantitative estimates of the amounts of chlorpyrifos produced, used, disposed, imported and exported. This presents some fundamental problems in making more than the most general sorts of risk assessments. Improved information for any of these categories is considered a major data need.

Environmental Fate. Information regarding the fate of chlorpyrifos in air was limited in the literature. Although the available data indicate that the concentration of chlorpyrifos in air will be low (Carey and Kutz 1985), more information would help predict the residence time and distance of its aerial transport. Knowledge about the fate of chlorpyrifos in water is also limited. Although it has been estimated that sorption onto particulates and settling into the sediment are important for chlorpyrifos in water, more information regarding the relative importance of sorption for removal of chlorpyrifos from water to sediment would be helpful. There is some evidence in the literature

regarding the mobility of chlorpyrifos in soil. Additional information on the degradation of chlorpyrifos in water and air and the fate of the degradation products in soil would be helpful.

Bioavailability from Environmental Media. Available information regarding the rate of chlorpyrifos absorption following inhalation, oral, or dermal contact has been discussed in Section 2.3, Toxicokinetics. Although no data on the bioavailability of chlorpyrifos from contaminated air are available, the bioavailability from inhalation exposure is expected to be high because chlorpyrifos is likely to be present in the vapor phase and not in the particulate phase in the adsorbed state. Similarly, no data on the bioavailability of chlorpyrifos from water, soil, or plant material are available; however, chlorpyrifos is adsorbed rather strongly to soil. Since the part that remains adsorbed to soil or sediments may be, at most, partially bioavailable, chlorpyrifos is expected to have reduced bioavailability from soil and water. Data on the bioavailability of chlorpyrifos from actual environmental media and the difference in bioavailability for different media need further development.

Food Chain Bioaccumulation. Measured BCF values for chlorpyrifos are available for a large number of aquatic invertebrate and fish species (Odenkirchen and Eisler 1988; Racke 1993). Research on accumulation of chlorpyrifos applied to soils in the roots, stems, and leaves of plants has also been undertaken (Rouchaud et al. 1991).

Exposure Levels in Environmental Media. A number of studies have been conducted dealing with chlorpyrifos concentrations in indoor air. Although some data on the levels of chlorpyrifos in ambient air are available (Carey and Kutz 1985), these data are neither current nor general enough to estimate inhalation exposure to chlorpyrifos for the general population in the United States. Limited data on the level of chlorpyrifos in drinking water were located in the literature. More recent data regarding the levels of chlorpyrifos in ambient air, drinking water, and soil are needed. Data on chlorpyrifos levels in food and recent estimates of the human intake of chlorpyrifos from foods are available (Duggan et al. 1983; FDA 1990, 1991, 1992, 1993; Gelardi and Mountford 1993; Gunderson 1988; Luke et al. 1988; Schattenburg and Hsu 1992; Yess et al. 1991a, 1991b).

Reliable monitoring data for the levels of chlorpyrifos in contaminated media at hazardous waste sites are needed so that the information obtained on levels of chlorpyrifos in the environment can be used

in combination with the known body burden of chlorpyrifos to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Aside from the NHANES III and Hill et al. (1995) data, no other quantitative information on chlorpyrifos levels in human tissues and body fluids for a control population, populations near hazardous waste sites, or occupationally exposed groups were located. Additionally, data on the levels of chlorpyrifos and its metabolites in body tissues and fluids in symptomatic, exposed individuals, as well as RBC and plasma ChE activity levels in these persons, are needed to correlate exposure levels with adverse symptoms and to identify levels of ChE inhibition associated with the onset of toxic manifestations. One potential source of this information is the American Association of National Poison Control Centers.

Exposure Registries. No exposure registries for chlorpyrifos were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries establishment. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to a substance.

5.7.2 Ongoing Studies

As part of the National Pesticide Impact Assessment Program, research is in progress at North Carolina State University (Leidy) to study the movement of herbicides into poorly drained soils of the Tidewater region of North Carolina and to determine the dislodgeable residue of chlorpyrifos from carpet samples.

Research is in progress at the University of Florida, Belle Glade (Snyder) to quantify organophosphate losses in percolate, retention in soil and thatch, and removal in grass clippings.

Research is in progress at the University of Florida, Gainesville (Moye and Wheeler), Texas A&M (Plapp), and Clemson (Camper) to determine the metabolic fate of chlorpyrifos in different media.

Researchers at the University of Puerto Rico (Singmaster and Acin-Diaz) are determining the dissipation and persistence of chlorpyrifos in surface and vadose-zone soils and water.

The USDA Agricultural Research Service (ARS) (Wauchope) is determining chlorpyrifos residues for 22 minor food crops at Tifton, Georgia, 7 crops at Yakima, Washington (Toba), and chlorpyrifos residues in coffee in Puerto Rico (Acin-Diaz, Liu, Armstrong).

The USDA-ARS in Riverside, California (Spencer and Yates) is studying water and pesticide management systems for minimizing groundwater and air contamination, as well as the persistence (fate and transport) of chlorpyrifos (Gaston).

The USDA-ARS in Beltsville, Maryland (Wright and Hapeman) are quantifying chlorpyrifos volatilization, transport, partitioning, and deposition.

The University of Nevada at Reno (Seiber), with funding from the U.S. Department of Agriculture, is studying the aerial transport and deposition of organophosphate pesticides, including chlorpyrifos, in Sierra Nevada forests.

The National Taiwan University (Hsu and Epstein), with funding from the USDA, is investigating the effects of different processing/cooking variables on chlorpyrifos residues in meat and poultry products.

Research is in progress at the University of Nebraska (Shea) to determine the mobility and bioavailability of chlorpyrifos in soil and at Iowa State University to compare degradation kinetics at high as opposed to low concentrations, persistence of TCP, and effect of temperature and moisture on degradation of chlorpyrifos (coats).

The U.S. Department of Energy (DOE) is funding a cooperative research and development agreement (CRADA) between Argonne National Laboratory (Kakar), the University of Notre Dame, and COGNIS, Inc., to study the biodegradability of pesticides by direct enzyme treatment.

