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OFFICE OF
PREVENTION, PESTICIDES AND
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SUBJECT: Review of Chlorpyrifos Poisoning Data

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I. INTRODUCTION

Chlorpyrifos (trade name Dursban, Lorsban and others) is an organophosphate insecticide widely used in the United States. As a result of this widespread use, there have been numerous exposures and poisonings. Detailed analysis of the incident data identified specific use patterns that are more likely to be associated with pesticide poisoning. Depending on the type of use, risk mitigation measures are recommended to reduce the associated types of poisoning. In addition to acute poisoning, chlorpyrifos and other organophosphate insecticides have been reported to be associated with chronic effects in humans, including peripheral neuropathy, chronic neurobehavioral effects, and the reported development of a sensitivity to chemicals previously tolerated which is associated with a wide variety of symptoms. Evidence for these effects is also reviewed.

The purpose of this document is to summarize the case reports, case series, statistical surveys, and epidemiologic studies of acute and chronic health effects reported to be related to chlorpyrifos. By its nature, such information suffers a number of limitations including inadequate documentation of exposure and effects, reporting biases, and absence of denominator information on the population at risk. Where consistent patterns of risk factors are identified, it is also the purpose of this document to recommend measures to mitigate those risks. To facilitate the reader's review the following listing of contents is provided:

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II. SUMMARY AND CONCLUSION

Chlorpyrifos is one of the leading causes of acute insecticide poisoning incidents in the United States. This finding is based largely on an examination of Poison Control Center reports (Litovitz et al. 1995, AAPCC 1995, Blondell 1994). Much of this frequency is accounted for by the widespread use of this chemical both inside and outside the home. Not counting synergists, chlorpyrifos was the fourth most common insecticide found in U.S. homes in a survey conducted by EPA in 1990 (Whitmore et al. 1992).

Chambers and Schneider (1995) report that chlorpyrifos was first registered in 1965 and that currently there are 972 active labels of pesticide products with this active ingredient. Dursban sales have increased 26 fold since 1975. By examining existing reporting systems and various usage patterns, certain types of use appear to pose greater health risks while other types of use are associated with little or no significant health impacts. This finding may be biased by problems with surveying certain user groups (e.g., agricultural fieldworkers). Available limited data suggest that incidence of human poisonings associated with use of flea collars and spray cans in residential settings and agricultural use of chlorpyrifos are comparable to other insecticides. Additional surveys of poisoning are needed to confirm this finding.

The main concern with chlorpyrifos appears to be liquids (not including aerosol cans) used by homeowners or Pest Control Operators (PCOs) indoors or outdoors, termite treatments, and liquid sprays and dips applied to domestic animals. The number of homes and applications involving PCOs is needed to better understand the population at risk. This information would help determine the incident rate, the primary measure of risk.

In order to better understand the circumstances of poisoning and the nature of the health effects, a comprehensive prevalence survey is recommended (see recommendations 1-2 below). However, several common-sense interim measures to reduce risk from chlorpyrifos (recommendations 3-9 below) can be implemented immediately to reduce the risk of poisoning. Most of the more serious poisonings appear to involve misuse or inappropriate use (e.g., spills, inadvertent contamination) by a Pest Control Operator. This was found to be true in reports received by DowElanco, the California Pesticide Illness Surveillance Program, and the Office of Pesticide Programs (OPP). Measures to reduce poisoning have been suggested by DowElanco and others to reduce the likelihood of these incidents. Though limited data is currently available to support the efficacy of some of these measures, nevertheless, they are consistent with a program of product stewardship.

A review of chlorpyrifos incident data involving domestic animals has been completed as a separate review. Please see the Analysis of Chlorpyrifos IDS Data for Domestic Animals Memorandum dated January 24, 1996 from Virginia Dobozy to Bruce Kitchens. This memorandum found considerable evidence of serious adverse effects resulting from misuse of chlorpyrifos-based sprays and dips intended for use on domestic animals and premise application products.

III. RECOMMENDATIONS

1. HED (Health Effects Division) recommends that DowElanco arrange for a more detailed analysis of the 1993 and 1994 Poison Control Center data. Analyses comparable to the 1985-1992 data, omitting intentional cases, would permit analysis for trends. Additional analysis by specific products, grouping by liquid, aerosol, or solid (dust, granular or impregnated material) and by consumer use versus Pest Control Operator use (and by percent active ingredient) would be helpful. This analysis should include a review of symptoms and medical outcome. To determine whether odor is a significant factor associated with symptoms, an analysis of each symptom as a proportion of total symptoms is suggested for Dursban TC and Equity. These two termiticides are used in the same manner and Equity reportedly has no significant odor.

2. A prospective epidemiologic study or statistically valid survey is recommended for the purpose of determining the extent (how common or rare), circumstances (intensity, duration, and type of exposure), and persistence and severity of chronic health effects. Health effects to be surveyed include chronic neurobehavioral effects (see Appendix 1), symptoms of peripheral neuropathy, multiple chemical sensitivity, and reactive airway disease or asthma. Consultation with psychologists and pediatricians is recommended to determine how these endpoints can best be assessed by questionnaire. Prospective studies require a large number of cases to obtain meaningful results. The single largest source of chlorpyrifos poisonings is the Toxic Exposure Surveillance System maintained by the American Association of Poison Control Centers (AAPCC). Based on the chlorpyrifos reports submitted by DowElanco, this system receives a total of 1,000 poisonings (symptomatic cases deemed related to exposure by the poison specialist) each year. Relative risks as low as 2.5 could be detected with 80% probability for illness complaints prevalent in 1% or more of the general population. This number would be the minimum appropriate number for follow-up. A control group made up of symptomatic cases exposed to other poisons known not to be associated with chronic neurobehavioral or respiratory effects (e.g. non-cholinesterase inhibiting insecticides) is strongly recommended. A control group

would help exclude any background occurrence of chronic symptoms incidental to the chlorpyrifos exposure. A questionnaire would be administered to each documented case by Poison Control Centers initially to document exposure circumstances and subsequently, 45 days after the incident, to document symptoms and signs of chronic effects. If possible, interviewers should be blinded to case status of subjects. A quality assurance plan will be needed covering all aspects of data collection. All cases exhibiting chronic symptoms would receive follow-up every 2 months after initial exposure to determine persistence and severity of symptoms. Results from this study would be used to determine whether further restrictions of chlorpyrifos uses were warranted.

3. The Health Effects Division recommends that registrant-sponsored training and education programs be developed and implemented for PCOs using liquid chlorpyrifos indoors or for termite treatment. A pamphlet that is to be given to homeowners describing the application, advising on precautions, health effects including symptoms of adverse reactions, potential routes of exposure, protective measures for young children, what to do and who to contact in event of a spill or other accident is recommended. Input from EPA, state regulatory agencies, university extension and other interest groups should be solicited and the pamphlet field tested before being distributed.

4. Potentially hazardous applications involving broadcast or fogger treatments indoors should be considered for cancellation. Termiticide treatment of existing structures should be restricted and require the presence, onsite, of a certified applicator. Such a restriction is based partly on the potential for poisoning incidents and partly on the complexity of use and history of inadequate performance linked with improper application.

5. Based on incident reports received by the Agency, the following additional precautionary statements have been incorporated into Pesticide Regulation Notice 96-7 issued on October 1, 1996 for all termiticides (including chlorpyrifos) involving post construction treatment for termites:

a. When treating adjacent to an existing structure, the applicator must check the structure for cracks and holes to prevent any leaks or significant exposures to persons occupying the structure.

b. Persons residing in the structure during application should be advised that they and their pets should vacate the premise if they see any signs of leakage.

c. After application, the applicator should be required to check for leaks (especially into duct work). If such leaks occur, it is the applicator's responsibility to arrange for cleanup. Persons and pets should not be exposed to contaminated areas until cleanup is complete. Cleanup may include use of cleaning substances and absorbent materials along with ventilation, or replacement of contaminated materials, if they cannot be cleaned satisfactorily.

6. HED recommends measures to reduce the risk to pets including consideration of cancellation of chlorpyrifos products intended for direct application to dogs and/or cats, except flea collars. Exploration of improved methods of risk mitigation for premise application products containing chlorpyrifos is also recommended. Measures to be considered include assuring that animals are not present during treatment and reassessing the amount of time required before animals can be safely reintroduced into a treated area.

7. HED recommends that consumers not be permitted to handle chlorpyrifos concentrates intended for structural or residential application indoors or most outdoor uses. Based on calculations that would protect against infant poisoning by the oral route, HED recommends a maximum allowable concentration of 1.5% active ingredient for these types of uses. This restriction may not be practical for outdoor uses requiring large volumes of material. One way to limit the risk to young children is to permit only larger size containers that would be harder for children to pick up. For example, certain outdoor concentrates would be permitted, but only for containers larger than 1 quart. Such instances should be well-justified and involve the minimum percentages of active ingredient practical.

8. All labels of Dursban products used by PCOs and homeowners need to be upgraded to include an explicit statement about the permitted frequency of application. For example, a statement may be added stating "do not apply indoors more than once every 6 weeks". Exceptions may be needed for products used for flea control that must be reapplied more often. Similarly, home foggers (if their use is allowed to continue) should be checked to be sure they specify how many containers can be used in one application. Other label statements need to be considered to be sure that Dursban is not applied to drapery, furniture, clothing, and other surfaces likely to receive human skin contact. Specific protective measures are needed to reduce potential exposure to young children.

9. Labels for indoor use by PCOs (both homes and offices) should specify that other persons not involved in the application (e.g., office workers, children) should not be in the immediate vicinity during application. In the case of prisons, hospitals and other institutions arrangements to transport potentially sensitive persons away from the immediate vicinity of the application may be needed until sprays have dried or ventilation has reduced the odor. For heavy applications indoors (i.e., broadcast applications or foggers, if use is allowed to continue), a time interval after application when reentry would be prohibited should be considered. Methods of decontamination should be assessed to determine appropriate procedures that could be placed on the label.

10. Literature currently distributed to PCOs and homeowners by registrants needs to be rewritten in certain sections to properly warn of the poisoning hazard from this product. Statements that any symptoms that may occur are likely due to odor are not advised. Anyone experiencing headache, unusual weakness or fatigue, nausea, or dizziness should be advised to seek immediate medical attention. While some such symptoms can occur due to odor, they can also be early signs of acute cholinesterase-inhibition poisoning.

IV. DETAILED CONSIDERATIONS

A. Acute effects

1. Introduction

Chlorpyrifos is a member of the class of organophosphate (OPs) insecticides. The organophosphate insecticides are among the most widely used agents for control of insects in agricultural and residential settings. There are more than 40 organophosphates (OPs) currently registered with the EPA with a widely varying range of acute toxicity.

Chlorpyrifos and the other OPs poison humans and insects through their effects on nerve enzymes (Morgan 1989). Chlorpyrifos combines chemically with the acetylcholinesterase enzyme and inactivates it. This enzyme is essential for control of nerve impulse transmission. Loss of acetylcholinesterase allows the accumulation of acetylcholine, the substance secreted by nerves that activates muscles, glands, and other nerves (Morgan 1989). Accumulation of sufficient levels of acetylcholine at junctions between nerves and muscles will cause muscle contractions or twitching. Accumulation of acetylcholine at junctions between nerves and glands results in gland secretion. And accumulation of acetylcholine between nerves in the brain will result in sensory and behavioral disturbances.

The principle signs and symptoms of acute chlorpyrifos poisoning are headache, nausea, dizziness, pinpoint pupils, blurred vision, hypersecretion, tightness in chest, difficulty breathing, muscle weakness or twitching, difficulty walking, vomiting, abdominal cramping, and diarrhea (Namba 1971; World Health Organization 1986; Minton and Murray 1988; Karalliedde and Senanayake 1989; Morgan 1989; Gallo and Lawryk 1991). Hypersecretion of glands often results in profuse sweating and salivation, as well as tearing, runny nose, and bronchial secretions. Effects to the central nervous system may include confusion, anxiety, drowsiness, depression, difficulty concentrating, slurred speech, poor recall, insomnia, nightmares, emotional lability, or a form of toxic psychosis resulting in

bizarre behavior. In any one poisoning episode, varying combinations of these symptoms may occur at different times after exposure, varying from a few minutes to several hours. The number of symptoms present also varies depending on the dose and mode of exposure. According to Morgan, unconsciousness (coma), incontinence, convulsions, or depression of respiratory drive are evidence that the poisoning is life-threatening (Morgan 1989). Pulmonary edema (fluid in the lungs), marked miosis (pinpoint pupils) with loss of pupillary reflex, loss of reflexes and extreme muscle weakness (flaccid paralysis), ataxia (jerky movements), slurring or repetitive speech are also signs of severe, life-threatening poisoning (Namba et al. 1971; Eskenazi and Maizlish 1988; Minton and Murray 1988; Gallo and Lawryk 1991).

Poisoning due to unrecognized dermal absorption (as well as other routes of exposure) can be easily misdiagnosed, which suggests that some individual cases of poisoning are missed (Midtling et al. 1985; Coye et al. 1986). Table 1 lists symptoms and signs commonly associated with acute organophosphate insecticide poisoning. These symptoms were selected based on a review of the literature (Morgan 1989, Minton and Murray 1988, Gallo and Lawryk 1991, Namba et al. 1971).

Table 1. Examples of symptoms and signs that may be reported in acute organophosphate insecticide poisoning. Note that the presence of one or more of these symptoms can occur from other diseases and differential diagnosis by a physician is needed.

Common early or mild signs/symptoms	Present in moderate or severe poisoning	Presence signifying life-threatening severity
Headache	Tightness in chest	Coma
Nausea/Vomiting	Difficult breathing	Seizures
Dizziness	Bradycardia*	Incontinence
Muscle weakness	Tachycardia	Respiratory arrest
Drowsiness/lethargy	Hypertension	Pulmonary edema
Agitated/anxiety	Hypotension	Loss of reflexes
	Pallor/cyanosis	Flaccid paralysis
	Abdominal pain	
	Diarrhea	
	Anorexia	
	Tremor/Ataxia	
	Fasciculations*	
	Lacrimation*	
	Heavy salivation*	
	Profuse sweating*	
	Bronchorrhea*	
	Blurred vision	
	Pinpoint pupils*	
	Poor concentration	
	Confusion/delusions	
	Memory loss	

* Presence of these signs and symptoms are considered relatively specific for organophosphate insecticide poisoning (Morgan 1989, O'Malley 1992).