The University of California at Davis (Kilgore), with funding from the U.S. Department of Agriculture, is developing methods to measure exposure, ab,sorption, and toxicity of pesticides to

workers and is preparing guidelines for best management practices to reduce worker exposure to pesticides.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring chlorpyrifos, its metabolites, and other biomarkers of exposure and effect to chlorpyrifos. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Methods for the determination of chlorpyrifos and its metabolites are shown in Table 6- 1. Chlorpyrifos has been measured in human whole blood, plasma, and urine at concentrations as low as 10 ppb (Drevenkar et al. 1994; Jitsunari et al. 1989; Nolan et al. 1984). The chlorpyrifos oxygen analog (oxon) has been reported to be recoverable from serum and urine by hexane extraction, but no limit of detection (LOD) or recovery was reported (Drevenkar et al. 1993). The chlorpyrifos metabolite TCP has been measured at concentrations as low as 0.5 ng/mL weight per volume (0.5 ppb, w/v) in human blood and urine (Bartels and Kastl 1992; Jitsunari et al. 1.989; Nolan et al. 1984). The hydrolysis product diethyl phosphate (DEP) has been measured in urine and plasma (Drevenkar et al.1994; Takamiya 1994) and the hydrolysis product diethylthiophosphate (DETP) has been measured in plasma (Drevenkar et al. 1994) with LODs of approximately 50 ppb. Chlorpyrifos and its oxon can be extracted directly into organic solvent while TCP, DEP, and DETP can be isolated after acid hydrolysis of the conjugated forms. Chlorpyrifos and its oxon can be determined directly using gas chromatography (GC) and selective detection methods (see below). The metabolites TCP, DEP, and DETP are typically derivatized to improve the chromatography and, hence, detectability. No methods were found for chlorpyrifos and its metabolites in human tissue, but methods have been reported for animal tissue (see Table 6-2) (Brown et al. 1987; Clabom et al. 1968; Dishburger et al. 1977; Ivey and Clabom 1968; Lino and Noronha da Silveira 1994) and could most likely be applied to human tissues.

Table 6-1. Analytical Methods for Determining Chlorpyrifos and Metabolites in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood, urine (chlorpyrifos and TCP)	Blood: Chlorpyrifos extraction with acetone and solvent exchanged to hexane. Water was removed from the extract followed by clean-up using silica gel. TCP was recovered via SPE from separate aliquot of acidified blood. TCP elution from SPE with methanol then extraction into benzene and derivatization with N,O-bis(trimethylsilyl)acetamide. Urine: Chlorpyrifos extraction with hexane. Hydrolysis of conjugates of TCP with H_2SO_4 at 90 °C for 1 hour. TCP isolation via SPE, extraction into benzene, and derivatization as for blood.	Chlorpyrifos: GC/FPD; TCP: GC/ECD	Chlorpyrifos: No data; TCP: 10 ng/mL (10 ppb, w/v)	Chlorpyrifos: No data; TCP: 91.5% (4% RSD) at 0.1 µg/mL (0.1 ppm, w/v)	Jitsunari et al. 1989; Nolan et al. 1984
Urine (TCP)	TCP isolation from urine by acid hydrolysis of urine aliquots followed by extraction with diethyl ether. Residues dissolved in *o*-xylene followed by derivatization with N-(*tert*-butyldimethylsilyl)-N-methyl-trifluoroacetamide.	GC/NCIMS	0.5 ng/mL (0.5 ppb, w/v)	Relative recoveries 80.6 to 89.9% over concentration range of 4.1 to 411 ng/mL of urine	Bartels and Kastl 1992
Urine (DEP)	Inorganic phosphate removal by addition of $Ca(OH)_2$. DEP isolation using ion exchange and derivatization to pentafluorobenzyl derivative.	GC/FPD	No data	149% (9% RSD) at 0.50 ppm	Takamiya 1994

Table 6-1. Analytical Methods for Determining Chlorpyrifos and Metabolites in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Plasma (chlorpyrifos, DEP, DETP)	Chlorpyrifos extraction into hexane. DEP and DETP were recovered from hexane-extracted plasma as follows: plasma saturation with NaCl, acidification with 6N HCl, and extraction with diethyl ether. DEP and DETP methylation using diazomethane.	Chlorpyrifos: GC/ECD; DEP, DETP: GC/AFID	50 ng/mL (50 ppb, w/v)	DEP: 97% (3% RSD) at concentrations ≥ 2 µg/mL; DETP: 97% (11% RSD) at concentrations ranging from 0.1 to 2.8 µg/mL	Drevenkar et al. 1994
Serum and urine (chlorpyrifos, chlorpyrifos oxon, DEP, DETP)	Chlorpyrifos and its oxon recovered via extraction with hexane. Extracted sample was acidified and saturated with NaCl followed by extraction with diethyl ether. DEP and DETP derivatization with diazomethane.	GC/MS	No data	No data	Drevenkar et al. 1993

AFID = alkali flame ionization detector; DEP = diethyl phosphate; DETP = diethyl thiophosphate; GC = gas chromatography; ECD = electron capture detector; FPD = flame photometric detector; MS = mass spectrometry; NCIMS = negative ion chemical ionization mass spectrometry; TCP = 3,5,6-trichloro-2-pyridinol

Table 6-2. Analytical Methods for Determining Chlorpyrifos and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Known volumes of air drawn through XAD-2 adsorbent. Desorption with toluene.	GC/FPD (OSHA Method 62)	0.23 ppb (mole/mole); 0.003 mg/m^3	96.6 (5.3% standard error at 0.014 ppm)	OSHA 1986
Air	Known volumes of air drawn through polyurethane foam (PUF). Desorption via Soxhlet extraction using 5% diethyl ether in hexane. Extract volume reduction and further clean-up using Florisil if needed.	GC/ECD (EPA Method TO-10) May also use GC/FPD, GC/NPD, GC/MS	Approximately 0.01 µg/m^3 (0.7 ppt, mole/mole) This limit depends on the sampling volume	87 (20% RSD) for 10–1,000 ng/m^3 concentration and 24 h sampling	EPA 1988b
Air, surfaces	Air: Known volume of air pulled through ORBO-44 tubes (Supelpak 20) and elution with toluene. Surfaces: wiping with surgical gauze moistened with distilled water. Gauze extraction with toluene.	GC/ECD	Air: 83 ng/m^3 (5.8 ppt, mole/mole) Surface wipes: 0.6 ng/cm^2	Air: 85 (SD=6); Wipes: 84 (SD=10)	Fenske et al. 1990
Drinking Water (chlorpyrifos and TCP)	Chlorpyrifos: Water extraction with hexane. Water removal from extract followed by volume reduction. TCP: Water acidification, NaCl addition, and extraction with benzene. Water removal from extract followed by volume reduction.	TLC	100 ng/L or 100 ppb (w/v) for chlorpyrifos; 25 ng/L or 25 ppb (w/v) for TCP	Chlorpyrifos: 87 (8% RSD) at 5 ppb; TCP: 84 (5% RSD) at 5 ppb	Sherma and Slobodien 1984
Well water (drinking water)	Direct injection of 20 µL onto GC retention gap.	GC/ECD	<0.9 ppb (w/v)	95 (16% RSD) at 0.9 ppb	Gerhart and Cortes 1990

Table 6-2. Analytical Methods for Determining Chlorpyrifos and Transformation Products in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
River water, fish	Water: Water passage through C_{18} SPE cartridge and analyte elution with ethyl acetate. Solvent removal and redissolution in ethyl acetate. Fish: Sample lyophilization and Soxhlet extraction with ethyl acetate. Extract clean-up using SPE and GPC.	GC/NPD, GC/MS, GC/NCIMS	Water: 0.1 µg/L (0.1 ppb, w/v) NPD; 0.02 µg/L (0.02 ppb, w/v) NCIMS. Fish: 2 ng/g (2 ppt, w/w) NCIMS	Water: 94 (4% RSD) at 10–15 µg/L. Fish: 92–136 at 0.1 µg/g	Lacorte et al. 1993
Surface water	Water passage through XAD-2 and XAD-7 resins and analyte elution with methylene chloride. Internal standard addition, water removal and extract concentration.	GC/Ion Trap MS	0.005 ppb (w/v) or 5 ng/L	86.7 (17% RSD)	Mattern et al. 1991
Surface water	Water passage through C_8 SPE cartridge and elution of analytes with methanol.	HPLC/UV	5.0 ppb (w/v) or 5 µg/L	93 (14% RSD)	Bogus et al. 1990
Waste water	Extraction using methylene chloride. Water removal, solvent exchange to hexane and extract volume reduction.	GC/NPD or GC/FPD (P mode) (EPA Method 622)	0.3 µg/L (0.3 ppb, w/v)	98 (5.5% RSD over concentration range 1–50 µg/L)	EPA 1992b
Groundwater, soil, sludges, wastes	Aqueous samples: Extraction using methylene chloride; water removal and extract volume reduction. Soils, sludges, wastes: Extraction (sonication or Soxhlet) using methylene chloride after mixing sample with sodium sulfate. Additional clean-up using Florisil if needed.	GC/NPD or GC/FPD (EPA Method 8140); GC/MS (EPA Method 8270)	3 µg/L (3 ppb, w/v) for groundwater; 3 mg/kg (3 ppm, w/w) for high level soil and sludges	98 (5.5% RSD)	EPA 1986a (Method 8140); EPA 1986b (Method 8270).

Table 6-2. Analytical Methods for Determining Chlorpyrifos and Transformation Products in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater, soil, wastes	Extraction of aqueous samples at neutral pH using methylene chloride, water removal, and volume reduction. Extraction of solid samples with methylene chloride/acetone. Additional clean-up using Florisil if needed.	GC/NPD or GC/FPD (EPA Method 8141A)	0.7 µg/L (0.7 ppm, w/v) for groundwater; 5 mg/kg (5 ppm, w/w) for water-immiscible wastes	89±6% from water at 1.56 µg/L; 79±7% from soil at 52 µg/kg	EPA 1992a
Pesticide formulations (chlorpyrifos, TCP)	Liquids: Weighing sufficient sample to contain ca. 80 mg into vial and addition of 25 mL of acetonitrile containing 1,4-dibromonaphthalene (internal standard). Solids: As for liquids with added filtration step before analysis.	HPLC/UV	No data	No data	Helrich 1990a
Turkey and chicken (muscle, skin, heart, gizzard, brain, liver, fat)	Extraction of 250 mg of ground sample ground with petroleum ether. Water removal using sodium sulfate followed by centrifugation.	GC/ECD	0.05 ppm (w/w)	79–99 (at 0.05 and 0.10 ppm, w/w)	Hunt et al. 1969
Fatty and non-fatty foods (eggs, pasta)	Homogenization of sample with acetone (water addition needed for certain foods) and extraction with methylene chloride/acetone after NaCl addition. Water removal using sodium sulfate and extraction twice with methylene chloride. Water removal from extract and solvent evaporation. Further extract clean-up using carbon/Celite, Extrelut-3, or C_{18}-SPE. Solvent evaporation and redissolution in benzene.	GC/FPD	5.2 ppb (w/w)	80 at 0.03 ppm spike	Leoni et al. 1992

Table 6-2. Analytical Methods for Determining Chlorpyrifos and Transformation Products in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Beef fat	Tissue extraction sweep co-distillation to isolate analytes.	GC/ECD	No data	83.5% (5.3% RSD) at 0.16 mg/kg (0.16 ppm, w/w)	Luke and Richards 1984
Rumen content, liver	Homogenization of 5 g sample with methanol:methylene chloride (1:9, v/v). Water removal from extract followed by volume reduction prior to clean-up using GPC and silica SPE.	GC/FPD	0.01 to 0.05 µg/g (ppm, w/w)	Rumen content: 99 (3% RSD) at 0.1 µg/g. Liver: 105 (2% RSD) at 0.05 µg/g	Holstege et al. 1991
Fats and oils	Sample mixing with light petroleum and extraction five times with light petroleum-saturated acetonitrile. Chlorpyrifos isolation using C_{18} SPE followed by solvent exchange to acetone for analysis.	GC/FPD	<0.08 µg/g (0.08 ppm, w/w)	85–97 at 0.16–0.5 µg/g (ppm, w/w)	Gillespie and Walters 1991
Peppermint oil (chlorpyrifos, TCP)	Chlorpyrifos: Oil application to silica gel column and elution with 3% water-saturated diethyl ether in hexane followed by volume adjustment. TCP: Oil dissolution in benzene: pentane (2:3) and extraction with 0.5% sodium carbonate. Aqueous phase washing with chloroform, acidification and extraction with chloroform. Further extract purification via acidic alumina column chromatography. Trimethysilyl derivative formation.	GC/FPD (chlorpyrifos); GC/ECD (TCP)	0.1 ppm (µg/g, w/w) for chlorpyrifos; 0.5 ppm for TCP	73–104 for chlorpyrifos over concentration range 0.11–10 ppm; 70 to 101% at 0.5–1.0 ppm	Inman et al. 1981

Table 6-2. Analytical Methods for Determining Chlorpyrifos and Transformation Products in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Chicken muscle, skin	Homogenization of weighed tissue once with acetonitrile and twice with 70% acetonitrile/water followed by filtration. Filtrate extraction with zinc acetate/water, filtration and filtrate extraction with dichloromethane. Solvent exchange to hexane and Florisil clean-up.	GC/NPD	2.5 µg/kg (ppb w/w) for muscle; 2.2 µg/kg (ppb, w/w) for skin	Muscle: 91.9 at 6.6 µg/kg (6.6 ppb, w/w) Skin: 105 at 19 µg/kg (ppb, w/w)	Lino and Noronha da Silveira 1994
Bovine milk, tissues (muscle, liver, heart, kidney, brain, spleen, omental fat)	Fat: Sample dissolution in hexane, water removal and extraction with acetonitrile. Extract volume reduction, dilution with aqueous sodium sulfate and back-extraction with hexane. Water removal from extract, concentration and clean-up using silicic acid column chromatography. Tissue: Sample blending with Celite and acetone. Acetone removal and aqueous phase extraction with hexane; clean-up as for fat. Milk: Milk combined with activated Florisil. Application of mixture to Florisil column and elution with 10% (v/v) methylene chloride in hexane.	GC/ECD	0.002 ppm (w/w) for tissues and 0.005 ppm (w/v) for milk	Tissue: 75–100 at 0.012 ppm; Milk: 84 at 0.05 ppm	Claborn et al. 1968