2. Vital Statistics on Poisoning Deaths

Only a few studies have been conducted on the national level to assess the mortality and morbidity from pesticide poisoning. Wayland Hayes, Jr. measured mortality by obtaining death certificate data from each of the 50 states for those deaths coded in categories related to pesticides (Hayes,WJ,Jr and Vaughn 1977). For each case which appeared to be pesticide-related, a letter was sent to the physician or coroner who signed the certificate. In 1973 and 1974, the last years Hayes surveyed, there were a total of 61 and 52 (respectively) accidental or possibly accidental deaths due to pesticides. Two of the cases reported in 1974 were attributed to chlorpyrifos, though the diagnosis in one of these cases was considered open to question. Given the 26 fold increase in sales of chlorpyrifos since 1975, a thorough survey of more current death certificate data could be useful. However, it is

generally acknowledged that death certificate records are a poor source for ascertaining the extent of fatalities (Friedman 1987).

More recent reporting by the National Center for Health Statistics for the years 1980 through 1992 found 73 deaths due to organophosphates and 41 deaths due to other unspecified insecticides (Center for Disease Control Wonder online service). Unlike the Hayes data, no validation was done to verify the classification of death. Also, cause of death is only identified by chemical group never by specific pesticides.

3. American Association of Poison Control Center Database

This section describes Poison Controls Centers operation and their nationwide system of data collection. The use of a standardized form for data collection, definition of key data elements, and quality assurance procedures are outlined.

Starting in 1984 the American Association of Poison Control Centers (AAPCC) made available a computerized system to collect data on all poison exposures reported to the Poison Control Centers (PCCs) nationwide (Litovitz and Veltri 1985). The system had been piloted in 1983 (Veltri and Litovitz 1984). Sixty-five Poison Centers participated in the system in 1994 representing 83 percent of the poison cases reported to all Centers in that year (Litovitz et al. 1995). Twenty-seven percent of the pesticide-related calls to Poison Centers come from health care facilities; the rest come from private individuals. Of the 1,926,438 human poison exposures reported in 1994, 109,761 were unintentional exposures due to pesticides. Of the unintentional pesticide exposures, 5,189 or 5% were due to chlorpyrifos.

Poison Centers receive telephone calls from individuals and health care providers seeking information on how to manage an exposure to a poison. Typically the Poison Center itself is run by a hospital or university. "Poison Centers function primarily to provide poison information, telephone management and consultation, collect pertinent data, and deliver professional and public information" (AAPCC 1988). Each center must have a poison information specialist available on site at all times. Written operational guidelines must be used to assure a consistent approach to the handling of all poison exposures. Included in the guidelines must be provision for follow-up of each case to determine patient's final disposition or medical outcome.

The Poison Centers participating in the Toxic Exposure Surveillance System (formerly the National Data Collection System) complete a form or computer record describing each case that contains standard data elements and a narrative section. Information collected includes the date of call, age and sex of the victim, location of victim at time of exposure (e.g., home, work

place), substance, route of exposure, initial symptom assessment, treatment received (e.g., referred to physician, hospitalized), and medical outcome. Starting in 1993 information about specific symptoms reported was also collected. Data from the form are then sent to the AAPCC for processing. A computer record is prepared and returned to the local centers (AAPCC 1988).

Patients treated at home or any other non-health care site are classified as "managed on site" (Interpretation of the AAPCC Data, AAPCC 1987). Those seen in a health care facility may be classified as either treated and released or admitted for medical care. "Admitted for medical care" is used when "the patient is observed and/or treated and subsequently admitted as an inpatient primarily to receive medical care rather than psychiatric evaluation".

When symptoms occur they are categorized into minor, moderate, or major depending on their severity and whether recovery is complete. Definitions used by the Poison Control Centers to categorize medical outcome are given in summary form below (Veltri et al. 1987).

Minor: Minimal symptoms with no residual disability (e.g., mild gastrointestinal symptoms, skin irritation, drowsiness).

Moderate: Symptoms are more pronounced, prolonged, or more of a systemic nature than minor symptoms with no residual disability. Usually some form of treatment is indicated. Examples include: high fever, disorientation, hypotension which rapidly responds to treatment and isolated brief seizures.

Major: Symptoms are life-threatening or result in residual disability or disfigurement. Examples include patients who require intubation plus mechanical ventilation, who sustain repeated seizures, cardiovascular instability, or coma.

Poison Centers collect data on each call they receive and transfer the information to the Toxic Exposure Surveillance System. Many poisoning cases seen in emergency rooms or by private physicians do not result in calls to a PCC. A study of all acute care hospitals in Utah compared all inpatient and outpatient records of poisoning with calls to the Poison Center serving Utah and found that only about one-third of the cases matched (Veltri et al. 1987). Characteristics of unmatched cases were not studied so it is not possible to say how PCC cases might differ from hospital cases that do not result in a call to a PCC. All Poison Centers supplying data to the Toxic Exposure Surveillance System must be certified, which means that certain quality assurance procedures for the data collection must be in place.

Validity of the data collected by different poison centers is an important concern of the Toxic Exposure Surveillance System. Some 65 Centers staffed by five or more personnel each are responsible for collection of the information on each case, properly coding the information and submitting it to the AAPCC which maintains the national database. Reporting by individual PCCs is dependent on how well their service is known and advertised. PCCs must meet certain minimum data quality standards in order to participate in the Toxic Exposure Surveillance System and a variety of quality assurance checks are made when the data are edited and computerized.

The use of a standard format by different Poison Centers with standard definitions for each data element means that studies can be done using two or more centers (Veltri et al. 1987). The voluntary nature of the PCC system means that not all exposures to poisons are reported in any given catchment area served by the PCC. The extent of under-reporting is not known. More importantly, it is not known whether or how reported cases differ from unreported cases. Thus, any study using PCCs as a source for cases can only be judged representative of the universe of exposures reported to PCCs and not the entire universe of all poison exposures. PCC data is a simple form of a case series and therefore is not appropriate for complicated statistical analysis or extrapolation to the general population. However, given the large proportion of the U.S. population served by PCCs and the large number of poison exposures, factors identified within this selected series are likely to be helpful for targeting particular types of exposure situations for risk mitigation.

There is an incentive for individuals and health care providers to report cases because of the immediate service provided in the form of treatment recommendations available 24 hours a day, 365 days a year. Each Poison Center must keep records on all cases handled by the Center in a form that is acceptable as a medical record (AAPCC 1988). The standardized form that is used must contain all data elements filled out and sufficient narrative to permit peer review and medical or legal audit. These forms must be submitted to the AAPCC's Toxic Exposure Surveillance System within deadlines and meet quality requirements as specified in guidance of the AAPCC.

To participate in the Toxic Exposure Surveillance System, a PCC must be certified. To be certified a PCC must fulfill the following criteria (AAPCC 1988):

1. Have a board certified physician on-call at all times with expertise in medical toxicology.
2. Have specialists in poison information who have completed a training program and are certified by the AAPCC (once eligible for certification).
3. Maintain a comprehensive file of toxicology information sources and have ready access to a major medical library.

4. Maintain written operational guidelines which provide a consistent approach to evaluation and management of toxic exposures.
5. Have an ongoing quality assurance program including regularly scheduled conferences, case reviews and audits.
6. Keep records on all cases handled by the Center with data elements and sufficient narrative to allow for peer review.
7. Submit all case data to the Toxic Exposure Surveillance System, meet deadlines and quality requirements and include all required data elements. Taken together all these criteria help assure the quality of the data.

Examination of AAPCC annual reports from 1985 through 1994 found that 13 states had little or no coverage during most of that time period (Litovitz et al. 1986-1995). They were Nevada, Oklahoma, Texas, Arkansas, Mississippi, Illinois, Iowa, North Carolina, South Carolina, Delaware, Connecticut, Vermont, and Maine. Of the 73 reported organophosphate-related deaths reported from 1980 through 1992 (reported above), 44% occurred in these 13 states that lacked coverage by the AAPCC. This suggests that the most serious cases of poisoning may be under-represented in AAPCC data. This problem of under-reporting limits the ability to extrapolate beyond the areas served by the AAPCC.

Over-reporting may also occur when symptoms are reported over the phone which cannot be confirmed by a physician or laboratory tests for exposure or effects. Though some 25% of cases are referred to the PCC by a physician, the majority involve a phone call from the victim or relative. Poison Specialists must rely on their experience and judgment to determine which cases have symptoms consistent with the toxicology, dose, and timing of the exposure. While some misclassification can be expected to occur from this approach, it is not expected to be differentially biased among pesticides. That is, there is no reason to believe that Poison Specialists are likely to misclassify chlorpyrifos more or less than other pesticides.

4. American Association of Poison Control Center Data 1985-1992

As part of a Data-Call-In (procedure requiring pesticide registrants to generate data or perform studies), registrants for 28 organophosphate and carbamate pesticides obtained 8-year summaries of the national database maintained by the AAPCC (Blondell 1994a). The 28 pesticides were selected based on the Office of Pesticide Program's concern for acute worker poisonings, especially in agricultural settings. An examination of cases reported to the California Pesticide Illness Surveillance Program found that PCCs captured only 22% of the occupational cases reported to the state (Blondell 1996). Chlorpyrifos was one of the 28 chemicals but did not rank high as a risk for worker poisoning.

The following table reports the number of cases due to chlorpyrifos.

Table 2. Number of exposures to chlorpyrifos in occupational, non-occupational adults, and children (0-5 years) reported to PCCs, 1985-1992.

Age/Occup. group	single*	mixed*	total	% mixed
Occupational** Adults	994	353	1347	26%
Non-occupational Adults	9104	1423	10527	14%
Children 0-5 years	10916	565	11481	5%
Total	21014	2341	23355	10%

* Single: cases involving exposure to single products containing chlorpyrifos. Mixed: cases involving exposure to two or more products.

** Occupational cases are defined as those that are a direct result of the victim being on the job or at the workplace when exposed.

Four measures were selected to assess the amount of hazard associated with chlorpyrifos relative to other insecticides, most of which were used primarily in agriculture. These were: percent of all cases that were seen in a health care facility; percent of cases seen in health care facility requiring hospitalization; and, of those case receiving follow-up to determine outcome, percent with symptoms and percent with life-threatening symptoms. Health care facility use and hospitalization vary regionally and are subject to socio-economic factors. Therefore, these measures have drawbacks as measures of risk. Tables 3 and 4 below summarize these data for 21,014 chlorpyrifos exposures involving single products and compare these measures with the median for all 28 insecticides.

Table 3. Percent chlorpyrifos cases seen in or referred to Health Care Facility (HCF) and percent hospitalized, compared to the median for 28 organophosphate and carbamate insecticides, by age and occupational group, Poison Control Centers 1985-1992.*

Occupational group/age	Percent seen in HCF		Percent Hospitalized	
	chlorpy-rifos	median	chlorpy-rifos	median
Occupational Adults	59.7	68.2	4.4	12.2
Non-occupational adults	33.5	44.0	8.1	9.9
Children 0-5 years	17.2	21.0	12.2	13.3

* The percent hospitalized is based on only the cases seen in HCF.

Table 4. Percent chlorpyrifos cases with known outcome with symptoms or with life-threatening symptoms, compared to the median for 28 organophosphate and carbamate insecticides, by age and occupational group, Poison Control Centers 1985-1992.*

Occupational group/age	Percent cases with symptoms		Percent with life-threatening symptoms	
	chlorpy-rifos	median	chlorpy-rifos	median
Occupational Adults	85.8	85.8	1.0	0.0
Non-occupational adults	74.9	74.0	0.3	0.0
Children 0-5 years	19.4	18.8	0.3	0.2

* Percents based on only those cases where outcome was determined.

As can be seen from table 2, chlorpyrifos has been involved in a large number of cases of exposure, averaging nearly 3,000 per year. However, analysis of cases receiving proper follow-up determined that about 1,000 cases had symptoms of poisoning consistent with their exposure. Though the numbers are high, when adjusted for the extent of use (e.g., number of containers or applications), the estimated incidence of chlorpyrifos cases is comparable with other organophosphate and carbamate insecticides (Blondell 1994a).

Relative to the other 27 organophosphates and carbamates, chlorpyrifos was responsible for roughly the same or an improved record in terms of cases seen in a health care facility or requiring hospitalization (Table 3). For occupational cases, the percent requiring hospitalization for chlorpyrifos exposure (4%) was well below the median for all 28 insecticides (12%). For either symptoms or life-threatening symptoms, chlorpyrifos was generally responsible for the same percentages as other organophosphates and carbamates (Table 4). The percentages for life-threatening cases appear higher for chlorpyrifos and, as shown below, some of this may be due to the more concentrated chlorpyrifos products used by Pest Control Operators.

Product Specific Analysis of Poison Control Center Data

More detailed analysis was needed to determine which products intended for residential use posed the greatest hazard. A review of brand-name specific data for chlorpyrifos Poison Control Center exposures was performed for the 1985-1992 data. In 25% of 21,014 exposures, no specific product name was identified. Only those products with 30 or more exposures each was included in the analysis. Of the 75 such products identified, 17 had to be excluded because of multiple formulations (with different percent active ingredients) or absence of information on the formulation. A total of 54 of the remaining 58 products were identified according to product brand name and formulation that would be used in residential areas. Ten (10) of the 54 products (including Dursbans' 1E, 2E, 4E, LO, M, TC and Empire 20) were determined to be primarily used by Pest Control Operators. The remaining 44 products appeared to be typical of products likely to be used in the home by the homeowner.

Table 5 shows 9,458 exposures to these 54 products. Of these total exposures, 16.7% involved the 10 PCO-type products and 83.3% involved homeowner-type products. A separate analysis was performed on just those cases (5,843) with outcome determined, a total of 226 (4%) had a moderate or major medical outcome and 29% of these involved PCO-related products (see Tables 6 and 7). **Thus, though PCO products account for only about 17% of the exposures, they account for a disproportionately higher proportion (29%) of the more serious cases.**

Table 5. Number of exposures and determined outcomes for 54 chlorpyrifos products in non-occupational adults, and children (0-5 years) reported to PCCs, 1985-1992.

Age group	exposures	outcome determined
Non-occupational Adults	3998	2373
Children 0-5 years	5460	3470
Total	9458	5843

Duplicating the analysis shown in Tables 3-4 gives a comparison of percents for products primarily by homeowners and primarily by PCOs (see Tables 6-7). **In every case, the measure of risk (proportion with adverse effects such as symptoms or provision of medical care) was greater for PCO products than for homeowner-type products. This is partly due to the greater percent active ingredient and, hence, inherent toxicity of PCO products, but it is also likely due to misuse and carelessness on the part of many PCOs. Though based on relatively small numbers, PCO products were 3-4 times more likely to be involved in a life-threatening exposure than homeowner products (Table 7) supporting a special effort to mitigate this type of poisoning through a comprehensive product stewardship program. In general, the increase in the proportion of adverse effects for PCO products was more pronounced in children.**

Table 6. Chlorpyrifos cases seen or referred to Health Care Facility (HCF) and percent hospitalized, by type of product and age group, Poison Control Centers 1985-1992.* Based on 9,458 exposures (N = number or numerator on which percent is based).