Table 6-2. Analytical Methods for Determining Chlorpyrifos and Transformation Products in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Bovine milk, tissues (muscle, liver, heart, kidney, brain, spleen, omental fat); chlorpyrifos oxygen analog	Fat: Sample dissolution in hexane, water removal and extraction with acetonitrile. Extract volume reduction, dilution with aqueous sodium sulfate and back-extraction with hexane. Water removal from extract, concentration and clean-up using silicic acid column chromatography. Tissue: Sample blending with Celite and acetone. Acetone removal and aqueous phase extraction with hexane; clean-up as for fat. Milk: Milk combined with silicic acid followed by water removal and elution with hexane. Application of mixture to silicic acid column and elution with water-saturated methylene chloride.	GC/ECD	0.1 ppm (w/w) for fat and muscle; 0.025 ppm (w/v) for milk	70 and 92 for muscle and fat, respectively, at 0.1 ppm; 80 from milk at 0.025 ppm	Ivey and Claborn 1968
Bovine tissue (muscle, liver, kidney, fat); TCP	Tissue homogenization with methanol, filtration and mixing with acidified water containing NaCl. TCP extraction with benzene. TCP isolation using alumina column chromatography and derivatization to trimethylsilyl derivative. Total TCP (free plus conjugated) also examined after alkaline hydrolysis (any chlorpyrifos also converted to TCP).	GC/ECD	<0.05 ppm (w/w)	81–89 without hydrolysis; 86–101 with hydrolysis	Dishburger et al. 1977
Bovine fat	Tissue extraction and sweep co-distillation to isolate analytes. Extract clean-up using activated Florisil followed by extract volume reduction.	GC/NPD	No data	92 (5% RSD) at 0.4 mg/kg (ppm, w/w)	Brown et al. 1987

Table 6-2. Analytical Methods for Determining Chlorpyrifos and Transformation Products in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Butter fat, potatoes	Dispersion of homogenized sample with pelletized diatomaceous earth (Hydromatrix), packing into high pressure extraction cell, and extraction with supercritical carbon dioxide. Collection of extracts from fatty samples into a flask and clean-up using GPC and Florisil adsorption chromatography. Extracts from non-fatty samples trapped onto a Florisil column. Chlorpyrifos elution with acetone.	GC/NPD	<0.06 ppm (w/w)	Butter fat: 90 (0.06–0.6 ppm) potatoes: 97 at 0.120 ppm	Hopper and King 1991
Lettuce, strawberries, and tomatoes	Sample homogenization with acetone followed by filtration; pesticide extraction into organic phase by shaking with petroleum ether and methylene chloride. Water removal from extract and organic phase volume reduction in presence of petroleum ether and then acetone to remove methylene chloride.	GC/NPD (AOAC Method 985.22)	No data	No data	Helrich 1990b
Cucumbers, lettuce, radishes, strawberries, tomatoes, witloof chicory	Extraction of homogenized sample with acetone. Analytes recovered via back extraction with methylene chloride followed by water removal and clean-up using activated carbon-silica gel.	GC/NPD (German Pesticides Commission Method S8)	0.05 mg/kg (0.05 ppm, w/w) at 0.5 mg/kg	>70	Thier and Zeumer 1987a

Table 6-2. Analytical Methods for Determining Chlorpyrifos and Transformation Products in Environmental Samples (continued)

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Potatoes, lettuce, citrus fruit	Extraction of homogenized plant material with acetone and saturation of this extract with NaCl and dilution with methylene chloride. Clean-up of organic phase using GPC and silica gel column chromatography.	GC/FPD (German Pesticide Commission Method S19)	No data	>70	Thier and Zeumer 1987b
Non-fatty foods (chlorpyrifos and chlorpyrifos oxygen analog.)	Sample homogenization with acetone followed by filtration. Residues partitioned into methylene chloride and petroleum ether after addition of NaCl. Alternatively, acetone solution passage through Hydromatrix (diatomaceous earth) and residue elution with methylene chloride.	GC/FPD, GC/HECD, GC/NPD (US FDA PAM1 Method 302)	Approximately 20 ppb (w/w, µg/kg) depending on analytical system used	>80	FDA 1994a
Dates (chlorpyrifos and oxygen analog)	Extraction of homogenized sample with benzene. Application of extract to silica gel column and elution with benzene to collect chlorpyrifos and then with acetone to recover the oxygen analog.	GC/NPD	0.01 ppm (w/w, mg/kg) for chlorpyrifos; 0.05 ppm for oxygen analog	93 for chlorpyrifos and 84 for oxygen analog over concentration range 0.01–2.0 ppm	Mansour 1985

[a] Unless otherwise specified, method is for chlorpyrifos. If method was applied to transformation products, these are indicated in parentheses with the matrix studied.

AOAC = Association of Official Analytical Chemists; ECD = electron capture detector; EPA = Environmental Protection Agency; FPD = Flame photometric detector; GC = gas chromatography; GPC = gel permeation chromatography; HPLC = high performance liquid chromatography; MS = mass spectrometry; NCIMS = negative ion chemical ionization mass spectrometry; NPD = nitrogen phosphorus detector (thermionic); OSHA = Occupational Safety and Health Administration; RSD = relative standard deviation; SD = standard deviation; SPE = solid phase extraction; TCP = 3,5,6-trichloropyridinol; TLC = thin layer chromatography; UV = ultraviolet absorbance detection; v/v = volume/volume; w/v = weight/volume

6.2 ENVIRONMENTAL SAMPLES

Methods for the determination of chlorpyrifos and environmental transformation products are shown in Table 6-2.

The analytical methods for chlorpyrifos in air are based on GC with some form of selective detection. For air matrices, collection methods rely on the entrapment of chlorpyrifos onto a polymeric material, such as XAD or polyurethane foam, as the air is pulled through the sorbent (EPA 1988c; Fenske et al.1990; OSHA 1986). The analyte is subsequently recovered from the sorbent through solvent extraction. Losses of chlorpyrifos can occur during Soxhlet extraction or extract concentration using Kudema-Danish devices as a result of the boiling chips used (Hsu et al. 1988). Thus, it is very important that the performance of any method be verified prior to its application in a study. The proper use of field control samples is also very important. Reported LODs were as low as sub parts per trillion (EPA 1988c). Although chlorpyrifos can be converted to its oxygen analog (thiophosphate to phosphate) under normal environmental conditions (see Chapter 5), none of the methods surveyed indicated that this conversion was problematic for the determination of chlorpyrifos in air.

In the case of water, soils, and wastes, sample preparation is based on liquid/liquid extractions (EPA 1986c, 1986d, 1992b, 1992c; Sherma and Slobodien 1984), solid phase extraction (SPE) (Bogus et al.1991; Johnson et al. 1991; Lacorte et al. 1993; Mattem et al. 1991), or Soxhlet extractions (EPA 1986c, 1986d). Humic material in natural waters can reduce recoveries of chlorpyrifos in SPE-based sample preparation (Johnson et al. 1991). The decreased recovery is hypothesized to be the result of inefficient trapping of the chlorpyrifos/humic material complex. EPA Method 507 for the determination of nitrogen- and phosphorus-containing pesticides in drinking water (EPA 1991) should be applicable to chlorpyrifos but has not been validated for this compound. Soxhlet extractions are commonly employed in methods used to study chlorpyrifos residues in carpet dust and on surfaces sampled using wiping approaches (Fenske et al. 1990; Lewis et al. 1994). Supercritical fluid extraction (SFE) has shown promise for the recovery of chlorpyrifos from environmental solids (Lopez-Avila et al. 1991; Miles and Randall 1992). Chlorpyrifos in sample extracts is typically determined using GC, although thin-layer chromatography (TLC) and high-performance liquid chromatography (HPLC) have also been employed (Bogus et al. 1990; Sherma and Slobodien 1984). Sherma and Slobodien (1984) also used TLC to quantify the chlorpyrifos transformation product TCP in drinking water. Gerhart and Cortes (1990) have reported a method for chlorpyrifos that used direct

injection of well water into a GC retention gap. Reported lower LODs for chlorpyrifos ranged from 5 ppt (w/v) for surface water (Mattem et al. 1991) to 3 ppm (w/w) for soils and sludges (EPA 1986c).

The determination of chlorpyrifos and its transformation products, especially chlorpyrifos oxygen analog and TCP in foods has received considerable attention. Foods are generally divided into fatty (animal products, oils) and non-fatty types (produce). Chlorpyrifos is fairly non-polar and thus tends to partition into fat. This dictates that slightly different methods be used for the extraction of fatty and non-fatty samples. In general, chlorpyrifos, chlorpyrifos oxygen analog, and TCP are extracted from fatty foods using petroleum ether (Hunt et al. 1969), methylene chloride/acetone (Leoni et al. 1992), methanol/methylene chloride (Holstege et al. 1991) acetonitrile (Clabom et al. 1968), or methanol (Dishburger et al. 1977). The sample or initial extracts are usually acidified followed by additional extraction steps to recover TCP (Dishburger et al. 1977; Inman et al. 1981). Non-fatty samples are most often extracted with acetone (FDA 1994a; Helrich 1990b; Thier and Zeumer 1987a, 1987b), although the use of benzene has also been reported (Mansour 1985). Supercritical fluid extraction has been successfully used to recover chlorpyrifos from potatoes and butter fat (Hopper and King 1991) and grass (Cortes et al. 1991).

The determinative step for chlorpyrifos, chlorpyrifos oxygen analog, and TCP is usually GC in conjunction with selective detection such as flame photometric detection (FPD), nitrogen phosphorus thermionic detection (NPD), or electron capture detection (ECD). Depending on the original sample matrix, additional clean-up can be required to remove fats or other material that can interfere with the chromatography (Walters 1990) or with detection (FDA 1994a). In addition, natural sample constituents, such as large amounts of sulfur-containing compounds in cauliflower, onions and broccoli, can increase the FPD background detector signal and make the method less sensitive (Lee and Wylie 1991). Common approaches to further extract purification include SPE (Gillespie and Walters 1991; Leoni et al. 1992; Thier and Zeumer 1987a, 1987b), gel permeation chromatography (GPC) (FDA 1994a; Holstege et al. 1991; Thier and Zeumer 1987b), Florisil column chromatography (Brown et al. 1987; Clabom et al. 1968; FDA 1994a; Hopper and King 1991; Leoni et al. 1992), sweep co-distillation (Luke and Richards 1984) and HPLC (Gillespie and Walters 1986, 1989). The adequate recovery of the desired compound must be validated for the fractionation technique to be used. For example, SPE cartridges from different vendors or production lots have been shown to affect retention and recovery (Gillespie and Walters 1991). Chlorpyrifos oxygen analog has been found to be hydrolyzed by activated silica (Braun 1974). Florisil can also give rise to poor recoveries

of chlorpyrifos oxygen analog (FDA 1994a, 1994b; Leoni et al. 1992). The FDA method for fatty foods or cornposited food (Method 304) can be applied with limited success to chlorpyrifos (variable recovery) but not at all to the oxygen analog (FDA 1994b).

TLC has been used to separate chlorpyrifos and TCP (Judge et al. 1993) and to screen for 170 commonly used pesticides, including chlorpyrifos (Erdmann et al. 1990). Additional analytical techniques that have been applied to chlorpyrifos include GC with atomic emission detection (Lee and Wylie 1991), GC with pulsed positive ion/negative ion chemical ionization mass spectrometry (Stan and Kellner 1989), simultaneous analysis on two GC columns with both ECD and electrolytic conductivity detectors (Hopper 1991), and two-dimensional GC with simultaneous detection by ECD, NPD, and FPD (Stan and Heil 1991).

6.3 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 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.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Chlorpyrifos and TCP can serve as biomarkers of exposure. TCP will be present at much greater concentrations relative to chlorpyrifos, so it is a better and more sensitive marker of exposure (He 1993; WHO 1975). The method for TCP in urine published by Bartels and Kastl (1992) should be adequately sensitive to study

background concentrations in the general population because they measured low concentrations in control urine from presumably unexposed individuals. A LOD of 0.5 ng/mL (0.5 ppb, w/v) for TCP in urine was stated. The methods of Nolan et al. (1989) and Jitsunari et al. (1989) for TCP in blood and urine claim an LOD of 10 ppb with a reproducibility of 4% at 100 ppb. Chlorpyrifos oxon was not detected in serum and urine of poisoned persons, presumably because of the rapid rate of hydrolysis of the oxon relative to its rate of formation from chlorpyrifos (Drevenkar et al. 1993). The metabolites DEP and DETP can serve as markers of exposure to chlorpyrifos but can also be present as a result of exposure to organophosphorus compounds that have the same phosphate moiety. Thus, they are not specific. Exposure to organophosphorus pesticides also results in decreases in whole blood and erythrocyte acetylcholinesterase activities (Drevenkar et al. 1993; He 1993) and are not specific to exposure to chlorpyrifos. The best marker of exposure to chlorpyrifos appears to be TCP, for which there are adequate methods; therefore, no new methods for TCP are needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available for the determination of chlorpyrifos in air at sub-ppb concentrations (EPA 1988c; Fenske et al. 1990; OSHA 1986) and are adequate to estimate potential exposures of the general population. No methods were found for chlorpyrifos oxon in air. It has been reported that the oxon is more toxic than the parent compound (Drevenkar et al. 1993), but it does not persist (Walia et al. 1988). No additional methods are needed.