	Percent seen in HCF		Percent Hospitalized	
Age group	homeowner	PCO	homeowner	PCO
Non-occupational adults (N)	30.6 (877)	34.8 (393)	8.0 (70)	8.6 (34)
Children 0-5 years (N)	16.5 (828)	33.2 (150)	10.1 (84)	15.3 (23)

* The two types of product were homeowner and PCO. Homeowner refers to exposure to one of 44 products commonly used in the home by consumers and PCO refers to one of 10 products used mostly by Pest Control Operators.

Table 7. Chlorpyrifos cases with known outcome (N = 5,843) with symptoms or with life-threatening symptoms, by type of product and age group, Poison Control Centers 1985-1992.* (N = number or numerator on which percent is based).

	Percent cases with symptoms		Percent cases life-threatening symptoms	
Age group	homeowner	PCO	homeowner	PCO
Non-occupational adults (N)	72.4 (1233)	78.8 (529)	0.12 (2)	0.45 (3)
Children 0-5 years (N)	19.7 (631)	34.4 (92)	0.28 (9)	0.75 (2)

* The two types of product were homeowner and PCO. Homeowner refers to exposure to one of 44 products commonly used in the home by consumers and PCO refers to one of 10 products used mostly by Pest Control Operators.

1989 Poison Control Center Data Analysis for Children

Data on all oral pesticide exposures reported in children (aged less than 6 years) in 1989 were analyzed (Blondell 1994b). Out of 83 active ingredients used in pesticides, chlorpyrifos ranked 32nd with a ratio of 66 cases of oral exposure per 1 million containers reported in homes. The ratio was based on a total of 1,100 cases of oral exposure in 1989 and an estimated 16,652,000 chlorpyrifos containers in U.S. homes in 1990 (Whitmore et al. 1992). The median for all 83 active ingredients was 40 oral exposures per million containers. Nine of the top 10 pesticides ranked by this ratio were bait formulations which are often readily accessible to infants and young children. About half of the 1,100 chlorpyrifos exposures received successful follow-up to determine medical outcome, and none of the 1989 cases were found to have life-threatening or major medical outcome. This differs from the results in Tables 6-7 based on 1985 through 1992, where nine children exposed to products used by consumers and 2 children exposed to products used by PCOs experienced life-threatening symptoms.

5. American Association of Poison Control Centers Data 1993-1994

Fortunately, more current data have been provided, courtesy of DowElanco concerning Poison Control Center reports by the American Association of Poison Control Centers. DowElanco, on its own initiative, obtained data for two years 1993 and 1994. The total number of unintentional (i.e., not including suicide or homicide attempts) exposures reported was 4,021 in 1993 and 5,189 in 1994, a 29% increase. This large increase is primarily explained by increased reporting or coverage by Poison Control Centers. Estimated population coverage increased from 70% of the U.S. in 1993 to 83% of the U.S. in 1994, which would explain about two-thirds of the increase. However, about one-third of the increase in chlorpyrifos cases does appear to be due to other factors. It would be useful to know if sales or usage of particular types of chlorpyrifos increased markedly over this two year period. Number and percent distribution by age group is provided in the Table 8 below. Table 9 reports the medical outcome for all cases receiving follow-up. The following new categories have been added to this table:

Not followed, judged as nontoxic exposure: No follow-up calls were made to determine the patient's outcome because the substance implicated was nontoxic, the amount implicated was insignificant, or the route of exposure was unlikely to result in a clinical effect.

Not followed, minimal clinical effects possible: No follow-up calls were made to determine the patient's outcome because the exposure was likely to result in only minimal toxicity of a trivial nature (no more than a minor effect).

Unable to follow, judged as a potentially toxic exposure: The patient was lost to follow-up, refused follow-up, or was not followed but the exposure was significant and may have resulted in a moderate, major, or fatal outcome.

Unrelated effect: The exposure was probably not responsible for the effect.
Note that only 50-52% of all cases received follow-up.

Unfortunately, the number of work-related cases that were unintentional are not reported. Percent of unintentional cases requiring medical care or experiencing symptoms cannot be calculated as it was in the Tables 3-4 above. Therefore, any trends that might be present cannot be identified.

Table 8. Number of unintentional exposures to chlorpyrifos reported by Poison Control Centers, by age group in 1993 and 1994.

Age Group	Number 1993	Percent 1993	Number 1994	Percent 1994
<6 years	1966	49%	2348	45%
6-19 yrs	264	6%	357	7%
>19 yrs	1728	43%	2399	46%
unknown	63	2%	85	2%
Total	4021	100%	5189	100%

Table 9. Number of unintentional exposures to chlorpyrifos reported by Poison Control Centers, by medical outcome in 1993-4.

Medical Outcome	Number 1993	Percent of known	Number 1994	Percent of known
none	1083	53%	1138	46%
minor	825	41%	1109	45%
moderate	112	6%	186	8%
major	6	0.3%	10	0.4%
fatal	0	0%	0	0%
No follow-up, nontoxic	624	-	786	-
No follow-up, minimal	677	-	1063	-
Unable to follow, potentially toxic	217	-	249	-
Unrelated effect	477	-	648	-

Table 8 shows that young children and adults account for roughly equal numbers of calls to Poison Control Centers. Table 9 provides the information on these same cases according to medical outcome. For example, in 1994 there were 2,443 cases with known outcome (1138 none + 1109 minor + 186 moderate + 10 major + 0 fatal) or about half of the total cases. A total of 1,305 cases were judged symptomatic (minor, moderate, or major) and another 1,063 cases were judged potentially symptomatic based on the initial report, but not followed to determine medical outcome.

Starting in 1992 information was collected on the specific symptoms associated with each case of exposure. Table 10 below summarizes these reported symptoms by year and according to the severity of the symptoms as defined in Table 1. Only symptoms known to occur in systemic poisoning related to cholinesterase inhibition are included. Other symptoms of poisoning such as irritation to the eyes, skin, or respiratory tract have not been included in this table. Symptoms listed are those that were designated as likely related to the exposure to chlorpyrifos or unknown if related to exposure by the poison specialist at the Poison Control Center. These two categories were selected so that the chart below would represent the total number of cases that potentially experienced symptoms related to cholinesterase inhibition. Some of the milder symptoms (headache, nausea) may be due to the effects of odor from solvents rather than chlorpyrifos. However, these symptoms are also well-known early symptoms of organophosphate poisoning (see Table 1). Cases with symptoms deemed unrelated to the exposure were excluded. Intentional cases of exposure (e.g., suicide, homicide) were also excluded.

As would be expected, the early, generally milder, signs and symptoms of poisoning (see Table 1, page 9) are reported most frequently. Symptoms of life-threatening illness occur in 8-17 cases per year. The 8-17 range assumes either that the 8 people reporting seizures in Table 10 were also responsible for all other life-threatening symptoms reported in that section of the table or that the other life-threatening symptoms were all experienced by different cases, independent of one another. The exact number of cases is uncertain because one case may have more than one symptom. By AAPCC categorization there were 6 cases considered life-threatening in 1993 and 10 such cases in 1994. No deaths were reported in either of these two years.

Table 10. Symptoms and signs commonly reported in acute, accidental chlorpyrifos poisoning, Poison Control Centers, 1993 and 1994. (One individual may contribute more than one symptom.)

Symptoms	1993	1994
Common early or mild signs/symptoms:		
Headache	285	356
Nausea	319	414
Vomiting	213	305
Dizziness	151	211
Muscle weakness	53	67
Drowsiness/lethargy	46	79
Agitated/anxiety	26	29
Present in moderate or severe poisoning:		
Pain in chest	45	44
Difficult breathing	85	97
Bradycardia	4	5
Tachycardia	16	22
Hypertension	0	9
Hypotension	2	5
Pallor/cyanosis	3	2
Abdominal pain	82	98
Diarrhea	114	153
Anorexia	8	13
Tremor	17	29
Ataxia	9	7
Fasciculations	13	14
Lacrimation	41	56
Heavy salivation*	NA	NA
Profuse sweating	39	40
Bronchorrhea*	NA	NA
Blurred vision	26	34
Pinpoint pupils	5	8
Symptoms signifying life-threatening severity:		
Coma	2	2
Seizures	8	10
Incontinence	2-3	0
Respiratory arrest	3	1
Pulmonary edema	1	0
Loss of reflexes**	NA	NA
Flaccid paralysis**	NA	NA

* Poison Centers reported 15 cases with excess secretions in 1993 and 28 cases in 1994. Many of these may have been heavy salivation or bronchorrhea. NA = not available.
** 1 case of dystonia in both 1993 and 1994 and 2 cases of paralysis in 1993 and 1 case in 1994 may be the type of loss of reflexes and flaccid paralysis, respectively, seen in life-threatening cases, but it is not possible to be sure.

6. California Pesticide Illness Surveillance System

California is the one of only a few states that actively requires mandatory physician reporting of all occupational pesticide poisoning incidents (U.S. General Accounting Office 1993). California is unique in that its system of reporting has been in place much longer than any of the other states. Long enough, so that one can go back 20 years to determine patterns of poisoning by specific pesticide. Unlike other states, physicians treating worker compensation cases are not supposed to be paid unless a pesticide poisoning is properly reported. Many cases not covered by worker's compensation probably go unreported and some types of workers without coverage have a disincentive to see a physician.

The following excerpt from a publication by Edmiston and Maddy explains how the California pesticide poisoning reporting system works (Edmiston and Maddy 1987):

> Any physician in California who knows or has reasonable cause to believe that a person is suffering from any disease or condition caused by a pesticide is required by law to report such a case via telephone to the local health officer within 24 hrs of the initial examination. The health officer is then required to immediately notify the local County Agricultural Commissioner (CAC), and report to the CDFA and California Department of Health Services via a Pesticide Illness Report (PIR) within seven days. Once the CAC is notified an investigation of the incident is initiated to determine the circumstances of exposure.
>
> A Doctor's First Report of Work Injury . . . is sent by physicians, as required by Section 6409 of the California Labor Code, to the Division of the Labor Statistics (DLS) of the Department of Industrial Relations for any illness or injury resulting from circumstances within the workplace. The [physician's reports] are sorted by DLS staff and any case that might be related to pesticides is sent to the CDFA Worker Health and Safety Branch (WH&S). All [physician's reports] received by WH&S are screened for possible pesticide involvement; those cases potentially pesticide-related are to be sent to the appropriate CAC for follow-up investigation.
>
> When the investigations by CAC staff are complete, they are sent to the Worker Health and Safety Branch. An evaluation of each case is then completed as described in the section of data evaluation procedures.

The following excerpts, also from Edmiston and Maddy 1987, provide the data evaluation procedures:

> Information received from the CAC investigation, the physician's report(s), toxicological data and any other pertinent background information is used in the evaluation of each incident reported.

The incidents are first evaluated as to the completeness of the information submitted. Sufficient information is needed to be able to determine the relationship between the pesticide exposure incident and the reported illness or injury. . . .

Cases are classified as to the likelihood of a relationship between the reported pesticide exposure and the illness/injury occurrence. This determination is based on all available information including, but not limited to, information documenting exposure, the medical assessment, and chemistry and toxicology of the pesticide(s) involved. Each case is classified according to the following scheme: Definite; Probable--a high degree of circumstantial evidence suggesting the illness/injury was due to pesticides, but not a definite relationship; Possible--uncertain of circumstantial evidence, but some likelihood exists; Unlikely--very little likelihood of a relationship exists, but not enough information is available to exclude some chance the illness/injury was due to pesticides; and Unrelated--the incident is determined to be unrelated to pesticide exposure.

The type of illness or injury reported is classified as follows: "Systemic"--the physician reports signs/symptoms indicative of internal illness such as digestive, neuromuscular or respiratory system effects; [starting in 1989 respiratory symptoms distinct from systemic disease were reported separately] "Eye"--topical injury, such as conjunctivitis; "Skin"--topical injury, such as a chemical burn or rash; and "Eye and Skin"--topical injury involving both the eye and skin.

7. California Occupational Illnesses in Agricultural Settings

Cases of health effects attributable to exposure to chlorpyrifos used agriculturally, alone or in combination, reported to California from 1982-1992 were reviewed. Activity (type of work being performed during exposure), for purposes of this review, was categorized as applicator, residual, mixer/loader, coincident and other (combined categories).

During the years 1982 through 1992, there were 210 reports of adverse health effects involving agricultural exposure to chlorpyrifos. In 110 cases (52.4%), chlorpyrifos was used in combination with other pesticides and the cause of the health effects could not be determined. In 40 cases (19.0%), chlorpyrifos was used in combination but was judged to be responsible for the health effects. In 60 cases (28.6%), chlorpyrifos was used alone.

Table 11 presents primary illnesses associated with chlorpyrifos by work activity using 100 cases in which chlorpyrifos was used alone or in combination, but was judged to be responsible for the illness. Table 12 presents the illness data on a year-by-year basis.

Table 11. Work-related illnesses where chlorpyrifos was deemed the primary cause of illness, by type of work activity and type of illness, California, 1982-1992.

		Illness*			
Work Activity	Number of Reports	Systemic	Eye	Skin	Combi-nation
Applicator	38	21	6	9	2
Mixer/Loader	13	5	4	3	1
Drift	35**	32	2	-	1
Residual	6	3	-	3	-
Other	8	4	2	1	1
Total	100	65	14	16	5

* Systemic illnesses that included skin or eye effects are listed only under the systemic column. The combination category includes either eye/skin or respiratory/eye symptoms combined.
** Eighteen of the cases due to one drift incident in 1989.

Table 12. Cases where chlorpyrifos was the primary pesticide involved by type of illness in California, 1982-1992

Year	Systemic	Eye	Skin	Eye/Skin	Total
1982	0	0	0	0	0
1983	1	0	1	0	1
1984	5	3	0	0	8
1985	2	1	2	0	4
1986	4	1	0	1	6
1987	4	1	2	0	7
1988	9	1	2	0	13
1989	26	5	2	2	37
1990	3	0	0	0	4
1991	3	1	2	1	9
1992	7	1	5	Resp/eye= 1	14
Total	65	14	16	5	100

Use Comparisons

Data on the number of applications of chlorpyrifos per year in California were obtained from the Annual Pesticide Use Reports. Calculations of the number of incidents per 1,000 applications per year were made using the 93 cases previously described. Those data are presented in Table 13.

Table 13. Determination of ratios of poisoning incidents to number of applications by year in California, 1982-1992.