The predominant route of exposure to chlorpyrifos is through contact with contaminated environmental matrices such as food and water. Methods for the determination of chlorpyrifos in water, wastes, soils, and foods are available that have LODs in the ppb and sub-ppb range (e.g., EPA 1992c; FDA 1994a; Gerhart and Cortes 1990; Gillespie and Walters 1991; Mansour 1985; Mattem et al. 1991). Assuming an oral MRL of 0.003 mg/kg/day (Chapter 2), 2 L/day water consumption and a 70-kg person, this converts to a needed method LOD of 0.105 ppm (w/v) in drinking water. Reported LODs in water are 2 ppb (Sherma and Slobodien 1984), 0.9 ppb (Gerhart and Cortes 1990), 0.1 ppb (Lacorte et al. 1993), 0.005 ppb (Mattem et al. 1991), and 5 ppb (Bogus et al. 1990). These methods are sufficiently sensitive to detect concentrations at or below the MRL. Method reproducibilities range from 4 to 16% and will be adequate for most measurements. If 2 kg/day food consumption is assumed, method LODs of 0.105 ppm or 105 ppb (w/w) are needed. The methods of Hunt et al. (1969), Leoni et al. (1992), Lino and Noronha da Silveira (1994), Clabom et al. (1968), Ivey and Clabom (1968), Dishburger et al. (1977), Hopper and King (1991), Thier and Zeumer (1987a), FDA (1994a), and

Mansour (1985) claim method LODs that range from 2 to 100 ppb and are sufficiently sensitive to detect concentrations at or below the MRL. No reproducibility information was available. No additional methods for chlorpyrifos in foods are needed.

Methods are also available for the determination of the oxon in some foods (tissue and produce) (FDA 1994a; Ivey and Claborn 1968; Mansour 1985) at the sub-ppm level. Chlorpyrifos and its oxon are quickly hydrolyzed to TCP; some methods exist for the determination of TCP in drinking water (Sherma and Slobodien 1984), peppermint oil (Gillespie and Walters 1991), and bovine tissue (Dishburger et al. 1977).

6.3.2 Ongoing Studies

Researchers at North Dakota State University (Fargo) and at the University of Maine, Department of Food Science, have been working on immunochemical-based methods for the determination of chlorpyrifos.

Researchers at the U.S. Department of Agriculture in Beltsville, Maryland; at the University of Florida (Gainesville) Department of Food Science and Nutrition; and at the University of Puerto Rico (Mayaguez), Crop Protection, are working on fate and transport of chlorpyrifos in the environment and will be developing methods as needed to define the processes and to develop models to predict fate and transport.

Researchers at National Taiwan University (Taipei) are studying the degradation of chlorpyrifos residues in meat and poultry as a function of cooking methods for modeling purposes and might need to develop some methods.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding chlorpyrifos in air, water, and other media are summarized in Table 7-l.

ATSDR has derived a Minimal Risk Level (MRL) of 0.003 mg/kg/day for both acute (14 days or less) and intermediate (15-364 days) duration oral exposure to chlorpyrifos, based on a NOAEL of 0.03 mg/kg/day observed in human adult males exposed orally to chlorpyrifos (Coulston et al. 1972). An uncertainty factor of 10 was used in the calculation of the MRL to account for variability in susceptibility within the human population.

ATSDR has derived a chronic-duration oral MRL of 0.001 mg/kg/day, based on a NOAEL for acetylcholinesterase inhibition in rats exposed to 0.1 mg/kg/day chlorpyrifos in feed for 2 years (McCollister et al. 1974). An uncertainty factor of 100 was used in the calculation of the MRL: 10 for extrapolation from animals to humans and 10 for variability within the human population.

The U.S. EPA oral reference dose for chlorpyrifos is $3x10^{-3}$ mg/kg/day (IRIS 1994). No inhalation reference concentration exists for this compound.

Chlorpyrifos is one of the chemicals regulated under "The Emergency Planning and Community Rightto-Know Act of 1986" (EPCRA) (EPA 1988a). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

An Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for chlorpyrifos has not been set.

Chlorpyrifos is designated a hazardous substance and subject to regulations implementing Section 311 of the Federal Water Pollution Act (EPA 1978b) and Section 311 of the Clean Water Act (EPA 1986b). A maximum contaminant level in (MCL) drinking water does not exist.

Tolerances for chlorpyrifos in raw agricultural commodities, foods, and animal feeds have been established by EPA (EPA 1987, 1982, 1979) ranging from 0.05 to 25 ppm.

Table 7-1. Regulations and Guidelines Applicable to Chlorpyrifos

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
WHO	Drinking-water guideline values for health-related organics	None	WHO 1984
NATIONAL			
Regulations:			
a. Water			
EPA OW	Designation of Hazardous Substances	Yes	40 CFR 116.4 EPA 1978a
	Reportable Quantities of Hazardous Substances Pursuant to the Clean Water Act	1 lbs.	40 CFR 117.3 EPA 1986a
	National Pollutant Discharge Elimination System (NPDES) -- List of Toxic Pollutants and Hazardous Substances	Yes	40 CFR 122, App. D EPA 1993a
	Instructions -- Form 2c, NPDES Criteria and Standards	Yes	40 CFR 125 EPA 1984
	Proposed Rule: Water Quality Guidance for the Great Lakes System	Yes	58 FR 20802 EPA 1993b
b. Food:			
EPA OPTS	Tolerances for Related Pesticide Chemicals	Yes	40 CFR 180.3 EPA 1976b
	Tolerance Range for Agriculture Products	0.05–15.0 ppm	40 CFR 180.342 EPA 1987
	Listing of Pesticide Chemicals	Yes	40 CFR 180 EPA 1976a
	Tolerance in Food: Citrus Oil Corn Oil Mint Oil Peanut Oil	Yes 25 ppm 3.0 ppm 10.0 ppm 1.5 ppm	40 CFR 185.1000 EPA 1982a
	Tolerance Range in Animal Feeds	0.5–15.0 ppm	40 CFR 186.1000] EPA 1979
c. Other			
EPA OERR	Reportable Quantity	1 lb.	40 CFR 302.4 EPA 1989
Guidelines:			
a. Air:			
ACGIH	Threshold Limit Value for Occupational Exposure (TLV-TWA)	0.90 mg/m^3 (skin)	ACGIH 1994
NIOSH	Recommended Exposure Limit for Occupational Exposure (TWA)	0.2 mg/m^3	NIOSH 1992
	Recommended Exposure Limit for Occupational Exposure (STEL)	0.6 mg/m^3	NIOSH 1992
NRC	Recommended maximum air concentration in residential houses	10 µg/m^3	NAS/NRC 1982

Table 7-1. Regulations and Guidelines Applicable to Chlorpyrifos (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
b. Water:			
EPA OW	1-d Health Advisory	0.03 mg/L (child)	EPA 1994
	10-d Health Advisory	0.03 mg/L (child)	EPA 1994
	Lifetime Health Advisory	0.02 mg/L	EPA 1994
	Longer-term Health	0.03 mg/L (child 0.1 mg/L (adult)	EPA 1994
	Drinking water cancer classification	D (not assigned)	EPA 1995
c. Other			
EPA	RfD	$3x10^{-3}$ mg/kg/day	IRIS 1997
STATE			
Regulations and Guidelines:			
a. Air:	Average Acceptable Ambient Air Concentrations		NATICH 1992
CT	8-hour	4.00 µg/m^3	
FL-Pinella	8-hour 24-hour	2.00 µg/m^3 0.48 µg/m^3	
ND	8-hour 1-hour	0.002 mg/m^3 0.006 mg/m^3	
NV	8-hour	0.005 mg/m^3	
TX	30-minutes Annual	2.00 µg/m^3 0.20 µg/m^3	
VA	Annual	3.30 µg/m^3	
WA-SWEST	24-hour	0.70 µg/m^3	
b. Water:	Water Quality: Human Health		FSTRAC 1990
VT	Drinking Water Standard	21 µg/L	
AR	Water Quality Criteria: Human Health		CELDs 1994
	Toxic Substances - Chronic Toxicity 4-day avg	0.041 µg/L	
	Toxic Substances - Acute Toxicity - 1-hr avg	0.083 µg/L	
HI	Toxic Substances Applicable to All Waters		
	Fresh water acute	0.083 µg/L	
	Fresh water chronic	0.041 µg/L	
	Saltwater acute	0.011 µg/L	
	Saltwater chronic	0.0056 µg/L	
	Fish consumption	NS	
	Water Quality Criteria: Aquatic Life		CELDs 1994
CO	Aquatic Life Segments Organic Compounds to Second Power		
	Standard acute	0.083 µg/L	
	Standard chronic	0.041 µg/L	

Table 7-1. Regulations and Guidelines Applicable to Chlorpyrifos (continued)

Agency	Description	Information	References
STATE			
PR	Maximum Allowable Conc. for Organothiophosphorus and Other Non-Persistent Pesticides		
	Coastal estuaries	0.0056 µg/L	
	Surface waters	0.41 µg/L	
	Groundwaters	0.041 µg/L	
OK	Numeric Criteria for Toxic Substances to Protect Fish and Wildlife		
	Acute	.083 µg/L	
	Chronic	.041 µg/L	
VT	WQ Criteria for Protection of Aquatic - Biota		
	Acute	.083 µg/L	
	Chronic	.041 µg/L	
	Restricted Pesticides		
NJ		All conc. above 15%	CELDs 1994

ACGIH = American Conference of Governmental Industrial Hygienists; CELDs = Computer-assisted Environmental Legislative Database; EPA = Environmental Protection Agency; FSTRAC = Federal State Toxicology and Regulatory Alliance Committee; IRIS = Integrated Risk Information System; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; RfD = Reference Dose; STEL = Short-term Exposure Limit; TLV = Threshold Limit Value; TWA = Time Weighted Average

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9. GLOSSARY

Acute Exposure-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc})-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity-Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity-The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo-Occurring within the living organism.

Lethal Concentration($_{LO}$) (LC_{LO})-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration $_{(50)}$ (LC_{50})-A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose ($_{50}$) (LD_{50}) -The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose $_{(50)}$ (LD_{50})-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time $_{(50)}$ (LT_{50})-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced af this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1*- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 1.5 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50})-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 994991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for

establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name: Chlorpyrifos
CAS number: 508 15-00-4
Date: August 1997
Profile status: Final Post-public Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 5
Species: Human

MRL: 0.003 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Coulston et al. (1972)

Exnerimental design: 16 adult human male volunteers (4 per dose group) were treated with 0,0.014,0.03, or 0.10 mg/kg/day chlorpyrifos by capsule. Those subjects receiving 0.014 and 0.03 mg/kg/day were exposed for 20 days; those receiving 0.10 mg/kg/day were exposed for only 9 days.

Effects noted in study and corresnonding doses: Those subjects receiving 0.10 mg/kg/day were exposed for only 9 days because of blurred vision and a runny nose in one of the subjects. Plasma cholinesterase was decreased approximately 65% compared to controls in that group. No effect on plasma cholinesterase was seen at the lower doses and erythrocyte cholinesterase was unaffected by any of the chlorpyrifos doses. Thus, the NOAEL for chlorpyrifos plasma cholinesterase inhibition was 0.03 mg/kg/day. Based on this NOAEL, an MRL of 0.003 mg/kg was calculated: 0.03 mg/kg divided by an uncertainty factor of 10 for human variability. Please note that the combination of 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.

MRL = Human dose t Uncertainty factor

= 0.03 mg/kg ÷ 10

= 0.003 mg/kg

Dose endpoint used for MRL derivation: Plasma cholinesterase inhibition

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[] 1 [ ] 3 [ ] 10(for use of a LOAEL)

[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)

[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from num in food or water to a mg/bodv weight dose? No.

If so, explain:

If an inhalation studv in animals. list conversion factors used in determining human eauivalent dose:

APPENDIX A

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Was a conversion used from intermittent to continuous exposure? No.

If so, explain:

Other additional studies or pertinent information that lend support to this MRL:

Deacon et al. (1980) *Embryotoxicity and Fetotoxicity of Orally Administered Chlorpyrifos in Mice.*Toxicology and Applied Pharmacology. 54, 31-40.

The MRL study is further supported by a study by Deacon et al. (1980). Female CF-1 mice were exposed by gavage to 1, 10, or 2 mg/kg/day Dursban F® (96.8% chlorpyrifos) as a solution in cottonseed oil on gestation day (Gd) 6, Gds 610, or Gds 6-15. Controls received cottonseed oil alone. Five hours after the final dosing (Gds 6, 10, or 15) blood was obtained via cardiac puncture and plasma and erythrocyte cholinesterase activities determined. Plasma and erythrocyte cholinesterase levels were significantly decreased from control values among mice given 10 or 25 mg/kg chlorpyrifos on day 6 (plasma, 95 and 97%, respectively; erythrocyte, 40 and 20%, respectively) and, days 6-10 (plasma, 97 and 99%, respectively; erythrocyte, 43 and 71%, respectively), or Gds 6-15 (plasma, 96 and 98%, respectively; erythrocyte, 43 and 57%, respectively). Plasma cholinesterase levels were significantly reduced among mice given 1 mg/kg chlorpyrifos during the same time intervals (69, 78, and 85%, respectively). Erythrocyte cholinesterase levels were also reduced (43%) after 1 mg/kg chlorpyrifos, but only after exposure on Gds 6-10. In a concurrent study, no effects on plasma or erythrocyte cholinesterase activity were observed at 0.1 mg/kg chlorpyrifos.

Agency Contact (Chemical Manager): John F. Risher, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name: Chlorpyrifos
CAS number: 50815-00-4
Date: July 1997
Profile status: Final Post-public Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 15
Species: Human

MRL: 0.003 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Coulston et al. 1972.

Experimental design: 16 adult human male volunteers (4 per dose group) were treated with 0, 0.014, 0.03, or 0.10 mg/kg/day chlorpyrifos by capsule. Those subjects receiving 0.014 and 0.03 mg/kg/day were exposed for 20 days; those receiving 0.10 mg/kg/day were exposed for only 9 days.