Year	Number of systemic cases	Number of applications	Ratio incidents per 1,000 applications
1982	0		0.00
1983	1	8,661	0.12
1984	5	12,062	0.41
1985	2	9,542	0.21
1986	4	9,870	0.40
1987	4	12,710	0.31
1988	9	16,431	0.55
1989*	26		
1990	3	*41,709***	*0.07***
1991	4	*36,682***	*0.11***
1992	7	*39,190***	*0.18***

* Use data were not available for this year. Prior to 1989 only restricted or commercial use applications were reported. After 1989 all agricultural applications had to be reported.
** Greater use reporting requirements since 1989 mean ratios calculated after that year are not comparable with prior years.

Several conclusions can be drawn from these data:

1) The applicator activity category was most frequently associated with adverse health effects, accounting for 38% of the cases where chlorpyrifos was considered the primary pesticide associated with the illness. Drift was the second largest category with 35% of the incidents. However, half of the drift cases were due to a single incident in an orange grove in 1989. Note that many cases of drift or exposure to residue in field workers may go unreported because of disincentives associated with seeking medical care and lack of physician reporting.

2) Over one-half of all incidents were systemic poisoning involving applicators (21) and those directly exposed to spray drift (32, see Table 11). This indicates that even when diluted for application, chlorpyrifos exposure can lead to poisoning.

3) The data (number of cases, categories most frequently reported) are fairly consistent from year to year, with the exception of the 18 cases due to one drift incident in an orange grove in 1989.

4) Of the 35 cases involving skin, eye, or respiratory effects, 71% were pesticide handlers, either applicators or mixer/loaders.

5) The number of systemic poisoning cases per 1000 applications ranges from 0 to 0.55. This is fairly consistent with the median (0.41) reported for 28 insecticides analyzed as part of the acute worker risk analysis for the years 1982-1989 (Blondell 1994a). Data on usage suggest that only about one-half of the applications were reported prior to 1989, when only commercial and restricted applications had to be reported. The ratio of chlorpyrifos poisoning to number of applications was similar to that of most of the other 28 insecticide alternatives. Additional study in states other than California would be desirable to confirm this finding. The Acute Worker Risk Strategy is designed to reduce risks from all cholinesterase inhibitors. See Table A5 of the December 5, 1994 memorandum (Blondell 1994a).

8. California Chlorpyrifos Illnesses Involving Structural PCOs

A total of 304 incidents received by the California Pesticide Illness Surveillance Program involving exposure to chlorpyrifos applied by structural pest control operators (SPCO) from 1982 to 1993, inclusively, were reviewed and analyzed. In all of these cases, chlorpyrifos was deemed the primary chemical responsible for the illness, even though some cases involved exposure to other pesticides as well. The data base analyzed contained the following information: case number; relationship of pesticide to illness; illness (systemic, respiratory, eye and skin categories); activity of person exposed; registration number of pesticide product; and comments. All of the cases had either a definite, probable or possible relationship. Except for 16 cases, all were identified by the registration number of the chlorpyrifos product involved in the incident.

This set of California data includes all cases in which health effects were attributed to an exposure to chlorpyrifos applied by a Structural Pest Control Operator (SPCO). Note that one additional year of data (1993) is provided that was not available for the agriculturally-related cases reported in California. Excluding 1993, there were a total of 273 SPCO-related cases, almost three times as many as reported for agricultural use of

chlorpyrifos. As will be seen, this is partly because more people are present during an application by an SPCO than during agricultural use. Note that SPCO cases involving exposure to non-occupational persons (residential rather than business applications) are much less likely to be reported under the California mandatory reporting requirement. Such cases would not be covered by worker's compensation and, the payment incentive for physician reporting does not apply. Therefore, it is likely that these types of cases are greatly under-reported. Table 15 provides the number of illnesses in each category by year using the full data base of 304 cases.

Table 14. Number of illnesses in which health effects were attributed to exposure to chlorpyrifos applied by an SPCO in California, 1982-1993. (Some systemic cases may also have eye or skin effects.)

Year	Systemic	Eye	Skin	Respir-atory*	Combination Eye/skin/resp	Total
1982	3	3	0	-	0	6
1983	10	3	3	-	0	16
1984	3	4	1	-	0	8
1985	5	4	0	-	0	9
1986	2	5	0	-	0	7
1987	13	3	1	-	0	17
1988	59	10	0	-	0	69
1989	10	4	0	4	0	18
1990	35	6	2	0	1	44
1991	20	1	0	0	1	22
1992	46	5	1	4	1	57
1993	20	4	0	3	4	31
Sum	226	52	8	11	7	304

* The respiratory category was not used until 1989.

The comment section provides some insight into conditions which resulted in the large number of cases for several years, particularly 1988, 1990 and 1992. In 1988, there were three incidents in which a total of 48 people reported being ill as a

result of exposure to Dursban L.O. (42.76% chlorpyrifos). In one incident, eight bank employees became ill after working in a room that had been treated by a SPCO the night before. The application was a coarse fan spray to the entire carpet. An odor was noticeable to the employees the next morning. Symptoms included headache, nausea, light headedness, dry throat, and respiratory irritation. In the second incident, ten employees developed mostly dizziness and headache after exposure to an office which had been treated the night before by a SPCO. In the third incident, a SPCO performed a broadcast spray application to the carport of an office after hours on a Friday. The office was secured and not ventilated. On Monday, thirty people became ill with a variety of respiratory, gastrointestinal and neurological symptoms. In a similar incident in 1990 involving Dursban L.O., a SPCO made an application to an office on a Friday. When employees returned on Monday, they noticed a strong odor. Thirteen employees and a baby had gastrointestinal, respiratory and neurological symptoms. In 1992, an office was treated with Dursban L.O. two days prior to the reported incident. Nine people were seen by a physician with symptoms of nausea, dizziness and headache, mostly. The 304 cases were also analyzed by activity category. The following table lists the categories with a short description and the number of cases reported for each.

Table 15. Number of SPCO-related chlorpyrifos cases, by activity of the person exposed, California 1982-1993.

Activity Category Abbreviation	Description	Number of cases
RESISTRU	Worker exposed to pesticide residue from a structural application and eligible for worker's compensation	91
RESINON	Person exposed to pesticide residue but not eligible for worker's compensation	17
APPLHAND or APPLGROU	Worker involved in application	84
MIXLOAD	Mixer/loader for an application	5
DRIFTEXP or DRIFTNON	Exposed to drift during application	20
NONOCCB*	Exposure while working, but not assigned to deal with pesticide	73
OTHERNON**	Other non-occupationally related exposure	12
CLEAN/FIX	Exposure during equipment maintenance	1
EXPTOCONC	Exposed to pesticide after manufacture but before reaching its use site (e.g., transport, warehouse)	1

* Older category, replaced mostly by RESISTRU since 1989.
** Older category, replaced by mostly by RESINON since 1991.

The number of incidents due to accidents or failure to use protective equipment is also of interest. The comments were reviewed for any notation that these circumstances occurred. In 46 of the 304 incidents (15%), there was an indication that an accident occurred that resulted in the exposure, most commonly a hose breaking. Failure to wear safety protection (mostly goggles) or lack of safety training was reported in 21 cases (7%). The comments sections also contain several incidents where pesticide application was made while people were on the premises. Table 16 lists the year, product and description of the circumstances.

Table 16. Health effects attributed to application of chlorpyrifos by a SPCO where other people were present during the application.

Year	Product	Circumstances
1984	Dursban 2EC	Applied to work area while employees were present; one person became ill
1987	Dursban TC	Bank employee complained of nausea & shortness of breath while working in area where product was being applied; 2 people became ill
1987	Dursban L.O.	Office employees were present during crack & crevice application; three people became ill
1990	Dursban 4E Emulsifiable	SPCO treated a law office while staff were at their desks; one person became ill
1990	Dursban L.O.	Maid reentered hotel room within 15-30 mins. of application; Notice of Violation issued for failure to notify employees
1990	Dursban ME 20 Micro-encapsulated	SPCO made crack & crevice application within 2 feet of employee working at desk; one person became ill
1992	Dursban TC	Holes for treatment were not all plugged; family of 5 smelled residue for 8 days & then moved to hotel
1993	Dursban TC	SPCO injected product into drilled holes inside building while workers were present; was within 12 feet of one worker

The data on individual products were also analyzed. The number of incidents (1982-1993) and illness categories by product are tabulated in Table 17 below. Only those products with 25 or more incidents were included, accounting for a total of 236 cases. Table 18 provides the same information by activity of the person exposed. To simplify this table, the mixer/loader category (3 cases with Dursban 50W and 1 with Dursban 2E), Clean/fix category (1 Dursban TC case), and Exposure to Concentrate category (1 Dursban L.O. case) have been excluded.

Table 17. Health effects attributed chlorpyrifos exposure when applied by SPCO, by product brand name and type of illness, California, 1982-1993.

Product (% active ingredient)	Systemic	Eye	Skin	Respiratory /Combined*	Total
Dursban L.O. (42.76%)	112	3	1	2/1	119
Dursban TC (42.70%)	21	9	0	1/0	31
Dursban 2E or 2EC (24.75%)	17	9	2	1/1	30
Dursban 50W** (50.0%)	20	4	1	2/3	30
Whitmire PT 270 (0.5%)	12	13	1	0/0	26

* The respiratory category was not used until 1989. Cases listed here may include combined respiratory, eye, and skin effects. Cases assigned to the systemic category may have included eye, skin, or respiratory effects as well.
** Includes Dursban 50W Insecticide and Dursban 50W Insecticide in Water Soluble Packets

Table 18. Health effects attributed to chlorpyrifos exposure when applied by SPCO, by product brand name and activity of exposed case, California, 1982-1993.

Product (% active ingred.)	RESISTRU /RESINON	APPL	DRIFTEXP	NONOCC	OTHERNON
Dursban L.O. (42.76%)	45/3	9	4	53	4
Dursban TC (42.70%)	1/8	14	2	3	2
Dursban 2E/2EC (24.75%)	4/1	14	3	5	2
Dursban 50W* (50.0%)	7/3	12	3	2	0
Whitmire PT 270 (0.5%)	7/3	15	1	0	0

* Includes Dursban 50W Insecticide and Dursban 50W Insecticide in Water Soluble Packets

The comments section for Whitmire PT 270 were reviewed for insight into the high number of eye illnesses in relation to systemic cases. Of the 13 cases, 7 exposures were due to accidents, such as nozzle malfunctions or dropping the container. In 4 cases, it was noted that the applicator was not wearing safety goggles. There were 3 cases of applicators that were hospitalized for 1-2 days. In two of these cases a hose came off and, in the third, the applicator sprayed a steam generator leading to high levels of volatiles.

From 1991 through 1993, two additional data elements were collected on pesticide illnesses: violation, if the SPCO was charged with a misuse; and contributing factors such as odor (if mentioned by the victim), equipment failure, and sensitivity. For the four of the five pesticide products listed in Table 18 (excluding Whitmire PT 270), 18% of the applicators were charged with some kind of violation, 50% of the victims mentioned noticing an odor, and 7% involved equipment failure.

A primary cause of serious chlorpyrifos poisoning appears to be application of liquids by Pest Control Operators (Tables 15-18). One possible contributor to this problem was suggested by a PCO survey. A newsletter for PCO companies published a mathematics exam for PCOs and requested that company supervisors report back on the results (Pinto and Associates 1991a, 1991b). The exam was designed to test basic math skills that PCOs would need in their job. Results from this admittedly biased, self-selected sample found that on average PCOs got only 52% of the questions right. Among the most frequently missed questions were: three is what percent of 60; and, if the label says mix 2 and 2/3 ounces of concentrate with one gallon to get a 0.5% dilution, how many ounces of concentrate should you mix with 1/2 a gallon of water to get your 0.5% dilution? Upgrading requirements for certification and application should be considered for pesticides like chlorpyrifos that can result in damage to property and significant adverse health effects that may cost thousands of dollars per case.

9. NPTN and Incident Data System Case reports

Approximately 35 cases were referred to Dr. Sheldon Wagner, an EPA consultant, in 1995 with symptoms potentially related to chlorpyrifos exposure. Nearly one-third of these cases involved typical symptoms of cholinesterase-related organophosphate poisoning. Another one-third involved dermal or respiratory effects. And the remaining one-third involved a variety of complaints, including two cases of asthma and two seizures reported in young children. These cases were not positively diagnosed as being caused by the chlorpyrifos exposure.

Since June of 1992, EPA has maintained a computerized Incident Data System to capture all pesticide-related incidents sent to the Office of Pesticide Programs. As of September 3, 1996, there were 1,246 incident reports involving adverse effects to humans of which 1,032 were new reports and 214 were updates. The majority of these cases (921) were individual case reports, however there were 111 summary reports involving more than one incident each. The majority of the 1,032 new reports, 64 percent, were submitted by the registrant DowElanco.

In about 24% of the 1,032 new reports the specific product brand name for chlorpyrifos was not identified. Among cases that were identified, Dursban TC was the most often reported product responsible for about 192 incidents or 19 percent of the total. Dursban LO was the second most frequent mentioned product with about 119 incidents or 12 percent of the total. Together products used by PCOs account for 45% of the total incidents reported. Ortho Home Pest Control was the single largest consumer product reported with 49 incidents accounting for 5 percent of the total product-identified cases. Note that some of the PCO and homeowner incidents appear to be related to indoor broadcast use. This type of use has been voluntarily removed from the label by DowElanco.

10. Literature on Acute Effects

Determining Toxic and Lethal Doses in Humans

Gallo and Lawryk (1991) report the oral LD_{50} for chlorpyrifos in female rats to be 82-155 mg/kg. Human cases reported as life-threatening from intentional poisonings (suicides) appear to involve a dose in about the same range. Lotti et al. (1986) discuss a case of a 42 year old male who drank a dose of approximately 300 mg/kg of chlorpyrifos (twice the lethal dose in rats) and experienced a life-threatening poisoning (see Table 1) including symptoms of coma, incontinence, and respiratory insufficiency. Drevenkar et al. (1993) reviewed 3 case reports of suicidal ingestion of chlorpyrifos where the dose could be estimated. All three cases were admitted to the hospital 2-5 hours after ingestion and required hospitalization for at least 5 days each. It can be assumed that these poisonings were probably life-threatening and would have died without medical treatment. In two of these cases a 25 year old male and a 28 year old female ingested 30 to 60 milliliters of a 50% chlorpyrifos solution. To calculate the dose, a standard adult weight of 70 kg and a specific gravity of 1 mg/ml for the chlorpyrifos is assumed. This would mean that for each adult the approximate dose would be 15-30 grams divided by 70 kg or a dose ranging from 214 to 428 mg/kg (about twice the lethal dose in rats). A third subject (40 year old female) ingested 2 spoonfuls of 4% chlorpyrifos dust. Assuming 15 grams per spoonful (1 tablespoon = 15 grams) and a 70 kg body weight

would mean a dose of 17 mg/kg (about 1/7 the lethal dose for rats). This appears to be the lowest dose documented in the literature involving life-threatening poisoning in humans. It is not consistent with other reports which typically place lethal human dose at 10 times this amount.

Recent research has suggested that differences in amounts of paraoxonase could be responsible for unusual susceptibility to chlorpyrifos in some individuals (Furlong et al. 1989, Costa et al. 1990, Li et al. 1993). Animals with low levels of paraoxonase activity are reported to be more susceptible to poisoning by the organophosphate insecticides, parathion and chlorpyrifos. Paraoxonase hydrolyses the paraoxon and chlorpyrifos-oxon metabolites that are responsible for poisoning effects. Pretreatment with paraoxonase in animals has been found to protect against the poisoning effects (Costa et al. 1990). Human populations appear to have paraoxonase levels that vary by more than ten-fold and therefore, even among people with similar exposures, response in terms of cholinesterase depression and symptoms can be expected to vary markedly. More research is needed to determine whether there may be unusually susceptible members in the population that could not tolerate exposures commonly tolerated by the general population.

Poisoning is assumed to develop in people receiving one-tenth the oral LD_{50} dose for animals (Gosselin et al. 1984). Assuming a single swallow (5,000 mg) and a weight of 10kg for a one-year old means that any product with an LD_{50} of less than 5,000 mg/kg (5000 mg/10kg x 10) would receive a dose that could cause clinical symptoms in an infant (Jones and Work 1961). A study of chlorpyrifos (6.7% solution) in female rats found an oral LD_{50} of 1160 (OPP review 000208, Spencer 1978). Assuming no effect from other ingredients, a 1.5% solution would have an estimated LD_{50} of 5,181 (6.7/1.5 x 1160). Therefore, any chlorpyrifos containing a higher percentage than 1.5% could be expected to cause symptoms in 50% or more of one-year olds ingesting a single swallow. Therefore, eliminating such products from homeowner use should be considered where practical.

Human Exposures Related to Poisoning

Rosenberg and Quenon (1988) surveyed 24 pet groomers and found that 12 of them reported frequent use of flea dips including those containing chlorpyrifos and that they usually had symptoms of illness. The most common symptoms reported included headache, dizziness, nausea, fatigue, and dermatitis. Two of the 12 reported sweating, tearing, and confusion. Most pet groomer reported they did not wear gloves or aprons and did not use the pesticides according to label directions. They often reported handling undiluted concentrate with their bare hands. Other reports and

telephone discussions with pet groomers support this general pattern of misuse (Ames et al. 1989).

Hodgson et al. (1986) reported on five office workers poisoned primarily by inhalation exposure to chlorpyrifos. Exposure occurred through an air intake vent on a Friday, 2 of the workers were also present for 8 hours on Saturday and Sunday. All five workers reported symptoms the following Monday. Symptoms and number of individuals reporting them were: chest tightness (3), cough (2), visual symptoms (2), drooling (3), sweating (3), nausea (4), diarrhea (4), abdominal pain (3), weakness (4), fatigue (5), restless (2), anxiety (4), confusion (2), and disturbed speech (1). Measurements of red blood cell cholinesterase levels found that recovery to normal took up to 80 days. Three weeks later one person reported numbness and tingling in the fingertips of both hands which lasted one week. According to Berger and Schaumberg (1994), a case of paresthesia involving only the upper extremities should not be regarded as evidence of toxic neuropathy. Hodgson states that this application was in conformance with label directions and recommends that people stay outside of structures when they are being treated with chlorpyrifos and that a reentry interval be established before workers are allowed back inside. No residues were found on surfaces at this site 2 weeks after the application. This finding of poisoning by inhalation is contradicted by DowElanco scientist McCollister (1991) who stated that "acutely toxic levels of vapors cannot be attained at room temperature." However, no studies of human subjects exposed over a period of days have been located that would support this conclusion.

Zweiner and Ginsburg (1988) reported on 37 children seen in one hospital in Texas, ranging in age from 1 month to 11 years, with moderate or severe organophosphate poisoning. Ingestion of stored liquid was involved in 76% of cases and playing on carpet or floor after application was involved in 14% of cases. The initial diagnosis was not recognized as OP poisoning in 16 of the 20 children transferred for care. The most commonly reported symptoms included miosis (73%), excessive salivation (70%), muscle weakness (68%), respiratory distress (59%), lethargy (54%), nausea/vomiting (32%), seizures (22%) and coma (22%). Twelve (38%) of the children required mechanical ventilation to maintain respiration. Six of the total 37 cases were reportedly due to chlorpyrifos, more than any other organophosphate. Three of six chlorpyrifos cases were life threatening due to coma or respiratory arrest (Ginsburg, personal communication). The authors concluded that bradycardia and muscle twitching were less likely in childhood poisonings than in adults, but that seizures were more common in children. They noted that all children who had seizures also had respiratory insufficiency and that therefore hypoxia might be the underlying cause of the seizures.

Dunphy et al. (1980) reported a case of an 11 day old boy who was exposed to food and clothing in his home that had been contaminated with measurable levels of chlorpyrifos. His symptoms included cyanosis, miosis, excess salivation, vomiting, lethargy, and respiratory arrest. Red blood cell cholinesterase levels were reported to be 50% below normal in this life-threatening poisoning. This unusually severe case in such a young child suggests that children and infants may be far more susceptible to chlorpyrifos poisoning than adults. A study in rats supported this finding of greater susceptibility in the newborn. The maximum tolerated dose in the 7 day old rat injected subcutaneously was 1/6 that found in the adult (Whitney et al. 1995). One day old rats were found to be four times more sensitive to chlorpyrifos than 7 day olds. One day old rats were found to be deficient in DNA synthesis in the brain and in protein synthesis. The authors concluded "caution should be used in establishing standards for acceptable levels of chlorpyrifos exposure during pregnancy."

DowElanco (1994) states that "In 20 years of manufacturing with 'regular monitoring of the workers' health status, we have never observed significant depression in red blood cell cholinesterase or symptoms of cholinesterase inhibition." This statement did not include information about the number of workers monitored or what signs or symptoms where checked. In addition, DowElanco states "Also, in 15 years of use in the marketplace, there have been no incidences that we are aware of where signs or symptoms of organophosphate poisoning have occurred with the use of chlorpyrifos." Given the documents supplied by DowElanco and reviewed in the memorandum dated December 5, 1995 by Jerome Blondell, this statement is incorrect. Moreover, HED is greatly concerned that users of chlorpyrifos may take this statement to mean they do not need to be careful about following safety instructions with chlorpyrifos and may falsely assume that any symptoms reported from exposure are coincidental rather than caused by the exposure. Lack of concern among Pest Control Operators could lead to disregarding common-sense safety precautions and legal requirements for safe use. Table 22 (page 43) suggests that there are some users of chlorpyrifos that have adopted such a careless approach toward safety procedures. It may well be that statements such as the above have been responsible for some of the significant poisonings reported by DowElanco and others.

B.Chronic Effects

1. Description of chronic effects of concern

Partly as a result of news media coverage, over 150 people have contacted the National Pesticide Telecommunications Network or the Office of Pesticide Programs directly to report health problems experienced which they believe are related to chlorpyrifos exposure. To organize and assure comparability of the information provided, each person was asked the same questions regarding their exposure and symptoms. In some cases, medical records were also requested to further document health problems they had experienced.

The questions asked were designed to address chronic neurological problems potentially related to chlorpyrifos exposure. Three types of problems were addressed: peripheral neuropathy; neurobehavioral effects absent sensitivity to other chemicals; and multiple chemical sensitivity. Multiple chemical sensitivity is a syndrome that is not well understood or generally accepted as a disease entity by the medical community. Epidemiological studies are currently being conducted in the U.S. and Canada to better understand the medical and psychological components of this condition. Questions were also asked regarding exposure to pesticides, medical care sought, and documented cholinesterase depression demonstrating exposure. Cases where other pesticides could have been responsible and cases involving only acute effects (within one month of exposure) were excluded. A small number of cases involving health endpoints, such as asthma, that were not the primary focus of the questions were also excluded. After these exclusions, there were 155 self-selected reports of chronic effects related to chlorpyrifos received between January 1 and December 31, 1995.

A retrospective analysis of reported symptoms poses a number of difficulties in interpretation. Many of the symptoms of chlorpyrifos poisoning are the same as those for other diseases. Reported symptoms are subject to recall biases and some subjects may exaggerate the extent or severity of symptoms for various reasons. It should be noted that a number of respondents were involved in law suits. One strategy to reduce this reporting bias is to ask about symptoms, generally known not to be related to organophosphate insecticide exposure. Each of the 163 individuals was asked about chronic neck pain, nose bleeds, and skin rash. These symptoms are generally not reported to be associated with chlorpyrifos poisoning, therefore any individual reporting two or more of these unrelated symptoms were excluded from further study. The choice of these 3 symptoms and the criteria for exclusion (two or more) were based on professional judgment. Misclassification of some cases will undoubtedly occur using this scheme, but it was felt necessary to avoid over-counting of cases that might really be due to other causes. Note that this criterion was not used to

exclude cases of multiple chemical sensitivity because no agreed upon definition of it has been formulated.

It is often not possible in a single case, without documentation of exposure, to positively attribute health effects to a particular pesticide. However, when there are large enough numbers, and the same patterns of symptoms and exposure recur, it is possible to suggest an association between exposure and health effects.

Chronic symptoms and signs of neurobehavioral effects and peripheral neuropathy have been previously reviewed and are summarized in Table 19 below (see Appendix 1 and Berger and Schaumberg 1994). In order to be counted as a neurobehavioral effects case, an individual had to have 3 or more symptoms from the left side of Table 19. In order to be categorized as peripheral neuropathy, a patient had to have at least 2 symptoms from the right side of Table 19 and symptoms involving both legs or feet.

Table 19. Persistent symptoms and signs reported in chronic organophosphate insecticide poisoning.

Neurobehavioral effects	Peripheral Neuropathy*
Blurred vision/vision defect Persistent headaches Persistent muscle weakness Lethargy/sleepiness/fatigue Short term memory impairment Inability to concentrate/ Confusion Lowered intelligence scores Psychological depression/ Irritability	Progressive bilateral effects after a latency of 1-3 weeks. Paresthesia such as numbness, tingling, pain in extremities. Typically starts in feet or lower legs, not just the arms. Muscle weakness in legs/arms. Foot drop/toes stubbed easily. Difficulty walking and picking up feet. Loss of reflexes.

* Peripheral neuropathy is relatively rare in cases of chlorpyrifos poisoning and there is some question whether it can occur absent a life-threatening poisoning exposure.

Exposures to organophosphate insecticides have been associated with development of sensitivities to the odors of multiple chemicals. Odors most commonly reported to be a problem include insecticides, perfumes, auto exhaust, cigarette smoke, paint, solvents, new carpet or furniture, household cleaners, hair sprays, various petroleum by-products including gasoline, asphalt, and others.

Recently a guide to indoor air pollution for health professionals was issued jointly by EPA, the U.S. Consumer Product Safety Commission, the American Lung Association, and the American

Medical Association. The following statements concerning "multiple chemical sensitivity" are taken from this guide (U.S. EPA 1994)

> The diagnostic label of multiple chemical sensitivity (MCS)--also referred to as "chemical hypersensitivity" or "environmental illness"-- is being applied increasingly, although definition of the phenomenon is elusive and its pathogenesis as a distinct entity is not confirmed. Multiple chemical sensitivity has become more widely known and increasingly controversial as more patients received the label (Black et al. 1990).
>
> Some practitioners believe that the condition has a purely psychological basis. One study (Black et al. 1990) reported a 65 percent incidence of current or past clinical depression, anxiety disorders, or somatoform disorders in subjects with this diagnosis compared with 28 percent of controls. Others, however, counter that the disorder itself may cause such problems (Fiedler et al. 1992), since those affected are no longer able to lead a normal life, or that these conditions stem from effects on the nervous system (Heuser et al. 1992).
>
> The current consensus is that in cases of claimed or suspected MCS, complaints should not be dismissed as psychogenic, and a thorough workup is essential.

This view was echoed by Ryan and Morrow (1992) in their review of problems related to sick building syndrome:

> We suspect that many cases of SBS [sick building syndrome] and NTD [neurotoxic disorder] are misdiagnosed as MPI [mass psychogenic illness] because of a failure to conduct adequate investigations of the workplace. By the same token, a failure to thoroughly investigate psychosocial factors, including level of job satisfaction and workplace stresses and strains, may lead an investigator to attribute *all* symptoms to some physical source like ventilation problems.
>
> Many individuals with NTD show clinically significant elevations on measures of psychological distress . . . Although one might interpret that pattern of results as indicative of a long-standing neurotic or hysterical personality, it may be more reasonable to conclude that this profile is a *consequence* of the chemical exposure in the sense that following exposure, individuals are more likely to report disturbances of thinking, difficulties in concentration, unusual perceptual experiences, social alienation, apprehension, and nonspecific somatic disturbances.

Ryan and Morrow note that there appears to be a dose-response relationship between exposure level and degree of symptomatology that suggest a toxic effect directly on the central nervous system.

Table 20 below list the symptoms most commonly reported as a result of exposure to these odors according to Miller and Mitzel (1994) and Ross (1992). In Miller and Metzel's study of 37 cases of chemical sensitivity due to organophosphate exposure half were reportedly due to chlorpyrifos. Among individuals reporting to EPA, those developing any of these symptoms, subsequent to a pesticide exposure and, as a result of sensitivity, to other odors were counted as a multiple chemical sensitivity case. This procedure merely documents the number of cases where chlorpyrifos was plausibly related to the onset of a syndrome, not yet generally accepted as a disease by the medical community. Some have suggested that chemophobia, a psychological fear of chemicals, is the sole reason for development of these symptoms and that none of the reported symptoms are attributable to an underlying physiological process caused by the chemical (Terr 1989, Selner and Staudenmayer 1992). Others have hypothesized physiological processes in the brain by which chlorpyrifos poisoning could lead to multiple chemical sensitivity (Meggs 1993, Bell 1994). Further research will be needed to resolve this controversy.

Table 20. Chronic symptoms most commonly reported among individuals developing multiple chemical sensitivity.

Fatigue/lethargy	Shortness of breath
Impairment of memory	Chest discomfort
Difficulty concentrating	Loss of motivation
Dizziness/feeling spacey	Muscle aches and pain
Depression	Joint pain
Headache	Nausea
Confusion	GI symptoms (abdominal pain,
Irritability/tenseness	diarrhea, gas, constipation)

2. Description of Cases reported directly to EPA

Criteria for chronic poisoning were developed based on the symptoms in the tables above. Cases mentioning exposure to more than two pesticides were excluded from the analysis. The one exception to this rule was if the second pesticide were a pyrethroid, pyrethrum, or Dowcil 75. These pesticides are not known to cause the neurological effects described above and therefore, cases exposed to chlorpyrifos and one of these pesticides (a total of 11 cases) were included in the analysis. Forty-four of the 155 cases were excluded because the second pesticide individuals were exposed to had neurotoxic effects and therefore may have been responsible for their chronic health problems. Remaining cases were categorized based on symptoms reported as: 1) chronic neurobehavioral effects; 2) peripheral

neuropathy; and 3) multiple chemical sensitivity. After excluding an additional 10 cases with 2 or more non-specific symptoms (neck pain, skin rash, or nose bleeds), there were 101 cases left. These cases were classified as follows:

1. 38 Cases reported having chronic neurobehavioral effects without evidence of peripheral neuropathy. Of these, 27 (71%) of the chlorpyrifos applications were performed by a pesticide control operator (PCO) and 1 case was a PCO. Ages ranged from 2 to 76 years with a median of 43. Gender was divided - 63% female and 37% male. Interestingly, 60% of the applications involved termite application of Dursban TC to the victim's home. Medical records supporting these claims were generally not reported. Therefore, most of these cases cannot be medically documented and may be subject to reporting bias.

2. Four cases reported having symptoms of peripheral neuropathy without simultaneous exposure to a second pesticide besides chlorpyrifos or concurrent symptoms of multiple chemical sensitivity. Each of these four cases also had symptoms of chronic neurobehavioral effects based on reports of 3 or more symptoms from the left side of Table 19. Three of the applications (75%) were performed by a PCO and 1 case was a PCO. Ages ranged from 34 to 47 years with a median of 38. Gender was divided - 50% female and 50% male. Only one of these cases reportedly had abnormal nerve conduction studies. Lack of medical records for the other three cases makes them highly questionable.

3. A total of 59 cases reported symptoms consistent with multiple chemical sensitivity. Of these, 50 (85%) of the applications were performed by a PCO. Current ages ranged from 4 to 67 years with a median of 46. Age at time of initial illness ranged from 1 to 62 with a median of 42 and a mean of 40. Gender was divided 76% female and 24% male.

The information above is summarized in table 21. Given the lack of confirmation for any of these cases, little weight can be placed on these results. This self-selected group may or may not reflect the pattern that might be found if each case could be properly investigated and confirmed. While no strong conclusions can be drawn regarding the causal relationship with chlorpyrifos, these cases do provide a basis for requesting additional study of these types of effects. A more comprehensive review of organophosphates and neurobehavioral effects has been performed and is included as an appendix to this report. Most of these studies do not mention chlorpyrifos specifically. However, given the likely common mechanism of action among organophosphates and limited specific evidence concerning chlorpyrifos, a conclusion linking chlorpyrifos and chronic neurobehavioral effects can be made.

Table 21. Distribution of applications by PCOs, place of application, age and gender by type of reported chronic illness.

Type of chronic illness/symptoms	N	% PCO Appl.	% Appl. in home	Percent Female	Median Age
Neurobehavioral	38	71%	71%	63%	43
Peripheral Neuropathy including neuro-behavioral effects	4	75%	75%	50%	38
Multiple Chemical Sensitivity	59	85%	64%	76%	46
Total	101	79%	67%	70%	44.5

HED concludes, primarily on the evidence in Appendix 1, that chlorpyrifos may be a significant cause of chronic neurobehavioral effects. Further study is needed to determine the prevalence and severity of these effects, as well as the occurrence of self-reported multiple chemical sensitivity. The possibility that chlorpyrifos may also be a cause of peripheral neuropathy at sub-lethal doses has not been substantiated by the information collected for this review.

Clearly PCO applications of Dursban in the home or at work environment are overwhelmingly responsible for the majority of reported cases. To some extent this may reflect a reporting bias, because homeowners may be less likely to report their own misapplications. Termiticide applications of Dursban TC appear to be a particular hazard which is not surprising given the large volume of material used per application and the relatively poor education and training reported among many PCOs. Many victims reported blatant misuse on the part of the PCO as shown by the examples in Table 22.

DowElanco has prepared a pamphlet designed to help Pest Control Operators to respond to problems resulting from use of Dursban TC (DowElanco 1988). The pamphlet is titled "Dursban TC Odor Reduction and Cleanup". It states in part "It should be clarified that any odor that is detected will not be the active ingredient, but will be the solvents and emulsifiers needed to dissolve and carry the active ingredient." HED has considerable data suggesting that this statement is misleading (Blondell 1995). Spills and odors resulting from misapplication of Dursban TC can and have had sufficient levels of the active ingredient to cause human poisoning. A replacement statement should advise homeowners to vacate if there are leaks or strong odors. This would be an

appropriate precaution regardless of whether poisoning symptoms are due to active ingredient or solvent. Persons should not be readmitted to the contaminated area until a thorough clean-up has been performed. Cleanup may include use of cleaning substances and absorbent materials along with ventilation, or replacement of contaminated materials, if they cannot be cleaned satisfactorily.

Table 22. Examples of Pest Control Operator misuse reported by victims of chlorpyrifos exposure.*

1. After a 14 year old displayed typical poisoning symptoms (shortness of breath, tearing, blurred vision, twitching, headache), PCO advised taking boy outside, giving him ice water and putting cold towels on his face.
2. PCO reportedly applied Dursban directly to the victim's clothing (which was soaked) in her closet.
3. PCO reportedly went from applying in the home once per month for 1 year to once per week for 3 months. All four family members developed chronic illness.
4. After the customer expressed concern about Dursban, the PCO sprayed her directly on her forearms to prove it was safe.
5. Family returned to home a day or two after Dursban TC application and could see the pesticide running down the walls of the basement and even down on the floor in places.
6. Despite saturated soil and cracks in the basement walls, the PCO applied Dursban TC leaving puddles of material in the basement. Residents, who had developed poisoning symptoms, were told liquids on the walls and floors did not contain chlorpyrifos (only solvent) and that they could clean it up themselves (without warning them to use protective clothing).
7. PCO reportedly came back to home to retreat with Dursban TC a total of 16 times in 5 years.
8. Dursban TC applied under condominium and seeped through floor soaking the carpet, padding and baseboard. PCO told clients (2 males over 50 years old) that they would have to drink 1 or 2 gallons of this chemical and not even then would it be harmful. The contaminated area was never properly cleaned and the 2 residents had red blood cell cholinesterase values significantly below normal (63% and 68% of normal), two and a half years later.
9. 98 holes were drilled to apply Dursban TC, only 2 went into the soil, the rest into open space. Fire department was called. Family of 5-6 alleges $150,000 in clean-up and medical bills.
10. PCO company applied directly below work space every two weeks. Worker developed neurobehavioral effects and spent about $7,000 in medical bills.

* Note that most accounts listed above are based on reports by the victims and have not been validated by independent investigation.

3. Description of Cases submitted by DowElanco

Cases previously submitted by DowElanco have already been reviewed in the memorandum: Review of chlorpyrifos-associated cases of delayed neuropathy, January 19, 1995 (Blondell 1995). Additional cases related to legal claims have since been submitted by DowElanco. Among the over 100 claims involving a variety of pesticides and complaints, there was one case of mild peripheral neuropathy diagnosed in a 47 year old female whose office had been sprayed in 1984. She reportedly had below normal cholinesterase values 17 days after the initial exposure and chlorpyrifos was detected in cotton swabs samples taken at the work site. Evidence for the peripheral neuropathy included abnormal nerve conduction studies. By January 1986 the treating physician reported that the patient had apparently completely recovered from peripheral neuropathy. This is the only additional case with verified cholinesterase depression, a physician diagnosis of peripheral neuropathy, and supporting laboratory documentation. This patient also reported other chronic neurobehavioral effects, including depression, insomnia, concentration and memory problems. These latter symptoms were reported as persisting through 1987.

None of the other cases received from DowElanco provided convincing evidence of peripheral neuropathy related to chlorpyrifos exposure. Five of the other cases submitted involved a single work site -- a nurses lounge -- that was reportedly treated weekly with Dursban 2E. This application involved a non-ventilated area and treatment of furniture, such as counter tops, that would likely result in human skin contact. Given the evidence of Dursban's persistence indoors, the weekly applications were much too frequent, likely leading to accumulating levels over time. These cases clearly support the need for specifying permitted frequency of application on the label for all Dursban products used by PCOs.

These cases also illustrate another problem concerning physician diagnosis. Many physicians lack knowledge of chronic organophosphate health effects. For example, a physician who reviewed one of the cases reported above stated "The dilemma in this case has been that the chemicals involved are not known to cause mental changes or in fact cause changes that are more than transient in nature." This statement is contradicted by the scientific literature reviewed in appendix 1.

4. Cases Reported to EPA from Other Sources

EPA medical consultant

Dr. Sheldon Wagner has served as a medical consultant for cases of illness potentially related to pesticides since the late 1980s. The Office of Pesticide Programs at EPA has provided

funding for this consultation. In the first 20 months, Dr. Wagner consulted on over 300 referrals. The second most frequently raised concern, after chlordane, was chlorpyrifos which was responsible for 34 inquiries. Dr. Wagner noted "The most difficult problem has been encountered with chlorpyrifos. There have been 34 inquiries about this insecticide. The clinical problems most commonly raised have been complaints of long-term illness following acute exposure and/or intoxication (Wagner 1990)."

With the ban on chlordane in 1988, chlorpyrifos has become the number one source of referrals to Dr. Wagner. More recent reports specify the types of problems that are most common: An individual whose home was treated developed symptoms consistent with organophosphate poisoning. Dr. Wagner noted that the manner in which the PCO applied the product may have contributed to the problem: "It is my judgment that the label for Empire-20 is not clear as to whether this compound can be used in food dispensing areas such as the kitchen - as it was in this particular case. Furthermore, the label is also incorrect stating that any area in which the area has been applied may be treated simply by water (Wagner 1993)".

Another case reported in a school illustrates the potential for major costs associated with misapplication of Dursban: "This is another episode of acute illness developing in children as the result of pesticide treatment to a school in which the formulation was applied while children and teachers were in the building. Additionally, as is not unusual, the heat duct system became contaminated and illness became more severe when the heating system was turned on. This problem is similar to many other cases . . . many times the recommendation must simply be to put in an entirely new heat duct system (Wagner 1993)".

The following typical case of misuse was reported in 1994: "Her home was treated by 'crack and crevice' in an excessive manner whereby Dursban (chlorpyrifos) was applied and freely flowed down the walls and also got onto furniture. It also was applied in an eating area. She developed complaints of dyspnea and diarrhea. she eventually was hospitalized with a diagnosis of organophosphate intoxication (Wagner 1994a)". Summarizing the chlorpyrifos problem in 1994, Dr. Wagner concluded: "The most frequent organophosphate concern continues to be from chlorpyrifos use within homes, not from agricultural practices (Wagner 1994b)".

Though rarely reported, the following case suggests chlorpyrifos potential to bring on asthma:
"This was a child with no history of allergic or atopic problems. His room was treated with Dursban and he immediately developed an asthmatic syndrome which has been persistent. Documentation of an acute Reactive Airway Dysfunction Syndrome is excellent and correlates extremely well with the temporal relationship to the Dursban formulation (Wagner 1995)".

As a result of the Eye-to-Eye television program a large number of calls were referred to Dr. Wagner in 1995. Approximately 85 of these calls involved chronic health effect complaints. Of these 85, 13 involved MCS type symptoms, 9 neuropathy type symptoms, 5 peripheral neuropathy-type symptoms, and 5 asthma. Particular interest centered on peripheral neuropathy:

"During the first quarter of 1995 a large number of calls were received related to the application of chlorpyrifos - most of which were concerns related to application in the home. The high number of calls probably was the direct result of the presentation of an issue of chlorpyrifos use on the Connie Chung show in the first part of January. Of the 34 chlorpyrifos inquiries received, 12 of them had symptoms which suggested the possibility of a peripheral neuropathy, however, documentation of such neuropathy was not at all clear, i.e., records were not received or when received, did not substantiate the diagnosis as manifested by objective studies such as nerve conduction velocities. If neuropathy is occurring, it may instead have a central mechanism and not peripheral and would, therefore, require a different type of evaluation (Wagner 1995)".

Two cases of contaminated homes have been reported to Dr. Wagner and EPA where a DowElanco representative was involved and reportedly gave improper advice. Dr. Wagner reported on case number EPA 95-338: "This was a call from a family whose home became contaminated with chlorpyrifos after treatment to a lawn. This was during a period of heavy rains and not only was the lawn saturated but some flooding occurred and the rain water then entered the basement. A noxious odor was immediately present. The applicator was called and a representative from DowElanco also apparently appeared. The latter advised this family that there was no danger from any exposure to chlorpyrifos and that the odor was simply the result of the solvent which was used in this application. Analysis by the laboratory at the Oregon Department of Agriculture revealed that chlorpyrifos was present in this home at a level which would be consistent with an actual application with the home. There is an issue of possible illness occurring, either from acute respiratory irritation or from chlorpyrifos exposure at the onset of this problem. This could not be confirmed. This does represent, however, inappropriate and incorrect advice being given to this family by the manufacturer (Wagner 1995)".

A similar case was reported to EPA in mid 1995 involving application of Dursban TC to saturated soil. In this case there were cracks and holes in the basement wall and material leaked into the basement. A DowElanco representative reportedly appeared a couple of days after the incident and told the two residents that the material on the floor was only solvent and that they could clean it up themselves. The couple which had experienced acute signs of poisoning (difficulty breathing, headache, and dizziness)

reported that they were not given any warnings or cautions to avoid exposure during clean-up. Both adults now report persistent symptoms of memory problems, headache, weakness, and problems with memory and concentration. Some of these effects have reportedly been confirmed with appropriate psychological testing.

Cases reported to NPTN with possible chemical sensitivity

From 1984 through 1990 the National Pesticide Telecommunications Network received 1,022 calls complaining of unusual chemical sensitivity to pesticides. Many, perhaps the overwhelming majority of these calls, involved MCS type problems. Chlorpyrifos was the leading pesticide listed for chemical sensitivity, accounting for 158 calls during the 7 year period, or 15% of the total. Data from the 1990 survey of home and garden pesticide use permits a comparison based on the number of containers in U.S. homes (Whitmore et al. 1992) . The total number of pesticide containers was 247,650,000 and the total for chlorpyrifos was 16,652,000. The ratio of calls per million containers in U.S. homes was 9.5 for chlorpyrifos (158/16,652,000) and 4.1 for all pesticides (1,022/247,650,000). Although these ratios do not take into account the number of PCO applications in the home, it does appear that the chemical sensitivity problem associated with chlorpyrifos is not due solely to its widespread use.

Cases reported by Dr. Sherman and Dr. Lipsey

Both Janette Sherman, M.D. and Richard Lipsey, Ph.D. have served as consultants to patients on numerous cases (usually involving legal claims) involving health effects related to chlorpyrifos. At HED's request, they were asked to supply information on their cases. This information is summarized in the table below. Note that some of these cases may have been reported independently in other sections of this review. However, when duplicate reports have been identified they have been excluded.

Note that the table below includes 2 groups of people who were affected in two separate incidents. Cases identified as S111, S112, S113, S114, and S115 all occurred in one office building where 5 women were exposed to both chlorpyrifos and diazinon and later developed multiple-chemical-sensitivity type symptoms. Cases identified as L17, L18, L19, L20, and L21 involved 5 men involved in handling wood that had been treated with chlorpyrifos.

These reports support the need for a prospective study. The pattern of health effects and exposure were similar to that reported above. However, documentation of both the exposure and health complaints for these cases was often unavailable. As indicated in the table, many cases involved exposure to other pesticides at the same time. Therefore, it is not possible to conclude that these cases were caused by chlorpyrifos.

Table 23. Illnesses reportedly related to chlorpyrifos exposure reviewed by Dr. Sherman or Dr. Lipsey

ID#*	Year	Type of effects**	Age/sex	Appl./site	MCS/PNS symptoms	Exposed to other pesticides
S101	1989	h,v,f,m,c,d	41/M	PCO/home	MCS	
S105	1989	h,f,m,c,d	27/F	PCO/home and work	MCS	yes
S108	1989	h,f,m,c,d	40/F	PCO/home	PNS	yes
S110	1991	f,m,c,d	35/M	self/home		
S111	1984	h,v,f,m,c,d	64/F	PCO/work	MCS	diazinon
S112	1984	h,v,f,m,c,d	54/F	PCO/work	MCS	diazinon
S113	1984	h,v,f,m,c,d	67/F	PCO/work	MCS	diazinon
S114	1984	h,m,c,d	42/F	PCO/work	MCS	diazinon
S115	1984	h,v,m,c,d	41/F	PCO/work	MCS	diazinon
S124	1987	h,v,f,c	48/F	PCO/work	MCS	yes
S130	1974	v,f,m,c,d	53/M	PCO job	MCS	yes
S139	1988	f	43/F	PCO/work	PNS	(1 other pyrethroid)
S144	1994	h,v,f,m,c,d	?/M	PCO/work	MCS	
S152	1990	h,v,f,m,c,d	50/F	PCO/home	MCS	
S159	1989	h,v,f,m,c,d	57/F	PCO/home	MCS	safrotin
L1	1993	h,v,f,m,c,d	23/F	self/work	MCS	
L2	1992	h,f,m,c,d	35/F	PCO/home	?	
L3	1994	h,v,f,m,c,d	86/F	PCO/?	MCS	
L4	1994	h,f	50/F	PCO/?	?	
L5	1993	h,f,m,c,d	16/F	PCO/home	?	
L6	1993	h,f,m,c	20/F	PCO/home	?	
L7	1993	h,f,m,c,d	36/F	PCO/home	?	
L8	1993	h,f,m.c,d	11/F	PCO/home	?	
L9	1993	h,v,f,m,c,d	40/M	PCO/home	?	
L11	1992	h,f,m,c,d	38/F	PCO/?	?	
L12	1991	h,v,f,m,c,d	30/F	PCO/?	MCS, PNS	
L13	1991	h,f,m,c,d	35/M	PCO/?	?	
L14	1991	h,f,m,c	60/F	PCO/home	?	
L15	1991	h,f,m,c,d	60/M	PCO/home	?	
L16	1993	h,f,m,c,d	36/F	PCO/home	MCS	yes

ID#*	Year	Type of effects**	Age/sex	Appl./ site	MCS/PNS symptoms	Exposed to other pesticides
L17	1989	h,v,f,m,c,d	42/M	Wood tr.	MCS	
L18	1989	h,f,m,c,d	41/M	Wood tr.	MCS	
L19	1989	h,v,f,m,c,d	49/M	Wood tr.	MCS	
L20	1989	h,v,f,m,c,d	37/M	Wood tr.	?	
L21	1989	h,f,m,c,d	41/M	Wood tr.	MCS	
L22	1991	h,v,f,m,c,d	30/F	PCO/?	MCS	

* ID numbers indicate unique case numbers. Dr. Sherman's cases are proceeded by an 'S' and Dr. Lipsey's by an 'L'.
** h=persistent headache, v=visual difficulties, f=unusual fatigue, m=memory problems, c=inability to concentrate or confusion, and d=depression or irritability.

5. Literature on chronic effects

Broughton et al. (1990) report 2 cases of exposure to Dursban where chronic effects were experienced. A 40 year old female was exposed to spray in a pet shop and described sore throat and flu-like symptoms. Chronic effects reported for this case included bronchitis, joint pain, fatigue, and sensitivity to odors. The second case involved a 33 year old male exposed to Dursban used on cattle with one acute incident of a spill. The acute effects included headache, nausea, and slurred speech; chronic effects reported were fatigue, joint and muscle complaints, and effects to the central nervous and respiratory systems.

Kaplan et al. (1993) reported that 5 of their 8 subjects with peripheral neuropathy experienced problems with memory and confusion suggesting central nervous system dysfunction. They reported that 4 of the 5 with these effects got better after a period of months or years.

Rosenthal and Cameron (1991) reported that a 64 year old male had a termite application with chlorpyrifos and experienced severe abdominal pain, nausea, headache, difficulty breathing, fatigue, irritation of the eyes, nose and throat, anxiety, and irritability. Many of these symptoms reportedly continued for 2 years whenever he was present in the home. He also reported developing a sensitivity to new furniture and carpet odors.

Rouche (1988) reported on a 57 year old physician who was exposed to Dursban and Ficam (bendiocarb) when airing out a cabin that was treated monthly with these pesticides. Her initial symptoms included nausea, abdominal cramps, diarrhea, salivating, sweating, metallic taste in the mouth, tightness in chest,

palpitations blurred vision, muscle weakness, twitching in legs, and tingling on bottom of feet. Persistent symptoms included leg weakness, decreased strength, muscle twitching, and reduced sensory response in the legs. She was diagnosed with peripheral neuropathy.

Steenland et al. (1994) performed a case-control study on 128 workers poisoned by organophosphates. Ten of these subjects had primary exposure to chlorpyrifos at the time of poisoning and an additional seven cases had poisoning from chlorpyrifos and some other organophosphate insecticide. Among those with primary poisoning from chlorpyrifos, they had significantly worse peroneal nerve conduction velocity and ulnar sensory amplitude. Those with any exposure involving chlorpyrifos reported more tension on mood scales and performed worse on tests of finger vibrotactile sensitivity.

Thrasher et al. (1993) reported on 12 chlorpyrifos victims 1-4.5 years after exposure. Their chief chronic complaints included fatigue, headaches, dizziness, loss of memory, joint and muscle pain, gastrointestinal disturbances, and respiratory symptoms. Eleven of the 12 cases involved application by a Pest Control Operator. A number of immunologic differences were reported in this population, but unfortunately these results have not been duplicated by other labs and recent literature has raised questions about the significance of the lab techniques employed.

No attempt is made here to summarize the scant literature on chlorpyrifos and chronic effects. Appendix 1 contains a comprehensive review of the epidemiologic evidence concerning organophosphate insecticide poisoning and chronic neurobehavioral effects. This review includes a weight of evidence appraisal.

Reports of Birth Defects

Four cases of birth defects possibly related to chlorpyrifos exposure have been reported in the literature recently (Sherman 1996a, 1996b). Two of the four cases were siblings, raising the question of an autosomal recessive disorder as a competing explanation for the resultant birth defects. In all four cases brain defects including ventricular abnormalities were most notable. Cleft palate, growth retardation and low birth weight were reported in all four cases. Three of the four cases reported microencephaly, hydrocephaly, microphthalmia, abnormal genitalia, foot abnormalities and hypotonia.

Exposure in the four cases is documented only as the application of chlorpyrifos during the first trimester of pregnancy. Two of the mothers reported modest symptoms (headache and nausea) during their exposure, that may or may not have been related to exposure to chlorpyrifos. The estimates of exposure

that were calculated for two of the four cases appear to be quite low (ranging from 0.2 to 2.9 ug/kg/day). It should be noted that these four self-selected cases were referred to Dr. Sherman on account of legal claims.

Three additional cases of birth defects possibly related to chlorpyrifos exposure have been reported to OPP (Dr. Sherman, Fax dated 2/28/96). Reportedly, these infants have the same pattern of birth defects as seen for the four cases above. All three cases reportedly had ventricular abnormalities of the brain, atrophy of the brain, palate abnormality, and mental retardation. Two of the three reportedly had microencephaly, hydrocephaly, cataract, abnormal genitalia, and hypotonia. Medical records documenting these effects were requested and referred to Division of Birth Defects and Developmental Disabilities at the National Center for Environmental Health for consultative review. During the course of their review two additional cases were reported and also referred.

After examining the medical records for a total of ten cases the National Center for Environmental Health made the following conclusion:

> At present, there does not appear to be a consistent phenotypic pattern of anomalies among the infants whose records we reviewed. In addition, you reported that Dursban is used extensively in the United States. Based on the available medical records and the likely high frequency of this exposure, we would be hesitant to recommend pursuing major epidemiological studies at this point in time.

Studies of teratogenic effects of chlorpyrifos in mice and rats have not been supportive of a finding that chlorpyrifos is a teratogen (Deacon et al. 1980, Breslin et al. 1996). A significant increase in the incidence of exencephaly was observed at the lowest dosage tested in mice, but not in two higher dosages. Replication of this study at three dosages close to the low dose did not confirm this effect. In rats, microphthalmia was reported in 1 out of 278 controls (0.4%), 1 out of 230 (0.4%) at the intermediate dose, and 2 out of 244 (0.8%) at the high dose, a finding that was not statistically significant. Note that these studies have shown greater sensitivity in the mother than in the fetus, suggesting that fetal effects could not occur without overt maternal toxicity. In contrast, Whitney et al. (1995) found greater sensitivity in newborn rats receiving subcutaneous injections.

The metabolite of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (TCP), has also been tested for teratogenic effects in rats and rabbits (Levy 1988). The OPP review of these two studies found no significant increase in incidence of teratogenic effects in rats. The study of rabbits found "the suggestion of an increase in central nervous system anomalies (hydrocephaly/dilated cerebral ventricles) in both the number of fetuses and litters at doses of

100 [mid-dose] and 250 [high-dose] mg/kg/day." Overall, 15.4% and 23.1% of the litters in the mid- and high-dose groups, respectively, exhibited evidence of central nervous system (CNS) abnormalities, compared to 6.7% in the control group and none in the low-dose group. Note that the mid-dose with effects in rabbits is 34,000 times greater that the worst estimates reported for chlorpyrifos exposure in one of the human case reports. Also note that the HED evaluation of teratogenicity is based on the parent compound, chlorpyrifos, not TCP.

Epidemiologic studies of birth defects in agricultural populations have produced conflicting results for pesticides (Taha and Gray 1993, Willis et al. 1993, Romero et al. 1989, McDonald et al. 1988). Similarly inconsistent results have been reported for solvents, such as xylene often mixed into chlorpyrifos formulations (Holmberg and Nurminen 1980, Kucera 1968, Taskinen et al. 1989, Windham et al. 1991).

HED concludes the available evidence does not support a finding of teratogenicity based on human epidemiology studies and case reports. On rare occasion, case reports can lead to the identification of a new risk factor for a disease. However, the strength of evidence from case reports reported so far do not support a finding of teratogenicity.

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APPENDIX 1.

REVIEW OF EPIDEMIOLOGIC STUDIES OF CHRONIC NEUROBEHAVIORAL EFFECTS OF ORGANOPHOSPHATE INSECTICIDES

Neurobehavioral epidemiology is a comparatively new field and is dependent on practical, reliable, and sensitive tests of adverse effects. In a review sponsored by the National Research Council, Hanninen points out that more sensitive tests are needed to assess memory deficits, more valid and practical tests are needed to assess attention, and more comprehensive tests are needed to measure affect or mood states and personality (Hanninen 1990). Despite the lack of optimal tests, deficits in memory, attention, and mood have been identified repeatedly in epidemiologic studies of organo-phosphate poisoned workers as will be shown below.

In epidemiology the ideal is to have a well-controlled study. Anger emphasizes this in his review, also sponsored by the National Research Council: "An appropriate control group should consist of people who are not only unexposed to toxic chemicals, but are also similar to the exposed subjects in terms of age, education, job activities or movements, and socioeconomic variables. This is extremely difficult to achieve, and field researchers are virtually always concerned with the accuracy of the controls as a basis for judging the performance of the exposed group" (Anger 1990).

Case Reports

Several independent reports have noted long-lasting effects of OP poisoning. Case reports are not epidemiologic studies in the strictest sense but "it is recognized that such studies can be very useful as indicators of environmentally-induced disease" (Interagency Regulatory Liaison Group 1981).

Rosenstock et al. (1990) presented a case report of a 60 year old farm worker who experienced headaches, memory loss, confusion, and fatigue after applying parathion in an apple orchard. Two years later he was still reported to have an inability to concentrate, severe impairment of memory, confusion, and depression.

Grace (1985) reported on a 33-year old farmhand in California who was severely poisoned by parathion after working in the orchard for 10 days and repairing farm machinery in the field. The family of the worker reported that he usually drank a pint of whiskey a day and his serum alcohol level on admission to the hospital was 0.19%, legally drunk. This patient developed memory impairment, personality changes, thought disorders, confusion, and depression that persisted months after his poisoning. Alcohol may have contributed to these symptoms.

Two three-year olds who had been poisoned by parathion were examined 1-2 years later in a follow-up study of 8 acute poisoning cases (Harmon et al. 1975). Family history revealed that one child had become more nervous and emotionally less stable since his poisoning. This child who could not complete the physical examination because he was completely uncooperative and "his mother believed this type of behavior to be a direct result of the poisoning". The other victim of parathion poisoning was also reported to be irritable and less stable than his siblings. The investigators, who had not used any sophisticated neurobehavioral tests, judged their results inconclusive.

Case Series

Gershon and Shaw (1961) reported on 16 workers with 1-10 years duration of exposure to organophosphates. These 16 workers are not a representative sample of workers, but a selected group. Assessment of psychiatric symptoms revealed that 8 had impaired memory, 7 depression, 6 impaired concentration, 5 had schizophrenic reactions, 4 had irritability, and 4 had persistent headaches. Lack of controls and sampling methodology prevent concluding that the symptoms seen in this case series were necessarily due to the chronic exposure or poisoning from organophosphates.

Metcalf and Holmes (1969) examined two datasets based on workers involved in the manufacture of organophosphates. The first dataset examined 56 exposed workers and 22 controls. The OP exposed workers exhibited more forgetfulness (53% of exposed versus 20% of controls), visual difficulty (30% versus 0%), general fatigue (35% versus 5%), muscle aches and pains (12% versus 0%) and difficulty thinking (12% versus 5%).

Their subsequent study of the same workforce included psychological testing, electroencephalograms (EEG), and a neurological examination. The authors reported that the exposed group demonstrated "disturbed memory and difficulty maintaining alertness and appropriate focusing of attention" from the psychological testing. Direct interviews of these workers with multiple or severe exposures elicited complaints of being slowed down, less energetic, and having more memory difficulty and irritability than the minimally exposed workers. Neurological tests did not show differences between highly and minimally exposed workers on tests of sensory or motor deficits. The EEG examination was conducted on all workers in the study and did show changes. These changes were characterized as "a minimal type of EEG disturbance, but it mirrors, to a lesser degree, the more severe EEG disturbances seen after acute exposure".

Both this study and the earlier one by Metcalf and Holmes (1969) are marred by a lack of description of the sources of cases and controls, lack of case definition, absence of statistical

testing for significance, and lack of any discussion of possible biases or confounders. Due to these deficiencies, the study must be treated more as a case series than as a controlled epidemiologic study. This means that the findings can be characterized only as suggestive or supportive of the results from other studies.

Holmes and Gaon (1957) examined 600 patients who were factory workers with exposure to organophosphates, principally parathion and TEPP. In this survey 25 or 4 percent reported symptoms of irritability, nervousness, fatigue, lethargy, memory impairment, confusion, decreased mental concentration, and various problems with muscle aches and pains including sensations of numbness and weakness in the limbs. These persistent symptoms occurred "in the more severe exposures and in those with multiple exposures".

In one case of severe exposure to an organophosphate, Holmes and Gaon (1957) recorded the patients subsequent mental confusion in the patient's own words: "Get tired--hard to breathe--short of breath, just like I'd run up a hill. This usually happens when I do anything that requires some energy--(fast walking--short runs, etc.). Had a couple of restless nights--nervous. I still get quite nervous--lot more irritable than before. Very absent-minded since last exposure. My mind seems to like to wander--quite marked. I cleaned out garage just after the exposure and now I don't know where I put half the stuff. I distinctly remember trying to store it in places where I could remember, but now I have to go through all the stuff to find it. It was 2 weeks sometimes before I found what I wanted. My thinking seems rather flighty--I've been fairly good in arithmetic, but can't do it too well in my head now. Can't concentrate on more than one thing at one time".

Two physicians in California examined 114 OP poisoning cases 3 years afterward to look for chronic effects (Tabershaw and Cooper 1966). They originally sought 235 subjects that had OP poisoning in 1960, but only 114 were located, examined and included in the final analysis. Of the 114 cases, 6 were classified as severe (coma or convulsions present, hospitalized an average of 8 days), 54 were considered moderate based on clinical notes, and 54 were considered mild (patient remained ambulatory or recovered rapidly from limited therapy). Nearly half, 53 cases required hospitalization. In 6 individuals visual disturbances were reported which the patients insisted had not been present before the poisoning episode and which they attributed to the poisoning. Another 7 patients complained of persistent headaches. Five poisoning victims complained of nervousness or irritability. Notably 22 of the 114 workers (19%) reported they could no longer tolerate smelling or contacting pesticides. Of the 22, 16 had given up work involving contact with pesticides because of their intolerance and six continued to work on the farm but avoided contact as much as possible. One wonders how many of the 61 poisoned workers that could not be located for this study may have left because of persistent symptoms or intolerance. Other studies

attempting to measure such effects may miss recruiting affected individuals because they have left pesticide-related work after being sensitized. A controlled epidemiologic study would be needed to confirm the results identified in this report of a case series.

Hirshberg and Lerman (1984) collected data on 236 case records of organophosphate and carbamate poisoning from 8 hospitals in Israel from 1958 to 1979. OP poisoning was confirmed by laboratory evidence of cholinesterase depression. Carbamate poisoning was confirmed by unequivocal evidence of direct exposure. Only 5 cases of carbamate poisoning were included. Accidental exposure accounted for 89% of the cases and 26 or 11% were attempted suicides by oral ingestion. According to the authors: "Depression, confusion, and agitation were noted in nine patients after recovery from the acute phase of poisoning. Other complaints were insomnia and motor weakness without objective neurological deficits". Seven of these 9 cases were considered to have only mild poisoning based on their clinical symptoms. All of the 9 cases had been poisoned by organophosphates.

Controlled epidemiologic studies

Both the studies by Savage et al. (1988), Rosenstock et al. (1991), and Steenland et al. (1994), presented below, are examples of high quality epidemiologic studies. A study by Savage et al. (1988) in Colorado and Texas examined 100 cases poisoned by organophosphates and 100 matched controls for neurological and neuropsychological function. Controls were matched on age, sex, race, ethnic background, education, and occupational class. Significant differences were found on tests of memory, abstraction, depression, and mental impairment. On average the exposed subjects were poisoned 9 years before testing. Poisoned subjects scored significantly worse on 4 of 5 summary scores of psychoneurological function and on 18 of 34 subtests. Among the tests that poisoned subjects scored worse on were the Wechsler Adult Intelligence Scale, logical analysis, abstract reasoning, verbal fluency, problem solving, concentration, sensitivity to social stresses, and fine motor coordination and speed. Relatives of the 100 poisoned subjects and controls were questioned about psychological function in 22 areas. Statistically significant differences were found in four areas, depression, irritability, social withdrawal, and confusion. Again, the controls performed better in these areas than the case group.

It was not possible from this single study to state that organophosphate poisoning leads to adverse effects on psychoneurological function. A number of potential sources of bias, particularly selection factors may have affected the results of this one study. However, results from this study have been replicated on poisoned workers in Nicaragua and again in California.

Rosenstock et al. (1991) performed a retrospective cohort study of agricultural workers in Nicaragua who had been hospitalized with organophosphate poisoning. Of 52 eligible patients hospitalized over a two year period, 38 men were located, and 36 agreed to participate in the study. Controls were a close male friend or sibling from the same community who had never been treated for pesticide poisoning and was no more than 5 years different in age from the case participant. Both members of the pair (case and control) were examined during May-June 1989 before the onset of the 4-5 month spraying season. Six of the seven tests from the World Health Organization core neurobehavioral test battery were administered, along with a brief symptom inventory, 6 additional Spanish-translated tests, and a 16 item self-reported symptom inventory. These tests were administered an average of 2 years after the time of hospitalization for poisoning.

Poisoned workers scored significantly worse on five of the six WHO core neurobehavioral tests, 3 of the 6 Spanish-translated tests, and the 16 item self-reported inventory. Deficits were noted in auditory and visual attention, visual memory, visuomotor skills, steadiness and dexterity. These findings replicated, to a large degree, those of Savage et al., which is an important consideration when judging the weight of evidence for a conclusion that OP poisoning is a cause of chronic neurobehavioral effects.

Steenland et al. (1994) studied chronic neurological sequelae in 128 workers poisoned by organophosphates between 1982 and 1990 and 90 controls. The poisoned group performed significantly worse on measures of sustained visual attention and mood. If the poisoned group was restricted to those with documented cholinesterase inhibition or those who had been hospitalized, the poisoned subjects also showed poorer performance on vibrotactile sensitivity tests. This study concluded "The evidence of some long-term effects of poisoning is consistent with two prior studies."

This study had certain limitations common to many epidemiologic studies. However, these limitations do not effect the conclusion. The 128 poisoned cases were only 31% of the 416 potential participants sought for the study. Of the remainder 37% could not be located, 19% could not be contacted (mailings sent to their listed address were not responded to), and 13% refused to participate. Some of the individual were excluded from some or all of the tests. The first 16 individuals examined did not receive the test for mood which was added after the first round of testing. Eighteen subjects could not take the neurobehavioral tests primarily because of inability to read. Thirty-eight of the poisoned cases (30%) failed to bring a friend to serve as a control for the study. One disadvantage of the use of friends as controls is that they might be selected by the cases on the basis of similarities in mood and other personality factors under study that would tend to prevent discovery of significant effects.

Unlike the two earlier case-control studies, this report attempted to determine whether effects were associated with exposure to particular organophosphate insecticides. The Steenland et al. (1994) study mentions in their introduction that a subset of organophosphates may cause delayed-onset peripheral neuropathy by effects on the neuropathic target esterase, a property not shared by other organophosphates. No similar mechanism is suggested as to why in the current study some organophosphates and not others would effect either the peripheral nervous system or the central nervous system. All of the organophosphates under study poison primarily by their ability to inhibit the cholinesterase enzyme. Both central and peripheral nervous systems may be affected. Therefore, if chronic effects are brought about by depression of neural and brain cholinesterases, then such effects can be expected from any organophosphate insecticide.

Stephens et al. (1995) examined farmers exposed to organophosphate sheep dips. A total of 143 sheep farmers were recruited and 143 quarry workers from the same rural area were used as controls. Letters were used to recruit every tenth farmer from the Wool Marketing Board list of sheep farmers, but only resulted in a response rate of 33%. Subsequently telephone contacts were made which produced a response rate of 69%. The overall response rate for quarry workers was 35%. Subjects were tested so that they would not have had any organophosphate insecticide exposure in the past two months. Computer-administered psychological tests and questionnaires were completed at the subjects' homes. Farmer scored significantly worse on 3 of 8 psychological tests: Symbol Digit Substitution; Syntactic Reasoning; and Simple Reaction Time. These differences remained after adjusting for covariates that were both biologically plausible and statistically significant. Farmers apparently reported more symptoms suggestive of psychiatric disorder, however, these symptoms were not analyzed individually. The lack of a good response rate in both cases and controls is a potential source of bias in this study.

Levin et al. (1976), and in a separate report, Rodnitzky et al. (1975) examined 11 farmers and 13 commercial applicators. Farmers tested prior to the spraying season and farmers not involved in pesticide application were used as controls and matched on sex, age, and education. While no significant differences were seen on neurobehavioral tests, there was some increased anxiety in commercial applicators. In order to participate in the study, pesticide applicators had to have been exposed in the past two weeks to organophosphates. Therefore, this study tested for immediate neurobehavioral effects of exposure and has no bearing on long term neurobehavioral effects of poisoning or exposure. The study may have been confounded by selecting farmers as controls who did have neurobehavioral deficits as a result of previous exposure (more than two weeks ago) or even poisoning to organophosphates. Therefore, these studies are not relevant to a review of chronic neurobehavioral effects of organophosphate poisoning.

Weight-of-Evidence Conclusion

The studies presented above do provide surprisingly consistent results of neurobehavioral damage due to organophosphates. While the association is not especially strong, it is fairly specific and has been found in a variety of different populations. Evidence of the direct effects of organophosphates on the brain mean the effects observed may be considered biologically plausible. Alternative explanations such as chance, bias, and confounding are less likely explanations for the associations seen in these studies than exposure to organophosphates.

Taking these case reports and studies together, it now appears reasonable to conclude that some subset of organophosphate poisoned subjects probably experience persistent neurobehavioral effects (Karalliedde and Senanayake 1989, U.S. Congress, Office of Technology Assessment 1990, World Health Organization 1990). A recent review by Karalliedde and Senanayake (1989) came to a similar conclusion: "Behavioural changes have been documented following acute or chronic OP poisoning. These symptoms may take months to regress. In human subjects exposed to OP agents to an extent sufficient to depress plasma or erythrocyte [red blood cell] cholinesterase, some or all of the following observations have been made: (1) Impairment of vigilance, information processing, psychomotor speed and memory. (2) Poor performance and perception of speech. (3) Increased tendency to faster frequencies and higher voltages in EEG records" (Karalliedde and Senanayake 1989). Ecobichon's 1994 review of organophosphates and neurological disease concluded "Sufficient anecdotal information can be found in the medical literature to signify that there are persistent and serious complaints lasting from 6 months to several years and, possibly, forever".

The World Health Organization (1990) suggests that 5 percent of occupational poisonings due to organophosphates result in these effects. The Office of Technology Assessment of the U.S. Congress (1990) has arrived at a similar conclusion: "The pesticides parathion, mevinphos (Phosdrin), and malathion are frequently reported as causing health problems. Case reports and studies of acute poisonings of agricultural and other workers indicate that 4 to 9 percent of the acutely poisoned individuals experienced delayed or persistent neurological and psychiatric effects." These effects include "irritability, depression, mood swings, anxiety, fatigue, lethargy, difficulty concentrating, and short-term memory loss. These symptoms may persist for weeks and months after the initial exposure." Given the results from controlled studies by Savage et al. (1988) and Rosenstock et al. (1991) and others listed above this last sentence can be changed to read: "These symptoms may persist for months or years after the initial exposure."

Results from key studies supporting a relationship between organophosphate poisoning and chronic neurobehavioral effects.

Reference	study type	Latency	Symptoms
Case reports Rosenstock et al. 1990	case report	2 years later	severe memory impairment, deficits in attention, depression, psychomotor impairment.
Grace 1985	case report	months later	memory impairment, personality changes, thought disorders, confusion, depression.
Harmon et al. 1975	case report	1 year later	temper tantrums, irritability.
Harmon et al. 1975	case report	2 years later	Excitability, emotionally less stable than siblings.
Case series Gershon and Shaw 1961	16 OP cases	1-10 years later	8 had impaired memory, 7 had depression, 6 impaired concentration, 5 schizoid, 4 headache, 4 irritability.
Metcalf and Holmes 1969	56 OP cases	6 years average	disturbed memory, difficulty in maintaining alertness, irritability, visual difficulty, muscular aches and pains.
Holmes and Gaon 1957	600 OP cases	?	increased irritability, marked forgetfulness, confusion in thinking, inability to concentrate.
Tabershaw and Cooper 1966	114 OP cases	3 years later	7 persistent headaches, 6 visual disturbances, 5 nervousness and irritability, 22 chemically sensitive.

Hirshberg and Lerman 1984	236 OP cases	after acute poisoning	9 depression, confusion, and agitation.
matched case-control studies Savage et al. 1988	100 cases and controls	9 years later on average	case performed poorer on: academic skills, motor skills, abstraction, flexibility in thinking, memory, depression, irritability, withdrawal, confusion.
Rosenstock et al. 1991	36 cases and controls	2 years later on average	cases performed poorer on: auditory and visual attention, visual memory, visuomotor skills, steadiness, dexterity.
Steenland et al. 1994	128 cases and 90 controls	5 years later on average	cases performed poorer on: visual attention and mood (confusion and tension).
Stephens et al. 1995	146 cases and 143 controls	based on exposure rather than poisoning	cases performed worse on sustained attention and speed of information processing.

Most often reported effects

Irritability
Memory impairment
Inability to concentrate
Confusion
Depression

Reported in two or more studies

Visual disturbances
Persistent headaches
Muscle aches and pains
Fatigue
Psychomotor impairment
Nervousness

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