Effects noted in study and corresnonding doses: Those subjects receiving 0.10 mg/kg/day were exposed for only 9 days because of blurred vision and a runny nose in one of the subjects. Plasma cholinesterase was decreased approximately 65% compared to controls in that group. No effect on plasma cholinesterase was seen at the lower doses and erythrocyte cholinesterase was unaffected by any of the chlorpyrifos doses. Thus, the NOAEL for chlorpyrifos plasma cholinesterase inhibition was 0.03 mg/kg/day. Based on this NOAEL, an MRL of 0.003 mg/kg was calculated: 0.03 mg/kg divided by an uncertainty factor of 10 for human variability. Please note that the combination of 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.

MRL = Human dose ÷ Uncertainty factor

$$= 0.03 \text{ mg/kg} \times \frac{1}{10}$$
$$= 0.003 \text{ mg/kg/day}$$

Dose endpoint used for MRL derivation: Plasma cholinesterase inhibition

[X] NOAEL [ ] LOAEL
Uncertainty factors used in MRL derivation:
[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a ma/body weight dose? No.
If so, explain:

If an inhalation study in animals, list conversion factors used in determining. human equivalent dose:

Was a conversion used from intermittent to continuous exposure? No.
If so, explain:

Other additional studies or pertinent information that lend support to this MRL:

Deacon et al. (1980) *Embryotoxicity and Fetotoxicity of Orally Administered Chlorpyrifos in Mice.* Toxicology and Applied Pharmacology. 54, 31-40.

The MRL study is further supported by a study by Deacon et al. (1980). Female CF-1 mice were exposed by gavage to 1, 10, or 2 mg/kg/day Dursban F® (96.8% chlorpyrifos) as a solution in cottonseed oil on Gds 6, 6-10, or 6-15. Controls received cottonseed oil alone. Five hours after the final dosing (Gds 6, 10, or 15), blood was obtained via cardiac puncture and plasma and erythrocyte cholinesterase activities determined. Plasma and erythrocyte cholinesterase levels were significantly decreased from control values among mice given 10 or 25 mg/kg chlorpyrifos on day 6 (plasma, 95 and 97%, respectively; erythrocyte, 40 and 20%, respectively) and, days 6-10 (plasma, 97 and 99%, respectively; erythrocyte, 43 and 71%, respectively), or Gds 6-15 (plasma, 96 and 98%, respectively; erythrocyte, 43 and 57%, respectively). Plasma cholinesterase levels were significantly reduced among mice given 1 mg/kg chlorpyrifos during the same time intervals (69, 78, and 85%, respectively). Erythrocyte cholinesterase levels were also reduced (43%) after 1 mg/kg chlorpyrifos, but only after exposure on Gds 6-10. In a concurrent study, no effects on plasma or erythrocyte cholinesterase activity were observed at 0.1 mg/kg chlorpyrifos.

Agency Contact (Chemical Manager): John F. Risher, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name: Chlorpyrifos
CAS number: 50815-00-4
Date: July 1997
Profile status: Final Post-public Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [] Intermediate [X] Chronic
Key to figure: 42
Species: Rat

MRL: 0.001 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: McCollister et al. 1974

Experimental design: Sherman rats (25 males and 25 females) were dose fed chlorpyrifos at 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 cholinesterase (ChE) determinations. Clinical observations, body weights, food consumption and mortality were monitored. At 6-month intervals, blood and urine samples were collected from selected rats receiving 0, 1, or 3 mg/kg/day. The packed cell volume, hemoglobin, erythrocyte count and total and differential leucocyte counts were determined in the blood. Urine was analyzed for total solids, pH, albumin, sugar, occult blood and ketones. The ChE activity of the plasma and red blood cells (RBC) was determined for all rats in the groups that were killed after receiving the test diets for 1 week, and 1, 3, 6, 9, 12, and 18 months, as well as for selected rats from those given each dose for 2 years. Brain ChE was measured in rats killed at 6, 12, 18, and 24 months. To characterize the recovery of the ChE activity in plasma, red cells and brain, some rats were maintained on the various diets containing chlorpyrifos for 12 months, and subsequently on the control diet for 7-8 weeks prior to sacrifice. Blood urea nitrogen (BUN), serum alkaline phosphatase (AP) and serum glutamic-pyruvic transaminase (SGPT) were determined on blood samples collected from rats killed at 12, 18, and 24 months. Necropsies were conducted on all rats killed at 12, 18, and 24 months and on those that received control feed for 7-8 weeks after having received chlorpyrifos diets for 12 months. These rats were fasted for 16 hours, decapitated, and weighed. The brain, heart, liver, kidney, spleen, and testes were removed and weighed. Portions of these tissues were preserved in 10% formalin, and histopathological examinations were performed on these tissues, as well as eye, pituitary, thyroid, and parathyroid glands, trachea, esophagus, lungs, aorta, stomach, pancreas, small intestine, colon, mesenteric lymph nodes, urinary bladder, accessory sex glands, ovaries, uterus, skeletal muscle, sciatic nerve, spinal cord, sternum, sternal bone marrow, adrenal gland, and any nodules or masses suggestive of tumor development or other pathological processes. Histopathological examinations were also conducted on the tissues of all rats exhibiting grossly visible nodules or masses, and on those killed in a moribund state or that died spontaneously, unless this was precluded by autolysis.

Effects noted in study and corresponding doses: Clinical observations did not detect evidence of a cholinergic overstimulation or any other compound-related effect. Brain cholinesterase (ChE) activity in both male and female rats displayed an overall reduction of 56% in rats fed 3 mg/kg/day chlorpyrifos during the 2-year study. No overall effect on brain ChE was observed at the lower doses. Plasma and RBC ChE activity were depressed for both male and female rats dosed with diets containing 1 or 3 mg/kg/day chlorpyrifos. At 1 mg/kg/day chlorpyrifos, plasma ChE was depressed

20-53%; RBC ChE activity was decreased 65-70% at that dose. 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 of rats fed chlorpyrifos-containing diets for 1 year returned to normal levels after switching to a control diet for 7-8 weeks. There was no effect of treatment on organ weights, histopathology, or number and types of tumors. It was concluded that 0.1 mg chlorpyrifos/kg/day fed in the diet for 2 years produced no significant toxicological effect in rats.

MRL = Human dose + Uncertainty factor (UF = 10 for extrapolation from animal data; UF = 10 for human variability)

$$= 0.1 \text{ mg/kg/day} \times \frac{1}{10} \times \frac{1}{10}$$

$$= 0.00\,1 \text{ mg/kg/day}$$

Dose endpoint used for MRL derivation: Acetylcholinesterase inhibition

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Was a conversion used from intermittent to continuous exposure? No.
If so, explain:

Other additional studies or pertinent information that lend support to this MRL: No.

Agency Contact (Chemical Manager): John F. Risher, Ph.D.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer endpoints, and EPA's estimated range associated with an upperbound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures aredeath, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more datapoints using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Freouencv/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset ofcarcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg /kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates-of the slope of the cancer dose response curve at low dose levels (q_l*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

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SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
					↓		
Cancer							
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer endpoints (if derived) and the endpoints from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram