NATIONAL TOXICOLOGY PROGRAM

EXECUTIVE SUMMARY OF SAFETY AND TOXICITY INFORMATION

CHLORPYRIFOS

2921-88-2

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NATIONAL TOXICOLOGY PROGRAM

Submitted by:

Arthur D. Little, Inc.

Chemical Evaluation Committee Draft Report

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OVERVIEW[1]

Nomination History: *Chlorpyrifos was nominated by the Citizens Against Pesticide Misuse (Helen Auten, Director) in 1989 for toxicity and carcinogenicity testing, with a low priority. The request is based upon the potential for extensive human exposure to this compound as the active ingredient in many pesticide and insecticide formulations and the existing evidence of its human toxicity.*

Chemical and Physical Properties: *Chlorpyrifos occurs as white, granular crystals with a mild mercaptan odor. Its melting range is 41.0-43.5 ℃. Chlorpyrifos is soluble in water, acetone, benzene, chloroform, methanol, and isooctane. It is incompatible with strong alkaline and acidic compounds and its decomposition results in the formation of chlorine, nitrous oxides, phosphorous oxides, and sulfur oxides.*

Production/Uses/Exposure: *No production data were available from the United States International Trade Commission's Publication Synthetic Organic Chemicals or from SRI's Chemical Economics Handbook. No production data were available from the public file of the EPA Toxic Substances Control Act (TSCA) Inventory. Chlorpyrifos is widely used as the active ingredient in pesticides (and insecticides) for both household and agricultural applications; it is effective against a broad spectrum of pests. One source reports that approximately 7,000-11,000 pounds of this compound are used annually in the production of pesticides and herbicides. Another source reports that 3.6-4.1 million kg of chlorpyrifos were used in 1982 for pest control (mostly agricultural applications), and that in 1988, California used 720,499 pounds in insecticide formulations for crops. Consumer exposure to this compound may result from inhalation of chlorpyrifos aerosols, dermal contact with chlorpyrifos-treated surfaces, or accidental ingestion of food products or other items contaminated with chlorpyrifos residues following treatment of living spaces, crops, or livestock. Occupational exposure to chlorpyrifos is common among workers involved in the manufacture, formulation, and application of the compound.*

[1]The information contained in this Executive Summary of Safety and Toxicity Information (ESSTI) is based on data from current published literature. The summary represents information provided in selected sources and is not claimed to be exhaustive.

Data from the National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and Health (NIOSH) during the years 1982-1983, estimated that 11,404 employees, including 842 females, were potentially exposed to chlorpyrifos. The current OSHA PEL and ACGIH recommended TLV-TWA for chlorpyrifos is 0.2 mg/m3 (skin). NIOSH has not recommended an exposure limit (REL) for this compound. The United Nations Food and Agricultural Organization (FAO) and World Health Organization (WHO) established an acceptable daily intake for chlorpyrifos of 10 µg/kg/day.

Toxicological Effects:

Human: *In human volunteers that were used to study the pharmacokinetics of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (TCP) was identified as the primary metabolite. Chlorpyrifos and TCP were found to be readily excreted in the urine and it was concluded that neither compound has significant potential to accumulate. In a case report describing occupational exposure to this organophosphate insecticide, two other metabolites were identified: O,O-diethyl, O-amyl phosphate and O,O-diethyl, O-amyl phosphorothionate. Numerous accounts of human exposure to chlorpyrifos have been reported. The symptoms associated with acute and prechronic exposure to this compound include headache, nausea, dizziness, vomiting, catatonia, meiosis, tachycardia, areflexia, muscle weakness, respiratory problems, lethargy cyanosis, and other clinical signs of toxicity. The most prevalent effect of chlorpyrifos exposure in humans was the inhibition of blood and plasma cholinesterase activity. In vitro, chlorpyrifos was found to have a dose- and time-dependent effect on the induction of the acrosome reaction in human sperm as well as sperm vitality indicating the compound may impair fertiliztaion. No data were found on the chronic, carcinogenic, or teratogenic effects of chlorpyrifos in humans.*

Animal: *Chlorpyrifos is absorbed by the dermal and oral routes of exposure in animals. This compound was found to be metabolized to 3,5,6-trichloro-2-pyridinol (TCP), diethylthiophosphate (DEPT), and diethylphosphate (DEP) in rats and mice. Chlorpyrifos is rapidly eliminated in both species. In rats administered ^{36}Cl-chlorpyrifos by stomach tube, 81% of the radioactivity appeared in the urine within the first day. After 74 hours, 90% was excreted in the urine and 11% was excreted in the feces after 66 hours. The estimated half-lives for chlorpyrifos and TCP were found to be 8.15 and 24.66 hours, respectively in rats that were*

intraperitoneally administered this compound. Chlorpyrifos and its metabolites have been found to accumulate primarily in fatty tissues. Following ^{36}Cl administration in rats, half-life values for the radioactive compounds in the liver, kidney, muscle, and fat were 10, 12, 16, and 62 hours, respectively. After intraperitoneal administration of ^{14}C-chlorpyrifos in mice, the highest concentrations of radioactivity were found in the liver and fat, with levels in both tissues decreasing over time.

Acute exposure to chlorpyrifos causes toxicosis in animals (laboratory and other), and includes the following symptoms; slight tremors, piloerection, exophthalmia, chromodacryorrhea, diarrhea, weakness, lethargy, ataxia, tremors, miosis, salivation, anorexia, ptyalism, dyspnea, prostration, reduced responsiveness, restlessness, loss of appetite, urination and defecation, and convulsions. The predominant effect in these animals was a decrease in blood and plasma cholinesterase activity, which returned to normal within 1-4 weeks of dosing. In rats, an intraperitoneal injection of chlorpyrifos (at half the LD_{50}) resulted in necrosis of the gonads, kidney, and liver. When applied to the backs of rabbits, this compound induced erythema, necrosis, and edema.

The oral LD_{50} of chlorpyrifos and formulations containing this compound ranged from 60-1173 mg/kg in rats, 60-152 mg/kg in mice, 1000-2000 mg/kg in rabbits, and 500-504 mg/kg in guinea pigs. The inhalation LC_{50} was 2.6-3.6 mg/L in rats and 94 mg/L in mice, and the intraperitoneal LD_{50} in mice ranged from 40-192 mg/kg. When applied topically, the LD_{50} of this compound and its formulations was 200-202 mg/kg in rats and 930-3360 mg/kg in rabbits. In addition, chlorpyrifos has been found to be toxic to aquatic organisms, birds, cows, goats, cats, and swine following acute exposure.

In prechronic studies, chlorpyrifos administered orally to rats caused decreased plasma and erythrocyte cholinesterase activity, decreased food consumption, weight loss, tremors, ulceration of the cornea and nostrils, and death. Monkeys treated orally with chlorpyrifos for 6 months also developed depressed cholinesterase levels. Long term oral exposure to chlorpyrifos inhibited plasma, blood, and brain cholinesterase in rats and dogs (blood and plasma only).

Oral doses of 25 mg/kg chlorpyrifos caused severe maternal toxicity in mice. However, this compound does not effect reproduction and is not teratogenic or fetotoxic. The cholinesterase activities in both the dams and fetuses were significantly depressed following treatment with chlorpyrifos.

Genetic Toxicology: Chlorpyrifos was negative in the Ames assay in Salmonella, in the rec assay with Bacillus subtilis, and did not cause reverse gene mutations or SOS induction in Escherichia coli. However, chlorpyrifos did cause DNA damage in a relative toxicity test in both E. coli and B. subtilis. Chlorpyrifos caused chromosomal aberrations and sister chromatid exchange in human lymphocytes and chromosomal aberrations in hamster lung fibroblasts. This compound did not, however, induce unscheduled DNA synthesis in human lung fibroblasts and rat hepatocytes, cause forward mutations in chinese hamster ovary cells, or mitotic gene conversion in Saccharomyces cerevisiae. In Drosophila studies, chlorpyrifos did not induce sex-linked recessive lethal mutations, but did cause chromosome loss. This compound was positive in micronucleus tests using mouse bone marrow cells, and produced chromosomal aberrations and abnormal pollen mother cells in plants.

Structure Activity Relationships: Organophosphorus insecticides, including chlorpyrifos, exert their toxic effects by inhibiting acetylcholinesterase. Many of these compounds have been found to be embryotoxic at maternally toxic doses. Trichlorophon and fenchlorphos have been reported to cause teratogenic effects in pigs and rabbits, respectively. In addition, some of the organophosphorus pesticides have been reported to show positive responses to in vitro mutagenicity tests. Specifically, dichlorvos, dioxathion, and dimethoate were positive in Salmonella, and dichlorvos was positive in mouse lymphoma cells. In studies conducted by the National Toxicology Program (NTP), it was determined that there was some evidence of carcinogenic activity in male rats administered dichlorvos by gavage. However, diazinon, dioxathion, and dimethoate have been tested in 2-year bioassays by oral administration using male and female rats and mice, and were found to exhibit no evidence of carcinogenicity. Chlorpyrifos-methyl (Reldan®), the dimethyl analog of chlorpyrifos, was not found to be carcinogenic or to induce tumor formation.

I. NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Source: Helen Auten, Director, Citizens Against Pesticide Misuse [CAPM, 1989]

2. Date: May, 1989

3. Recommendations: Toxicity
   Carcinogenicity

4. Priority: Low

5. Rationale/Remarks:

   - Potential for extensive human exposure
   - Evidence of human toxicity

B. Chemical Evaluation Committee Review

1. Date of Review:

2. Recommendation:

3. Priority:

4. NTP Chemical Selection Principle(s):

5. Rationale/Remarks:

C. Board of Scientific Counselors Review

1. Date of Review:

2. Recommendations:

3. Priority:

4. Rationale/Remarks:

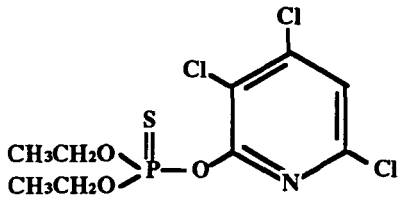
D. Executive Committee Review

1. Date of Review:

2. Decision:

II. CHEMICAL AND PHYSICAL DATA

A. Chemical Identifiers



CHLORPYRIFOS

CAS No. 2921-88-2
RTECS No. TF6300000

Molecular formula: $C_9H_{11}Cl_3NO_3PS$ Molecular weight: 350.57

B. Synonyms and Trade Names

Synonyms: Phosphorothioic acid, *0,0*-diethyl 0-(3,5,6-trichloro-2-pyridyl) ester (7CI) (8CI); *0,0*-diethyl *0*-(3, 5, 6-trichloro-2-pyridinyl) phosphorothioate (9CI); phosphorothioic acid, *0,0*-diethyl *0*-(3,5,6-trichloro-2-pyridinyl) ester (9CI); *0,0*-diethyl *0*-(3, 5, 6-trichloro-2-pyridyl) phosphorothioate; *0,0*-diethyl *0*-3, 5, 6-trichloro-2-pyridyl phosphorothorioate; chlorpyrifos; chlorpyrifos-ethyl; 2-pyridinol, 3, 5, 6-trichloro-, *0*-ester with *0,0*-diethyl phosphorothiate; trichlopyriphos

Trade Names: Brodan®; Dowco 179®; Dursban®; Killmaster®; Lorsban®; Pyrinex®; SuSCon®; ENT 27311®; EF 121®; Spannit®

C. Chemical and Physical Properties

Description: White, granular crystals [Budavari, 1989; Meister, 1990; US Coast Guard, 1985; USEPA, 1984b] with a mild mercaptan odor [US Coast Guard, 1985; Worthing, 1987; USEPA, 1984].

Melting Point: 41.0-43.5°C [Budavari, 1989; Howard, 1991; Verschueren, 1983; Meister, 1990; USEPA, 1984b]

Boiling Point: No data were found

Specific Gravity: 1.398 at 45°C [Verschueren, 1983]

Refractive Index: No data were found.

Solubility in Water:

2 ppm at 25°C [Budavari, 1989]
1.12 ppm at 24°C [Howard, 1991]
2 mg/L [Worthing, 1987]
73 µg/L (seawater) [Schimmel *et al.*, 1983]

Solubility in other Solvents:

acetone (6.5 kg/kg), benzene (7.9 kg/kg), chloroform (6.3 kg/kg) [Worthing, 1987], methanol to 43-45% w/w [Budavari, 1989; Kirk-Othmer, 1981] (450 g/kg [Worthing, 1987]), and isooctane to 79% w/w [Budavari, 1989; Kirk-Othmer, 1981]

Log Octanol/Water Partition Coefficient:

5.11 at 20°C [Verschueren, 1983]
4.96 [Howard, 1991]
5.2 [Schimmel *et al.*, 1983]

Reactive Chemical Hazards:

Chlorpyrifos is incompatible with strong alkaline materials [DowElanco, 1990] and strong acids [BRS, 1991]. This compound is corrosive to copper and brass [Worthing, 1987]. Decomposition products include toxic fumes of chlorine, nitrous oxides, phosphorous oxides, and sulfur oxides [Sax and Lewis, 1989].

Flammability Hazards:

- Combustible
- Flash Point: None [USEPA, 1984a]
- Vapor Pressure: 1.87×10^{-5} mm Hg at 25°C [Budavari, 1989; ACGIH, 1986]
  0.19 mm Hg at 25°C [Kirk-Othmer, 1981]
  1.87x10-5 mm Hg at 20°C [Verschueren, 1983]

III. PRODUCTION/USE

A. Production

1. Manufacturing Process

Chlorpyrifos is produced by partial hydrolysis and phosphorylation of 2,3,5,6-tetrachloropyridine [Kirk-Othmer, 1982] or by the reaction of 3, 5, 6-trichloro-2-pyridinol with diethyl phosphorochloridothioate in the presence of sodium carbonate [Hazardous Substances Database, 1991]. Another source reports that chlorpyrifos can be produced by reacting solid particulate sodium 3,5,6-trichloropyridinate with *0,0*-diethyl phosphorochloridothioate dissolved in a methylene chloride reaction medium in the presence of a catalytic amount of benzyltriethylammonium chloride [Freedman, 1976]. Dow Chemical produces 2,3,4,5,6-pentachloropyridine and converts this compound into 2-hydroxy-3,5,6-trichloropyridine, which is then used as the chemical intermediate for chlorpyrifos [SRI, 1991c].

2. Producers and Importers

U.S. Producers:

Producers	Reference
Dow Chemical U.S.A. Midland, Michigan	SRI, 1991a; SRI, 1991c

Foreign Producers :

Producers	Reference
Dow Chemical Company Limited King's Lynn, United Kingdom	SRI, 1991b
Makhteshim-Beer Shiva Israel	USEPA, 1984a; USEPA, 1984b

U.S. Importers:

Importers	Reference
Makhteshim Agan America New York, New York	Piers Imports, 1991
AJ Fritz Inglewood, California	Piers Imports, 1991

3. Volume

Production Volume

Chlorpyrifos is listed in the United States International Trade Commission's (USITC) publication Synthetic Organic Chemicals. However, no production data were available on chlorpyrifos from this source for the years 1985-1989[2] [USITC, 1986-1990].

No production data specific to chlorpyrifos were included in SRI's Chemical Economics Handbook. However, this source reports that in 1984, the pesticide market accounted for 41% of the U.S. consumption of phosphorus pentasulfide (P_2S_5). Diethyl phosphorochloridothioate which is captured from P_2S_5 and purchased by Dow Chemical, is used in the synthesis of chlorpyrifos. It is expected that the U.S. consumption of P_2S_5 for pesticide synthesis will grow slowly at an average rate of 1-2% per year between the years 1984 and 1989, but will remain below the 1980 volume (1980 volume not reported). This growth will be due to the increased demand for pesticide products. In addition to the use of P_2S_5, Dow chemical used 8 million pounds of alpha-picoline as a starting material for production of several pesticides, including chlorpyrifos, in 1988 [SRI, 1991c].

Import Volume

The amount of chlorpyrifos imported to the United States by the importers listed above was 222,341 pounds between January, 1990 and March, 1991 (range of 1,345-43,707 pounds). This value excludes the import volume of one shipment, which was reported only as 32 drums [Piers Imports, 1991].

4. Technical Product Composition

Chlorpyrifos is available as a technical grade with a minimum of 98% purity [US Coast Guard, 1985], or 97.4% purity [Palmer *et al.*, 1980]. This compound is available in a variety of formulations including baits, dusts, pellets, granules, wettable powders, flowables, impregnated plastics, pressurized liquids, and emulsifiable concentrates [USEPA, 1984a; USEPA, 1984b, Meister, 1990].

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[2]Production statistics for an individual chemical are given only when there are three or more producers, no one or two of which may be predominant. Moreover, even when there are three or more producers, statistics are not given if there is any possibility that the publications would violate the statutory provisions relating to unlawful disclosure of information accepted in confidence by the Commission. Data are reported by producers for only those items where the volume of production or sales exceeds certain minimums. Those minimums for all sections are 5,000 pounds of production or sales, or $5,000 value or sales with the following exceptions: plastics and resin material — 50,000 pounds or $50,000; pigments, medicinal chemicals, flavor and perfume materials, and rubber processing chemicals — 1,000 pounds or $1,000.

B. Use

Chlorpyrifos is used as the active ingredient in organophosphorus pesticides/ insecticides, and has been found to be effective against a broad range of common pests [Reynolds, 1989; Meister 1990] in both agricultural and nonagricultural applications [Brenner *et al.*, 1989]. For example, DowElanco uses chlorpyrifos as the active ingredient in the formulation Dursban®, which is used in professional pest management and household products [DowElanco, 1991a; USEPA, 1984a], and in Lorsban®, which is commonly used as an agricultural insecticide [DowElanco, 1991c; USEPA, 1984a]. Some of the crop applications include grain and nut crops, fruit crops, bananas, cole crops, field and vegetable crops, and cotton [USEPA, 1984a, USEPA, 1984b]. In addition to these agricultural uses, chlorpyrifos is used in pest control directly on cattle, as a sheep, turkey and horse premise treatment; and for treatment of dogs, dog kennels, dog bedding and quarters, domestic dwellings, farm buildings, storage bins, commercial establishments, ornamentals, lawns and turf, terrestrial structures (as a termiticide), and aquatic areas (mosquito control) [USEPA, 1984b]. It is also included in latex coatings to serve as a long-lasting (up to two years) insecticide [Polymer Paint and Colour Journal, 1986].

Application of chlorpyrifos may be dormant, delayed dormant, foliar (applied to the leaves of plants), a slurry seed treatment, or directly in soil. In addition, the pesticide may be applied as a spray using an aircraft, as in the case of corn, cotton, peanuts, sorghum and aquatic noncrop areas [USEPA, 1984b; Meister, 1990].

In 1982, chlorpyrifos was one of the most frequently used organophosphate compounds in the United States; 3.9 million pounds of this compound were applied to corn and 0.2 million pounds were applied to sorghum crops [Marquis, 1986]. Another source reports that domestic use of chlorpyrifos in 1982 was 3.6 million kg. The compound was used mostly for agricultural purposes, but 0.15 million kg were used to control mosquitos in wetlands, and 0.04 million kg were used to control turf-destroying insects on golf courses [USDI, 1988]. In 1988, California used a total of 720,499 pounds of chlorpyrifos as an insecticide for crops (alfalfa, almonds, and cotton) [Stinmann and Ferguson, 1990].

IV. EXPOSURE/REGULATORY STATUS

A. Consumer Exposure

The widespread use of pesticides containing chlorpyrifos by the agricultural industry creates a potential for consumer exposure to this chemical from ingestion of residues on, or in, food products.

The United States Food and Drug Administration (FDA) conducted a 3-year, 20-city, nation-wide Total Diet Study to determine potential dietary intake of selected pesticides, such as chlorpyrifos, using representative food stuffs purchased in retail stores [Gartrell *et al.*, 1985a; Gartrell *et al,* 1985b]. From October 1978-September 1979, the estimated daily consumption of chlorpyrifos by infants and toddlers was 0.0201 and 0.0905 µg, respectively. In both cases, the chemical was detected only in grain and cereal products. Chlorpyrifos residues were not detected in infant and toddler diets during fiscal years 1976 to 1978, but in fiscal year 1979, the daily intakes for infants and toddlers per unit of body weight were 0.002 and 0.007 µg/kg, respectively [Gartrell *et al.*, 1985a]. During October 1979 to September 1980, the average daily consumption of chlorpyrifos by adults was estimated to be 0.0460 µg. Residues of the chemical were detected in grain and cereal products (average of 0.001 ppm) and in garden fruits (average of < 0.0001 ppm). The adult daily intake per unit of body weight for chlorpyrifos was 0.005 µg/kg for fiscal years 1978 and 1979, and 0.001 µg/kg for fiscal year 1980; no chlorpyrifos was detected in the adult diet for fiscal year 1977 [Gartrell *et al.*, 1985b]. Chlorpyrifos was detected in 132 (7%) of 1872 individual food samples in an FDA Total Diet Study conducted during April 1982-April 1984, resulting in a daily intake of 1.7-5.1 ng/kg/day [Howard, 1991]. In a 1987 Total Diet Study, chlorpyrifos residues were found in 117 (12%) of the 936 food samples analyzed [Food and Drug Administration Pesticide Program, 1988], and in the study conducted in 1988, 124 (11%) of 1170 samples contained chlorpyrifos (daily intake of 6.1-14.1 ng/kg/day) [Howard, 1991].

In addition to indirect exposure (ingestion of contaminated foods), consumers may be exposed to pesticides containing chlorpyrifos by direct dermal contact with treated surfaces, inhalation of aerosols, or accidental ingestion (especially in children). In 1984, the California Department of Food and Agriculture documented illnesses in apartment residents and visitors, county and hospital employees, and a 4-month-old child following treatment of apartments, homes, and offices with chlorpyrifos products [Berteau *et al.*, 1989]. In Texas during 1969, of 15 total pesticide exposures reported, 1 exposure involved chlorpyrifos (Dursban®) [Smith and Wiseman, 1971].

Since many products used by professional pest control operators and homeowners to exterminate homes, schools, and businesses contain chlorpyrifos as the active ingredient, a number of studies have been performed to evaluate the potential for consumer exposure to this compound. Table 1 reports the concentrations of chlorpyrifos detected in air samples following the treatment of living spaces with the chemical; Table 2 summarizes the concentration of chlorpyrifos residues found on surface samples in treated rooms.

Table 1. Results of Air Sampling of Living Spaces (Homes, College Dorm Rooms...) Treated With Chlorpyrifos

Type of Dwelling	Treatment (Duration)	Sampling Time (Sampling Duration)	Sampling Location	Sample Results[a]	References
Homes; 8 with crawl space, 8 other	1.0% Commercial formulation (duration NS[b])	before treatment, 1 week, 1-6 months and 1-2 years after treatment	bedroom and kitchen	average range of 0.73-2.08; individual range of 0.10-8.54	Leidy and Wright,1987; Wright *et al.*, 1988
Home; plenum type construction on clay soil	perimeter soil treated with 4 gal/10 linear ft.; gravel footings treated with 1.25 gal/ft^3 of a 1% emulsion[c]	imm. following construction, and after 1-4 weeks and 1-21 months	inside (10 feet from door) and outside house	none detected	Moye and Malagodi, 1987
Home; plenum type construction on sandy soil	perimeter soil treated with 4 gal/10 linear ft.; gravel footings treated with 1.25 gal/ft^3 of a 1% emulsion[c]	imm. following construction, and after 1-4 months and 2-14 months	inside (10 feet from door) and outside house	0.037-0.175 inside; none outside	Moye and Malagodi, 1987
Homes; 2[d]	2.5 ounces/gal. H_20 applied as spray emulsion to cracks and crevices[e]	during application (8-hour)	inside homes where appl. was concentrated	0.2	Hayes *et al.*, 1980
Homes: 12	none (potential use of products containing chlorpyrifos)	NS	indoor air	0.3-150 ng/m^3	Anderson and Hites, 1988
Apartment; 2 rooms with ventilation	0.5% aqueous broadcast spray [f] (5-7 minutes per room)	0.5-24 hours after spraying (1.5 or 2 hours)	100 cm and 25 cm from the floor surface	approx. 3-20 at 100 cm, and 11-61 at 25 cm	Fenske *et al.*, 1990
Apartment; 1 room without ventilation	0.5% aqueous broadcast spray[f] (5-7 minutes per room)	0.5-24 hours after spraying (1.5-2 hours	100 cm and 25 cm from the floor surface	approx. 5-61 at 100 cm, and 32-94 at 25 cm	Fenske *et al.*, 1990
Homes; 9 in , Jacksonville, Florida	none (pilot study conducted to evaluate pesticide use)	not applicable (24-hour)	- 1.0 to 1.6 m from floor - 1.2 to 1.5 m from ground - carried by resident	- mean of 2.4 (0.014-15) - mean of 0.063 (0.009-0.30) - mean of 2.2 (0.056-8.8)[g]	Lewis *et al.*, 1988

Table 1. Results of Air Sampling of Living Spaces (Homes, College Dorm Rooms...) Treated With Chlorpyrifos (con't)

Type of Dwelling	Treatment (Duration)	Sampling Time (Sampling Duration)	Sampling Location	Sample Results[a]	References
Second floor hotel rooms	foggers released in rooms (6.0-7.8 min.); rooms vented for 30 min.	0-13 hours postventing	personal dosimeters worn while subjects did movements on floor	117 ± 46 to 1229 ± 514 µg/article[h]	Ross *et al.*, 1990
Rooms	0.5 or 1.0% aerosol spray injected to cracks and crevices (9.1-11.7 min.)	immediately after, and 1-3 days after treatment (4-hour)	center of room	46±31 to 986± 375 ng/m^3 (0.5%) 69±44 to 1796± 638 ng/m^3 (0.1%)	Wright and Leidy, 1978
Rooms	0.5 or 1.0% applied as an emulsion with a compressed air sprayer to cracks and crevices (6.4-9.6 min.)	immediately after, and 1-3 days after treatment (4-hour)	center of room	103±57 to 249± 157 ng/m^3 (0.5%) 158±75 to 403± 167 ng/m^3 (0.1%)	Wright and Leidy, 1978
Dormitory rooms; 49	0.5% applied as an emulsion to cracks and crevices (once a week for 4 weeks)[i]	before, immediately after, and 1-3 days after application (4-hour)	center of room	0.1 - 1.1	Wright *et al.*, 1981
Food preparation/ serving areas; 6	0.5% emulsion spray into cracks and crevices	immediately after and 24 hours after treatment (4-hour)	inside rooms	4 - 1488 ng/m^3	Wright and Leidy, 1980
Room (3 x 3.6 m with 2.8 m ceiling)	36 insecticide strips with 10% chlorpyrifos	Before treatment, 0.25-30 days after treatment	center of room, 25 cm from floor	0.03 - 0.23	Jackson and Lewis, 1981
Unventilated offices; 3	0.5% broadcast sprayj application onto floors (3-5 minutes/office)	before, during and at intervals up to 10 days (4-hour) after treatment	inside rooms, 1 m from floor	maxiumum cocentration of 27 (after 4 hours)	Currie *et al.*, 1990

[a] Unless otherwise stated sample results are reported as µg/m^3.
[b] NS = Not specified
[c] Chlorpyrifos applied as the commercial preparation Dursban® TC in water; A 4 millimeter thick Saranex® S-15 film sheet was placed over the entire plenum area following treatment with pesticide.
[d] Study done in conjenction with the occupational exposure study by Hayes *et al.*, 1980 described in Section IV.B.
[e] Chlorpyrifos applied as the commercial preparation Dursban® E-2 (23.5% active ingredient).
[f] Chlorpyrifos applied as the commercial preparation Dursban® L.O. (41.5% chlorpyrifos).
[g] Results are reported for positive findings (9/9 homes for indoor, 7/9homes for outdoor, and 8/9 homes for personal samples).
[h] Assuming a clothing penetration factor of 10% and a dermal penetration of 3%, the subjects potentially received a mean absorbed dosage of 43 µg of chlorpyrifos over the 2-hour exposure time.
[i] The amount of chlorpyrifos applied per room averaged 1.7 ± 0.1 g .
[j] Chlorpyrifos applied as the commercial preparation Dursban®.

Table 2: Concentrations of Surface Residues in Living Spaces (Homes, College Dorms) Following Treatment with Chlorpyrifos

Type of Dwelling	Treatment (Duration)	Sampling Time	Sampling Location	Sample Results	References
Apartment; 2 rooms with ventilation	0.5% aqueous broadcast spray[a] (5-7 min/ room	20-380 minutes, and 24 hours after application	3 wipes/room	0.28-1.69 µg/cm^2	Fenske *et al.*, 1990
Apartment; 1 room without ventilation	0.5% aqueous broadcast spray[a] (5-7 min/ room	20-380 minutes, and 24 hours after application	3 wipes/room	0.48-3.90 µg/cm^2	Fenske *et al.*, 1990
College Dorm Rooms; 6	0.5% applied as an emulsion spray[b] to cracks and crevices (duration NS[c])	immediately after and 1-42 days after treatment	2 swipes each from stainless steel and formica pieces in the center of room	0.04-2.6 µg/cm^2 (formica) and 0.0-1.3 µg/cm^2 (stainless steel)	Wright *et al.*, 1984
College Dorm Rooms; 6	0.5% aerosol spray[b] to cracks and crevices (duration NS)	immediately after and 1-42 days after treatment	2 swipes each from stainless steel and formica pieces in the center of room	0.0-0.7 µg/cm^2 (formica) and 0.0-1.3 µg/cm^2 (stainless steel)	Wright *et al*, 1984
Dormitory rooms; with running fans in windows	0.5% or 1.0% aerosol spray applied to cracks/ crevices (duration NS)	samples taken from food exposed for thirty minutes	residues measured on TV dinners and potatoes placed in rooms prior to and 4.5 hrs. after treatment	ND[d] - <0.02 ppm	Jackson and Wright,1975

[a] Chlorpyrifos was applied as the commercial preparation Dursban® L.O. (41.5% chlorpyrifos).
[b] Chlorpyrifos was applied as the commercial preparation Dursban®.
[c] NS = not specified
[d] ND= not detected; levels of chlorpyrifos were below the level of detection (0.02 ppm) on food placed in the room 4.5 hours after application and removed 30 minutes later.

B. Occupational Exposure

Those individuals involved in the manufacture, formulation, and application of chlorpyrifos are at risk of exposure. Occupational exposure to chlorpyrifos may occur among pest control operators (pet handlers, exterminators, crop dusters) using pesticides/insecticides formulated with this compound [Ames et al., 1990; NIOSH 1991; McConnell et al., 1990]. Many studies have been conducted to quantify the exposure to chlorpyrifos by individuals involved with such work; the results of these investigations are summarized below in Table 3 and 4.

Data from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) during the years 1981 to 1983, estimated that 11,404 employees, including 842 females were potentially exposed to chlorpyrifos. Of the workers potentially exposed to this compound, 910 (254 female) were janitors and cleaners, 10,452 (574 female) had pest control occupations, and 41 (14 female) were groundskeepers and gardeners (except farmers). The data were obtained from a total of 1,276 facilities comprising the food and kindred products (95), business services (1167), and health services (14) industries [NIOSH, 1991].

In California, physicians are required to report all illnesses and injuries believed to be related to pesticide exposure. In 1986, of the 2099 illness reports, 1065 (51%) were confirmed to be from occupational pesticide exposures. Chlorpyrifos was confirmed as the causal agent in 46 injury/illness reports and was one of the several combined compounds in an additional 37 illness/injury reports [Edmiston and Maddy, 1987]. In 1987, 1507 (86%) of the reported illnesses or injuries resulting from pesticide exposure were occupationally related. Chlorpyrifos was confirmed as the causal agent in 30 of these cases. An additional 46 reported cases listed chlorpyrifos as one of several pesticides involved [Maddy *et al.*, 1990]. In a survey conducted by the California Department of Health Services in 1987, it was determined that 496 of the 696 pet handlers interviewed experienced health symptoms following exposure to flea control products on the job; 68 of these potential exposures were associated with products containing chlorpyrifos [Ames *et al.*, 1989].

To assess the potential for illness or injury due to exposure to chlorpyrifos, the Dow Chemical Company conducted an 8 1/2 year morbidity survey (January 1, 1977-August 31, 1985) of employees potentially exposed to chlorpyrifos at the Michigan Division of Dow Chemical Company (chlorpyrifos has been solely manufactured and formulated at Dow Chemical's Midland plant since 1969). The results were compared with results from controls individually matched with the study group (year of birth, sex, race, and pay) who had no history of exposure or potential exposure. The incidence of illness or symptoms of illness were not significantly increased in the employees exposed to chlorpyrifos in relation to the control group [Brenner *et al.*, 1989].

A 1985 survey indicated that chlorpyrifos (Dursban TC®) was used for termite control by 61.4% of the pest control operators (PCO) questioned, and 28.6% reported that it was their principle termiticide. In 1986, these values increased to 63.6% for overall use and 33.8% for principle use [Mix, 1987]. In 1987, chlorpyrifos use was increased to 86.5% by termite PCOs and it had become the principle product for 75.0% of the PCOs surveyed. The reasons for this progressive increase included the fact that Dursban® was safer, had fewer legal restrictions, was more effective, and less expensive [Mix, 1988].

A Japanese study of termite control workers revealed that the workers working in basements are potentially exposed to levels of chlorpyrifos in the air about 10 times higher than the ACGIH threshold-limit value (0.2 mg/m^3). The study also found that the compound adhered to the work outfits with 5-12 µg/cm^2 detected on the arms, legs, and face. Since as much as 40% of the compound was able to penetrate through the clothing, the authors concluded that there is potential for dermal exposure to chlorpyrifos in termite control workers [Asakawa *et al.*, 1989]. In another Japanese study, it was determined that workers who sprayed chlorpyrifos in basements had higher concentrations of the compound in their breathing zone and on their skin than those individuals working around the house. The personal ambient chlorpyrifos levels of the under-floor sprayers were 0.012-0.145 mg/m^3 (8-hour time weighted average) [Sunaga *et al.*, 1989a].

In 1983, a study was conducted to evaluate the degree of dermal and respiratory exposure to chlorpyrifos following chemigation of sweet corn at selected stages of plant growth. Chlorpyrifos was applied to the fields at weekly intervals at a rate of 0.5 pounds (in 1.3 pints of peanut oil) per acre. Three workers entered the fields 4 and 48 hours after each chemigation treatment to sample foliage for pesticide residue (4 hours) and determine pest control efficacy (48 hours). Each exposure period was about 30 minutes. The potential exposure was evaluated by measuring the residues recovered from exposure pads and respirators worn by the entry teams. The level of chlorpyrifos on dermal pads varied with the age of corn. When the corn was only 1 meter high, the estimated dermal exposure (mean of 3 workers) ranged from 2.8±2.1 (measured on mid-chest) to 8.7±1.8 µg/100 cm^2/hour (measured on head). Approximately 6 weeks later, estimated dermal exposure following corn treatment ranged from 6.7±2.8 (meassured on mid-chest) to 129 µg/100 cm^2/hour (measured on hands; mean of only two workers). Chlorpyrifos recovered from respirator filters of workers exposed to treated corn less than 1 meter tall was <0.4 µg/100 cm^2. At later intervals, when corn was at least as tall as the workers, up to 1.8±0.6 µg/100 cm^2 was detected [Brady *et al.*, 1991].

The potential dermal exposure of pesticide applicators to chlorpyrifos was assessed by determining "estimated total body accumulations rates" (ETBARs) in the following employees of a commercial greenhouse (ventilated) facility: 5 handgunners who used either a fine spray, a coarse spray, or a pulse fogging device; a tractor driver who pulled either a boom sprayer or a span sprayer; a drencher; and an assistant to a fine spray handgunner. The workers applied Dursban® (commercial form of chlorpyrifos) as a 50% wettable powder for periods of about 30 minutes. To evaluate ETBARs, exposure pads were placed on the mid-back, chest, shoulders, forearms, thighs and shins of each subject, and on the outside of clothing (protective or everyday). After application, the pads were analyzed for chlorpyrifos residues. These results were used with data on pad area, exposure time, and estimated fractional and total body surface areas to determine the ETBARs. In addition to ETBARs, handwashes and air samples were collected. Table 3 below presents the mean ETBARs and the mean handwash and air sample deposits normalized (divided by) for spray rate (results in mg deposited/kg sprayed). The ETBAR values do not include the accumulation rates determined from handwash samples, except in instances where hand protection was not worn. In these cases, the hands were considered as additional external exposure pads [USEPA, 1988].

Table 3: Mean Estimated Chlorpyrifos Exposure to Greenhouse Applicators, Normalized for Spray Rate (mg Deposited/kg Sprayed ± Standard Error)

Occupation	Number of exposures	ETBAR	Handwash Deposits	Respirator Deposits
Handgunners (fine spray)	22-23	229±42	1.7±0.3	0.082±0.046[b]
Handgunner (coarse spray)	7-8	70±24[a]	7±4[a]	0.0046±0.0011[c]
Handgunners (pulse fog)	3	6±2	13±10	0.064±0.031[b]
Tractor driver (boom spray)	10-11	4.7±1.1[a]	0.61±0.10[a]	0.0051±0.0011[d]
Tractor driver (span spray)	3	0.98±0.23[a]	0.71±0.28[a]	0.0020±0.0002[d]
Drencher	1	44	0.55	0[b]
Assistant	1	4	0.04	0.0143[b]

[a] Subject did not wear gloves; ETBAR sample includes handwash samples.

[b] Applications were made in an enclosed structure.

[c] Applications were made in an open-sided structure.

[d] Applications were made in an open Siran® structure.

Table 4. Occupational Exposure to Chlorpyrifos

Profession (number)	Formulation (duration)	Location of Application	Type of Exposure Evaluated	Exposure Levels	References
Termite exterminator (1)	1.0% emulsion spray (avg. of 128 ± 34 and 171 ± 71 min.)	under homes on clay soil; 4 with crawl space and 4 on concrete slab	Respiratory (personal air monitors)	mn. of 24.9±48.7 μg/m^3 (homes with crawl space) mn. of 0.05±0.04 μg/m^3 (homes on concrete)	Leidy *et al.*, 1991
Termite exterminator (1)	1.0% emulsion spray (avg. of 128 ± 34 and 171 ± 71 min.	under homes on clay soil; 4 with crawl space and 4 on concrete slab	Respiratory (personal air monitors)	mn. of 2.9±4.4 μg/m^3 (homes with crawl space) mn. of 0.1±0.1 μg/m^3 (homes on concrete)	Leidy *et al.*, 1991
Termite exterminator (8)	mn. of 3.92 kg[a] (applied over mn. of a 6.39-hr. work day or 2.56 hrs. of application time)	sub-soil around exterior and interior perimeter of structures (1-2 sites)	Respiratory (personal air monitors)	mn. of 11.82 μg/m^3 (over work day); or mn. of 29.16 μg/m^3 (over application time)[b, c]	Fenske and Elkner, 1990
Termite exterminator	same as above	same as above	Dermal (deposition on internal and external skin patches; hand washes)	mn. total exposure of 5.94 ± 3.22 mg/hr.[c, d]	Fenske and Elkner, 1990

a Chlorpyrifos was applied as the commercial preparation Dursban® TC (1.8 kg chlorpyrifos/3.8L).

b Air concentrations reported in the table were converted to respiratory exposure estimates based on a total volume of 1.74 L/hour; the mean exposure estimate was 0.06 mg/hr for the application period.

c 100% of the mean respiratory exposure level was added to 3% of the dermal exposure level, and was adjusted for mean body weight (70 kg) to obtain an estimated daily dose of chlorpyrifos of 9.5 μg/kg/day.

d The values reported in the table were obtained from the mean rates of deposition on skin patches, which were extrapolated to the total surface area of individual body regions and added to mean levels of chlorpyrifos recovered in hand washes.

e Chlorpyrifos applied as the commercial preparation Dursban® E-2 (23.5% chlorpyrifos).

f ND = Not Detected (below detection limit).

4. Plants

^{14}C-Chlorpyrifos residues found in wheat, soybeans, and beets planted 119 days after treatment of loamy sand soil with labeled chlorpyrifos at 2 lb active ingredient/acre were 0.31, 0.31, and 0.03 ppm chlorpyrifos equivalents, respectively. However, chlorpyrifos was largely degraded in the soil before the crops were planted, and the plant residues consisted primarily of unidentified ^{14}C residues [Bauriedel *et al.*, as reported in USEPA, 1990].

The degradation rates of chlorpyrifos residues on the leaves and fruits of sweet pepper plants were measured. The plants were sprayed twice during the growing season at different time intervals following each application. Large samples of leaves and fruits were collected and analyzed to determine the residue levels. It was determined that the dissipation of chlorpyrifos in fruits to reach the maximum residue level (MRL) of 0.1 mg/kg took about 8 days. It was also found that residue levels of 0.2 mg/kg in harvested fruits did not drop below the MRL after an 11 day holding period [Al-Samariee *et al.*, 1988].

D. Regulatory Status

- The current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for chlorpyrifos is 0.2 mg/m^3 (skin) averaged over an 8-hour work shift {21 CFR Part 1910} [Office of the Federal Register, 1989].

- The United States Environmental Protection Agency (USEPA) has approved the use of the additive chlorpyrifos (insecticide) in accordance with the following prescribed conditions {40 CFR Part 185.1000} [Office of the Federal Register, 1991a]:

  — Application shall be limited to spot and/or crack and crevice treatment in food handling establishments where food and food products are held, processed, prepared, or served. Contamination of food or food contact surfaces shall be avoided, and food must be covered or removed during treatment.
  — Spray concentration for spot treatment shall be limited to a maximum of 0.5% of the active ingredient by weight; a coarse, low-pressure spray shall be used to avoid atomization or splashing of the spray.
  — Paint-on application for spot treatment and crack and crevice treatment shall be limited to a maximum of 2% of the active ingredient by weight; equipment capable of delivering a pin-stream shall be used for crack and crevice treatment.
  — Application by adhesive strips shall contain a maximum of 10% of the controlled-release product by weight in food handling establishments where food and food products are held, processed, prepared, or served. A maximum of 36 strips is to be used per 100 square feet of floor space; the strips cannot be placed in exposed areas where direct contact with food, utensils, and food-contact surfaces may occur.
  — The insecticide label and labeling shall conform to that registered by the United States Environmental Protection Agency; the insecticide shall be used in accordance with such label and labeling.

- The USEPA has established tolerance levels for residues of chlorpyrifos and its metabolite, 3, 5, 6-trichloro-2-pyridinol in animal feeds {40 CFR Part 186.1000} and in foods for human consumption {40 CFR Part 185.1000} resulting from the application of this insecticide to growing crops. Tolerances have been established in the following foods: citrus, corn, mint, and peanut oil {40 CFR Part 185.1000}; dried apple pumice; beets, sugar, and molasses; dried beets, sugar, and pulp; dried citrus pulp; corn soapstock; dried grape and pumice; sorghum milling fractions; and sunflower seed hulls{40 CFR 186.1000} [Office of the Federal Register, 1991a]. A chlorpyrifos petition filed in January 1992 would set a food additive tolerance of 0.1 ppm for residues of a microencapsulated form of the insecticide in all food additives in food service establishments where food and food products are prepared and served [Pesticide and Toxic Chemical News, 1992].

- Chlorpyrifos is regulated by the USEPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA); restrictions of this compound vary depending upon the label (Dursban® or Lorsban®) and the label language [USEPA, 1991a].

- Chlorpyrifos is also regulated by the United States Environmental Protection Agency (USEPA) under the following regulations [Roytech, 1991]:

  — Clean Water Act; Sections 304 (Water Quality Criteria) and 311 (Hazardous Chemicals)
  — Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) Hazardous Substances

E. Exposure Recommendations

- The ACGIH-recommended threshold limit value-time weighted average (TLV-TWA) for chlorpyrifos is 0.2 mg/m^3 (skin) [ACGIH, 1990].

- NIOSH has not recommended an exposure limit for chlorpyrifos.

- The USEPA has established an acceptable daily intake (ADI) for chlorpyrifos of 0.003 mg/kg/day, with a maximum permissible intake (MPI) of 0.18 mg/kg/day [USEPA, 1984a]. The United Nations' Food and Agriculture Organization (FAO) and World Health Organization (WHO) established the acceptable daily intake (ADI) for chlorpyrifos as 10 µg/kg/day [Food and Drug Administration Pesticide Program, 1988; Gartrell *et al.*, 1985a; Gartrell *et al.*, 1985b].

- The National Academy of Sciences (NAS) guideline level for chlorpyrifos in the air of dwellings is 10 µg/m3. This value is considered to be a "safe" level for individuals inhabiting the dwelling approximately 16 hours per day. Although these guideline levels expired in 1985, they are still used because no new recommendations have been made and sufficient data have not been generated to reassess the original proposed levels [Wright *et al.*, 1988].

V. TOXICOLOGICAL EFFECTS

A. Chemical Disposition

1. Human Data

- ***oral/dermal,humans***

The pharmacokinetics of chlorpyrifos was studied using six healthy Caucasian male volunteers (27 to 50 years old). Five men initially received 0.5 mg/kg chlorpyrifos orally, then, four weeks later, received 5.0 mg/kg chlorpyrifos dissolved in dipropylene glycol methyl ether (DPGME) by dermal administration. For the pilot test, one man (volunteer A) was given the same oral dose of chlorpyrifos about one month before the other subjects. In addition, this volunteer was given a dermal dose of 0.5 mg/kg chlorpyrifos when the other volunteers received their oral dose. Two weeks after the first dermal dose, volunteer A was given a second dermal dose of 0.5 mg/kg chlorpyrifos in DPGME.[3] The dermal application sites were not covered or occluded in any way. Blood samples were collected from each volunteer prior to dosing and at preselected intervals following dosing. All urine voided between 24 and 48 hours prior to dosing through 120 hours after dosing was collected. Separate collections were made for the intervals starting 0, 6, 12, 24, 35, 48, 60, 72, and 96 hours post-dosing. Two additional 12-hour urine samples were collected at 156 and 180 hours after the dermal dosing.

Extremely low concentrations of chlorpyrifos were detected in the blood (<30 ng/ml) and none was detected in the urine samples. 3, 5, 6-Trichloro-2-pyridinol (TCP), the primary metabolite of chlorpyrifos, was detected in the blood after a 1 to 2 hour delay in absorption of the oral dose. TCP concentrations increased rapidly ($t_{1/2}$=0.5 hr) and reached a maximum of 0.93 µg/ml (0.51-1.35 µg/ml) 6 hours after chlorpyrifos was ingested. Following the 5.0 mg/kg dermal dose, the average half-life for the appearance of TCP in the blood was 22.5 hours, and the highest mean concentration (0.063 µg/ml, range 0.029-0.122 µg/ml) did not occur until 24 hours after dosing. The apparent volume of distribution was 181±18 ml/kg, and the mean half-life for the elimination of TCP from the blood was 26.9 hours, following both the oral and dermal doses. Based on the model parameters determined in this study (see Table 5), 72±11% of the ingested and 1.35±1.0% of the dermal doses were absorbed. This finding is in agreement with the percentage of the oral (70±11%) and dermal (1.28±0.8%) doses actually recovered in the urine as TCP; thus, only a small fraction of the dermally applied dose was absorbed. These results suggest that since both chlorpyrifos and TCP are rapidly excreted in the urine, neither compound has significant potential to accumulate in humans following repeated exposures [Nolan *et al.*, 1984].

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[3]More chlorpyrifos was absorbed when DPGME was used as a solvent compared to methylene chloride; however less than 5% of either of the 0.5 mg/kg chlorpyrifos dermal doses was absorbed. Therefore, the other volunteers were given a dermal dose of 5.0 mg/kg chlorpyrifos dissolved in DPGME 4 weeks after the oral dose was administered.

Table 5. Model Parameters Describing Concentrations and Urinary Excretion of 3,5,6-TCP by Individual Volunteers Following Oral and Dermal Administration of Chlorpyrifos.

Volunteer	Weight (kg)	Absorption lag time (hr)	Absorption rate constant (h-1)	Absorption half-life (hr)	Volume distribution (ml/kg)	Elimination rate constant (hr-1)	Elimination half-life (hr)	Area under plasma time curve (ug/hr/ml)	Renal Clearance (ml/hr/kg)[a]	Model predicted % dose absorbed	% Dose recovered in urine
Oral administration (0.5 mg/kg)											
A	77.1	1.9	1.7	0.4	190	0.0318	21.8	24.4	6.0	52	49
B	80.7	1.6	0.1	6.9	192	0.0219	31.7	56.6	4.2	84	81
C	83.7	1.0	3.0	0.2	204	0.0232	29.9	45.3	4.7	75	67
D	71.7	1.0	0.3	2.1	180	0.0205	33.9	58.0	3.7	75	73
E	101.8	1.1	2.7	0.3	160	0.0326	21.3	37.1	5.2	69	70
F	85.0	0.9	1.3	0.5	160	0.0249	27.8	54.7	4.0	77	79
mean	83.3	1.3	1.5	0.5	181	0.0258	26.9	46.0	4.6	72	70
± SD	10.3	0.4	1.2		18	0.0051		13.3	0.9	11	11
Dermal administration (5.0 mg/kg)[b]											
A	77.1[c]	---	0.0223	31.1	---[d]	---[d]	---[e]	1.42	---	3.18	2.6
B	80.7	---	0.0270	25.7	---	---	---	7.06	---	1.05	1.00
C	83.7	---	0.0496	14.0	---	---	---	11.17	---	1.87	1.98
D	71.7	---	0.0335	20.7	---	---	---	6.16	---	0.80	0.70
E	95.0	---	0.0241	28.8	---	---	---	3.26	---	0.60	0.50
F	85.0	---	0.0287	24.2	---	---	---	3.18	---	0.45	0.90
mean	83.2		0.0308	22.5	---	---	---	6.17	---	1.35	1.28
+ SD	8.3		0.010					3.29		1.02	0.83

[a] Calculated as volume distribution times elimination rate constant
[b] Chlorpyrifos administered dermally with dipropylene glycol methyl ether
[c] Volunteer A was given 0.5 mg/kg dose
[d] Dermal data fit with volume of distribution and elimination rate constant obtained from oral data
[e] Not used to calculate mean ± SD

reference: Nolan *et al.*, 1984

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C	83.7	1.0	3.0	0.2	204	0.0232	29.9	45.3	4.7	75	67
D	71.7	1.0	0.3	2.1	180	0.0205	33.9	58.0	3.7	75	73
E	101.8	1.1	2.7	0.3	160	0.0326	21.3	37.1	5.2	69	70
F	85.0	0.9	1.3	0.5	160	0.0249	27.8	54.7	4.0	77	79
mean	83.3	1.3	1.5	0.5	181	0.0258	26.9	46.0	4.6	72	70
± SD	10.3	0.4	1.2		18	0.0051		13.3	0.9	11	11
Dermal administration (5.0 mg/kg)[b]											
A	77.1[c]	---	0.0223	31.1	---[d]	---[d]	---[e]	1.42	---	3.18	2.6
B	80.7	---	0.0270	25.7	---	---	---	7.06	---	1.05	1.00
C	83.7	---	0.0496	14.0	---	---	---	11.17	---	1.87	1.98
D	71.7	---	0.0335	20.7	---	---	---	6.16	---	0.80	0.70
E	95.0	---	0.0241	28.8	---	---	---	3.26	---	0.60	0.50
F	85.0	---	0.0287	24.2	---	---	---	3.18	---	0.45	0.90
mean	83.2		0.0308	22.5	---	---	---	6.17	---	1.35	1.28
± SD	8.3		0.010					3.29		1.02	0.83

[a] Calculated as volume distribution times elimination rate constant
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[d] Dermal data fit with volume of distribution and elimination rate constant obtained from oral data
[e] Not used to calculate mean ± SD

reference: Nolan *et al.*, 1984

- *oral, humans*

  Diethyl phosphate (DEP), diethyl thiophosphate (DETP), and 3,5,6-trichloro-2-pyridinol (TCP) were identified in the urine of a 3-year-old girl who accidentally ingested an unknown amount of Dursban®. Urinary concentrations of DEP dropped from approximately 20 µg/ml to less than 5 µg/mL within 24 hours. Urinary levels of DEPT followed a similar pattern, peaking within 24 hours (60 µg/ml) and rapidly dropped off. The urinary TCP concentration was also at its highest level within 24 hours (~34 µg/ml). Three days after chlorpyrifos ingestion, the three metabolites were no longer detected in the urine. No other data were reported [Davies *et al.*, 1979].

- *oral, humans*

  Pesticide residue analyses were performed on autopsy samples taken from a 61-year-old male with a history of heart disease, carcinoma of the tongue, and cirrhosis of the liver suspected of having accidentally ingested approximately 4 ounces of a pesticide formulation. The results of analyses, including gas chromatography, mass spectrometry, and nuclear magnetic resonance (NMR), indicated that a mixture of chlorpyrifos and malathion had been ingested. The *O,O*-diethyl phosphorothioate ester of a dichloro, methylthio, 2-pyridinol, a previously unreported chlorpyrifos metabolite, was identified in the liver extract. Although the exact ring position of the thiomethyl group could not be determined, it was concluded that, based on NMR analysis, there were only 2 possibilities: ring positions 3 and 5. In addition, all 4 of the expected alkyl metabolites (dimethyl phosphate, diethyl phosphate, dimethyl phosphorothioate, and diethyl phosphorothioate) were detected in the urine, as well as the phenol metabolite of chlorpyrifos, 2,3,5-trichloropyridinol. A high level of unmetabolized chlorpyrifos (0.47 ppm) was found in the brain. Chlorpyrifos was also detected in the blood (.210 ppm) and liver (0.08 ppm).

  The authors note that the identification of the thio-methyl derivative of chlorpyrifos in this poisoning case does not necessarily indicate the existence of a major metabolic pathway in humans. Since this case involved a person with cirrhosis of the liver and carcinoma of the tongue, an unusual pathway may have been induced by a particular drug, or by the illnesses themselves. Also, the presence of the malathion, or the large dose received, could have induced a secondary metabolic pathway [Lores *et al.*, 1978a,b].

- *oral, humans*

  As part of a study carried out to assess occupational exposure to organophosphates among pest control operators, urine samples were collected and analyzed for alkyl phosphates. The 25 pest control company employees evaluated had been working in the pest control industry for an average (mean, SD 1.7) of 2 years. The bulk of pesticide application involved the combined use of 3 organophosphorus insecticides, including Dursban E-2® (23.3% active ingredient).

Analysis of the urine samples of the pest control operators showed the presence of alkyl phosphates in 96% percent of the 8-hour specimens. There were no observable patterns of excretion within the 24-hour sampling period or among the pest control operators in general. Employees of the company who were not actually involved in the application of the organophosphates showed very low levels of urinary metabolites (< 15 μg/8 hours). Urine samples collected from 2 persons not previously exposed to organophosphates showed levels below the detection limit. Two of the metabolites identified, *0,0*-diethyl, *O*-amyl phosphate (DEP) and *O,O*-diethyl, *O*-amyl phosphorothionate (DETP), were attributed to Dursban® exposure. DEP and DEPT were detected in 96% and 28%, of the urine samples collected, respectively [Hayes *et al.*, 1980].

2. Animal Data

The studies described below concern the chemical disposition of chlorpyrifos in rats and mice. A summary of the chemical disposition of chlorpyrifos in cows, swine, sheep, and goats is presented in Table 6.

- *oral, rats*

Male white rats of the Wistar strain were used to examine the elimination and distribution of chlorpyrifos following a single exposure. The animals were administered, by stomach tube, a single-1 ml dose (containing ~ 10 mg chlorpyrifos) of ^{36}Cl-chlorpyrifos (lableled in the 3 and 5 position) in a corn oil solution. Urine and fecal samples were collected at 18, 26, 42, 50, 66, 74, 90, and 122 hours after dosing. Groups of 2 animals were sacrificed at 4, 72, 168, 240, and 480 hours after administration. Blood was collected and separated into plasma and cells. The liver, muscle, heart, lungs, spleen, kidney, testes, fat, bone, and skin were removed, weighed, and evaluated for the presence of radioactivity.

The majority of the radioactivity appeared in the urine within the first day (80.8% after 26 hours). After 74 hours, 89.4% had been excreted in the urine, and 11.4% was excreted in the feces after 66 hours. This indicated that chlorpyrifos is readily absorbed from the gastrointestinal tract and circulated through the body. The organs involved with the elimination of this compound and its metabolites such as the liver and kidney had high concentrations of radioactivity immediately after dosing (0.0690±0.0005 and 0.0924±0.0096 mmol/kg after 4 hours, respectively); however, these levels decreased dramatically over time. Chlorpyrifos was found to accumulate in fatty tissues. Four hours after dosing, levels of chlorpyrifos were measured at 0.0317±0.0042 and 0.0243±0.0007 mmol/kg in fat and skin, respectively. The other tissues analyzed varied in the amount of radioactivity found. There was a correlation between the amount of radiation and the blood content of the sample. For example, levels of radioactivity in the muscle (low blood content) were 0.0093 ± 0.0018 mmol/kg, while the lung (high blood content) had much higher levels of radioactivity (0.0406 ± 0.008 mmol/kg). Once the supply of radioactive chlorpyrifos in the gastrointestinal tract had been exhausted, there was a rapid drop in the level of activity in the other tissues.

The biological half-life ($T_{1/2}$) of the radioactivity in the tissues was estimated. The $T_{1/2}$ values for the radioactive compounds in the liver, kidney, muscle, and fat were approximately 10, 12, 16, and 62 hours, respectively. Since most of the tissues lost their radioactivity within a short time after chlorpyrifos administration, it was concluded that there was no significant accumulation of chlorpyrifos, or its metabolites, in the tissues with exception of the fat. Subsequent analysis with solvent distribution studies confirmed that the radioactive material detected in the fat was chlorpyrifos, and not one of its metabolites [Smith *et al.*, 1967].

- *oral, rats*

As a continuation of the study described above, Smith *et al.* identified chlorpyrifos metabolites that were detected in the urine and feces. Two male Wistar rats were administered, by stomach tube, 20 mg of ^{36}Cl-chlorpyrifos in corn oil (volume not specified). Urine and fecal samples were collected daily, and aliquots of each sample were chromatographed and analyzed for radioactivity.

Three compounds were identified in the urine and feces: 3,5,6-trichloro-2-pyridyl phosphate; 3,5,6-trichloro-2-pyridinol; and *O,O*-diethyl *O*-3,5,6,-trichloro-2-pyridyl phosphorothioate. The latter compound was detected in the urine and feces only in trace amounts. From 74.1±4.2 to 81.5±4.2% of the radioactivity in the 24-hour urine was associated with ^{36}Cl-3,5,6-trichloro-2-pyridyl phosphate while the remaining radioactivity (18.0±4.5 - 25.3±4.4) was largely ^{36}Cl-3,5,6-trichloro-2-pyridinol. A large percentage (83.4±3.6-86.5±2.4) of the radioactivity identified in 24-hour fecal samples was ^{36}Cl-3,5,6-trichloro-2-pyridyl phosphate; a smaller percentage (13.5±2.4 -16.6±3.2) was associated with ^{36}Cl-3,5,6-trichloro-2-pyridinol [Smith *et al.*, 1967].

- *oral, mice*

An unspecified number of female, ICR stain mice were used to investigate gastrointestinal absorption, distribution, and metabolism of chlorpyrifos, and other pesticides. The test animals were fasted for 12 hours before being administered a 1 mg/kg dose of ^{14}C-chlorpyrifos (2,6 ring-labelled) in 0.1 ml carrier (Emulphor:ethanol:water, 1:1:8), via stomach needle. The animals were kept in metabolism cages with a carbon dioxide (CO_2) trapping device until sacrifice (1, 5, 15, 30, or 60 minutes after dosing). The percentage of absorbed radioactivity in the gastrointestinal tract was determined at each time point. In addition, blood, liver and intestine were evaluated for radioactivity. The remaining carcass was homogenized to measure the amount of radioactivity present.

Chlorpyrifos was determined to have slow gastrointestinal absorption relative to the other pesticides studied. Its $T_{1/2}$ value, which was used as an indicator of relative gastrointestinal absorption, was determined to be 78.1±16.2 minutes. The percentages of the administered radioactivity absorbed in the gastrointestinal tract at 1, 5, 30, and 60 minutes after dosing were 0%, 15.2%, 19.5%, 43.1%, and 47.2%, respectively. The appearance of radioactivity in the blood of animals administered chlorpyrifos was observed within 5 minutes; these levels had still not reached a plateau within 60 minutes, at which time approximately 9-10% of the administered radioactivity was detected in the blood. The percentage (~5%) of

radioactivity recovered in the liver reached a plateau approximately 40 minutes after chlorpyrifos administration. Appreciable amounts of radioactivity (8-10% of the administered dose) were found in the intestinal fraction at the early time intervals, which decreased slightly during the 60-minute observation period. Approximately 10-20% of the administered dose was found in the carcass throughout the observed time intervals. The percentage of radioactivity detected in the urine was 1%, 1%, and 13.4% after 15, 30, and 60 minutes, respectively. Only trace amounts (<0.01% of administered dose) of radioactivity were detected in expired CO_2 at 15, 30, and 60 minutes [Ahdaya *et al.*, 1981].

- *oral, mice*

Stomach absorption of chlorpyrifos and 7 other insecticides was studied in female ICR mice. The test animals' stomachs were ligated at the pylorus prior to intubation with 1 mg/kg ^{14}C-chlorpyrifos (2, 6 ring-labelled) in 0.1 ml carrier (Emulphor:ethanol:water, 1:1:8). The animals were sacrificed at 15, 30, and 60 minutes after dosing. Bladder contents, blood samples, liver, stomach, and the remaining intestinal tract were collected to measure the levels of radioactivity present.

The absorption of chlorpyrifos through the ligated stomach at each interval was 8.3% at 15 minutes, 9.5% at 30 minutes, and 11.1% at 60 minutes. Small amounts of radioactivity were detected in all of the tissues examined. The stomach had the greatest percentage (~6%) of recovered radioactivity. The percentage of radioactivity recovered from the liver and blood was less than 1% of the total administered dose. To illustrate the contribution of gastric absorption to the overall process of gastrointestinal absorption, the authors compared the percent gastrointestinal absorption observed after 60 minutes (see Ahdaya *et al.*, 1981, above) to the percentage of radioactivity detected in the ligated stomach at this time point. Based on this comparison, a stomach to gastrointestinal penetration ratio of 0.24 was reported [Ahdaya and Guthrie, 1982a].

- *intraperitoneal, rats*

The metabolism and elimination of chlorpyrifos following intraperitoneal administration to an unspecified number of male Wistar rats was described in an abstract by Japanese authors (Sunaga *et al.*). Five rats received a single injection of chlorpyrifos at a dose of 0.2 mmol/kg body weight in an unspecified solvent. Blood and urine samples were collected at various intervals for 50 and 90 hours, respectively, following exposure. Urine was hydrolyzed with hydrochloric acid or *Beta*-glucuronidase with sulfatase, and analyzed to determine the concentration of chlorpyrifos and its metabolites (3, 5, 6-trichloro-2-pyridinol (TCP), diethylthiophosphate (DETP), and diethylphosphate (DEP)).

The maximum concentrations of chlorpyrifos (~0.7 ml) and TCP (~ 39 µmol/L) were detected in the blood 5 hours after injection. These levels rapidly decreased, and by 48 hours post-injection were ~ 0.01 and ~12 µmol/L for chlorpyrifos and TCP, respectively. The estimated half-lives for chlorpyrifos and TCP were 8.15 and 24.66 hours, respectively. Urinary excretion levels of the acid hydrolysis-released TCP and the enzyme hydrolysis-released TCP accounted for 86% and 54% of the administered chlorpyrifos, respectively. Forty-five percent of the administered chlorpyrifos was excreted in the urine as DETP, and 15% was excreted as DEP [Sunaga *et al.*, 1989b].

- ***intraperitoneal, mice***

The distribution of chlorpyrifos in mice was studied in conjunction with a study carried out to assess the incorporation of chlorpyrifos into nucleic acids (Section VG.3). Male mice of an unspecified strain received intraperitoneal injections of radiolabeled ^{14}C-chlorpyrifos (ethyl labelled) at concentrations of either 5 or 15 mg/kg. The test animals were sacrificed 6, 24, 48, and 192 hours after dosing and liver, fat, kidney, and urine samples were collected and evaluated for radioactivity.

The highest concentrations of radioactivity were found in the liver (12.2 and 20.8 µg/g) and fat (22.3 and 29.4 µg/g) after 6 hours; this amount decreased with time. The amount of radioactivity in the kidney, however, increased over time (12.9 and 30.6 µg/kg after 192 hours). The authors noted that the amount of ^{14}C-chlorpyrifos in the urine indicates that this compound is rapidly eliminated. The highest concentration (50.9 µg/ml and 120.7 µg/ml) of radioactivity occurred in the urine at 48 hours after dosing. These findings support the author's conclusion that chlorpyrifos does not accumulate in the tissues [Mostafa *et al.*, 1983].

- ***catheter insertion, mice***

The role of hepatic biotransformation in the production of chlorpyrifos oxon (*O,O*-diethyl *O*-3,5,6-trichloro-2-pyridyl) phosphate) from chlorpyrifos was studied in male Crl:CD-1 (CR) BR Swiss mice. Groups of 4 mice were subjected to *in situ* single-pass liver perfusions performed by inserting a cannula into the animal's bile duct. 2, 6-^{14}C-Chlorpyrifos (4.2 µM) or unlabelled chlorpyrifos (5, 10, or 15 µM)[4] were perfused through the liver at a flow rate of 3 ml/liver per minute. All exiting perfusate (including bile) was pooled from a single liver in order to increase the likelihood of detecting chlorpyrifos oxon. When the 2, 6-^{14}C-chlorpyrifos was included in the perfusate, fresh perfusate was used to "wash-out" each liver until no radiolabel could be detected in the outflow. At the end of each perfusion, liver cholinesterase activities were determined. The concentrations of chlorpyrifos and its metabolites were quantified by high performance liquid chromatography.

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[4]The lowest concentration of unlabelled chlorpyrifos (5µM), was chosen in an attempt to approximate apparent first-order kinetics because the *in vitro* Km_{app} for hepatic activation of chlorpyrifos to chlorpyrifos oxon in the mouse had previously been reported to be 20.9 ± 3.3 µM.

Perfusion with 5μM unlabelled chlorpyrifos resulted in a steady-state being achieved in 55 minutes. Under these conditions, 3, 5, 6-trichloro-2-pyridinol (TCP) was the only detectable metabolite in the effluent. Hepatic cholinesterase activities were reduced by 65-85% compared to control levels, indicating that activation to the oxon had occurred. Increasing the concentration of chlorpyrifos in the perfusate to 10 or 15 μM did not result in the presence of chlorpyrifos oxon in the effluent.

Concerning the perfusion experiments with radiolabeled chlorpyrifos, approximately 90% of the administered radioactivity added to the perfusate was accounted for as unchanged chlorpyrifos or TCP. About 5% of the radiolabel remained in the liver, and another 5% was accounted for as an unidentified metabolite(s). As was observed in the perfusion experiments with unlabelled chlorpyrifos, hepatic cholinesterase levels were decreased by 65-85% compared to control levels.

Under the conditions of this study, the capacity of mouse livers to destroy chlorpyrifos oxon exceeded their capacity to produce this metabolite from chlorpyrifos. The authors noted that the rates of nonenzymatic and enzymatic detoxification of chlorpyrifos oxon exceeded oxidative activation of chlorpyrifos, thus preventing chlorpyrifos oxon from exiting the liver. They concluded that the data indicate that the net result of hepatic biotransformation for chlorpyrifos is detoxification, but caution that careful consideration must be given to the relevancy of the substrate concentrations used in the perfusions before *in vivo* extrapolations can be attempted. They suggest that the acute toxicity of chlorpyrifos in mice is mediated exclusively by extrahepatic production of chlorpyrifos-oxon [Sultatos *et al.*, 1985].

- *intraperitoneal, mice*

Factors affecting hepatic biotransformation were studied following a single pass perfusion in male Hla: (SW) BR Swiss Webster mice which were pre-treated for 4 days with injections of either saline or sodium phenobarbital before being administered 160 mg/kg chlorpyrifos in 10% dimethyl sulfoxide in corn oil. An unspecified number of deaths occurred within 48 hours; surviving mice were observed for 7 days. Livers were perfused using a non-recirculating system and chlorpyrifos was added to the perfusate reservoir in volumes not greater than 100 μl in the presence of 1-4% borine serum albumin (BSA). Binding of chlorpyrifos to perfusate was evaluated by incubation in dialysis cells followed by extraction with ethyl acetate and quantification by high performance liquid chromatography. In addition, chlorpyrifos (and its metabolites) were extracted from the perfusate, and analyzed by high performance liquid chromatography (HPLC).

Biotransformation of chlorpyrifos occurred during perfusion of the mouse livers as evidenced by the difference between reservoir and effluent concentrations. Steady-state with respect to chlorpyrifos was achieved in 36-48 minutes at which time the extraction ratio was 0.46. In addition to chlorpyrifos, which was detected at concentrations ranging from 50-59% of the perfused dose, 3, 5, 6- trichloro-2-pyridinol (TCP) was detected in the effluent perfusate at concentrations ranging from 31-40% of the perfused dose. Chlorpyrifos oxon could not be detected in the effluent perfusate. However, the authors note that chlorpyrifos oxon was produced intrahepatically since hepatic cholinesterase levels were 70-80% of controls following perfusion.

Lowering the BSA concentration significantly ($P< 0.05$) increased the fraction of chlorpyrifos in perfusate and increased both the time to reach steady-state as well as the extraction ratio of chlorpyrifos at steady state. However, with BSA concentrations lower than 0.5%, a steady state could not be achieved during the course of the perfusion. Following the omission of BSA from perfusate, neither chlorpyrifos nor TCP were detected in effluent perfusate. Furthermore, all chlorpyrifos could be accounted for as unchanged within the liver, indicating chlorpyrifos partitioned from perfusate to liver. Varying the BSA concentration did not result in the appearance of chlorpyrifos oxon in effluent perfusate. Pretreatment of mice with phenobarbital was found to induce formation of chlorpyrifos oxon from chlorpyrifos; however, pretreatment antagonized the acute toxicity of this pesticide. Phenobarbital pre-treatment also increased the steady-state extraction ratio of chlorpyrifos to 9.4, but did not lead to the production of chlorpyrifos oxon in the perfusate.

The authors concluded that the data confirms that the capacity of mouse livers to biotransform chlorpyrifos oxon exceeds their capacity to produce this potent cholinesterase inhibitor from chlorpyrifos. Therefore, in the mouse, the acute toxicity of chlorpyrifos is medicated solely by extrahepatic activation to chlorpyrifos oxon [Sultatos, 1988].

- ***dermal, rats***

The percutaneous absorption of 2,6-pyridyl ring-labelled ^{14}C-chlorpyrifos having a specific activity of 1.99 mCi/mM, was studied in young (33 days old) and adult (82 days old) female Fischer 344 rats at the following 3 dose levels: 0.25 $\mu mol/cm^2$ (low) 0.536 $\mu mol/cm^2$ (medium), and 2.679 $\mu mol/cm^2$ (high). ^{14}C-Chlorpyrifos solutions in acetone were applied to clipped middorsal skin with treatment areas ranging from 2-3% of the body surface area for both young and adult rats. Following treatment, areas were protected with a perforated plastic blister. Seventy-two hours following dermal application, treated animals were sacrificed. Skin, urine, feces, carcasses, and blisters were analyzed to determine compound absorbtion and recovery of radioactivity. Comparison of the skin penetration between young and adult rats was made at the 3 dose levels using 3 animals per group. Fractional absorption was calculated by dividing the radioactivity in the body plus excreta by the total radioactivity recovered.

Chlorpyrifos exhibited a greater absorption in the young rats. In adult rats, penetration in the medium and high dose groups (no data were collected for the low dose level because of low specific activity) was 6.6% and 5.8%, respectively; in young rats, penetration in the two different dose groups was 81% and 90%, respectively. The ratio of fractional penetration in young and adult rats was found to be statistically significant ($P \leq 5$) at the medium- and high-dose levels. Young rats absorbed 23 and 53% more chlorpyrifos than adult rats at the medium and high dose levels, respectively [Shah *et al.*, 1987; Hall *et al.*, 1988].

- *dermal, mice*

The dermal penetration of 2,6-carbon labelled chlorpyrifos (^{14}C-chlorpyrifos) was studied by Shah *et al.* A 1 mg/kg dose of ^{14}C-chlorpyrifos in 0.1 ml acetone solution was applied, using a syringe, to a shaved area (1 cm^2) of the upper shoulders of 3 female Duplin ICR mice. The test animals were observed for any changes in their behavior, specifically with regard to grooming. The animals were sacrificed at 1, 5, 15, 60, 480, and 2,880 minutes post-application. A 3-4 cm^2 area of the skin surrounding the application site was removed immediately after death to determine the quantity of unabsorbed compound. The half-life ($T_{1/2}$) was determined as a measure of the penetration rate. The amount of radioactivity in the animals' blood, urine, feces, heart, lungs, brain, kidney, bladder, fat, spleen, ear, bone marrow, muscle, stomach, intestine, liver, and carcass were evaluated to assess chlorpyrifos distribution.

There were no signs of toxicosis at any of the dose levels tested. The dermal penetration of chlorpyrifos (as measured by disappearance of radioactivity from the application site) ranged from 15.7% at 1 minute to 73.9% after 480 minutes. The $T_{1/2}$ value for dermal penetration was determined to be 20.6±5.9 minutes. Small amounts (based on % administered radioactivity detected) of radioactivity were detected after 5, 15, and 60 minutes in the blood (<0.1, 0.4, and 0.9%, respectively), liver (<0.1, 0.4, and 0.7%, respectively), fat (<0.1, 0.1, and 0.3%, respectively), excretory products (<0.1, 0.1, and 0.7%, respectively), and carcass (22.8, 63.5, and 66.6%, respectively). After 8 hours, the highest percentage (38.4%) of recovered radioactivity was found in the excretory products (approximately one third in the urine and two thirds in the feces). High levels of ^{14}C were also detected in the carcass (24.1%) and amounts ranging from 0.8 to 2.7% of the administered dose were found in the kidney, intestine, liver, and blood). Trace amounts (<.5% of the administered dose) were found in all other tissue examined, including the fat (0.2%) [Shah *et al.*, 1981].

Table 6. The Chemical Disposition of Chlorpyrifos in Cows, Swine, Sheep, and Goats

Route	Species/Strain (Sex)/No.	Dose/Duration of Chlorpyrifos Administration	Chlorpyrifos/ metabolite detected	Distribution-predominant tissue/ maximum concentration	Comments	Reference
Oral	Cow/Hereford (F)/15	0, 3, 30, or 100 ppm/ 30 days in feed	chlorpyrifos	fat/3.28 ppm[a]	Low conc. of chlorpyrifos in muscle, liver, kidney; no chlorpyrifos in fat residue by day 35. No oxygen analog (*O,O*-diethyl *O*-(3,5,6-trichloro-2-pyridyl)phosphate) detected.	Dishburger *et al.*, 1977
			3,5,6-trichloro-2 -pyridinol	liver/2.41 ppm kidney/1.75 ppm		
Oral	Cows/Holstein (F)/6	0.3, 1, 3, 10, or 30 ppm/14 days in feed	chlorpyrifos	milk/0.01 ppm cream/.10 ppm	All residues decreased rapidly when chlorpyrifos was removed from feed.	McKellar *et al.*, 1976
			3,5,6-trichloro-2 -pyridinol	milk/0.01 ppm cream/<0.025 ppm		
			oxygen analog	milk/<0.01 ppm cream/<0.01 ppm		
Dermal	Swine/Yorkshire, Duroc,Hampshire (M&F)/20, 1, and 1 respectively	1 ml/22.68 kg bw single application of Dursban 44 applied to back/35 days	chlorpyrifos	fat /0.406 ppm[b] muscle/0.007 ppm	Chlorpyrifos not detected in liver and kidney; chlorpyrifos and 3,5,6-trichloro-2-pyridinol not detected in any tissue 3 weeks post-treatment.	Ivey and Palmer, 1979
			3,5,6-trichloro-2 -pyridinol	fat/0.317 ppm[b] muscle, liver, kidney /0.170 ppm		
Dermal	Sheep/NS (M)/22	1 ml/22.68 kg bw single application of Dursban 44 applied to back/42 days	chlorpyrifos	fat/0.655 ppm[b]	Chlorpyrifos detected in fat 6 weeks post-treatment; 3,5,6-trichloro-2-pyridinol detected in liver and kidney at 3 weeks.	Ivey and Palmer, 1981
			3,5,6-trichloro-2 -pyridinol	liver/0.132 ppm kidney/0.190 ppm		
Dermal	Goat {weanling}/NS (M)/2	22 mg/kg/single application of ^{14}C-chlorpyrifos applied to shoulder/18 hours	chlorpyrifos	fat/0.65 ppm[b] heart/0.25 ppm	Highest ^{14}C residues in fat (0.40-0.83 ppm), kidney (0.44-0.73 ppm), and liver (0.36-0.60 ppm).	Cheng *et al.*, 1989
			3,5,6-trichloro-2 -pyridinol	kidney/0.44 ppm liver/0.33 ppm		
			unidentified metabolite	muscle/0.02 ppm		

Table 6. The Chemical Disposition of Chlorpyrifos in Cows, Swine, Sheep, and Goats (Continued)

Route	Species/Strain (Sex)/No.	Dose/Duration of Chlorpyrifos Administration	Chlorpyrifos/ metabolite detected	Distribution-predominant tissue/ maximum concentration	Comments	Reference
Dermal	Cow/Hereford (M&F)/12	3.3 g per plastic ear band single application to each ear/105 days	chlorpyrifos	fat/0.091 ppm[c]	Chlorpyrifos detected only in fatty tissues, with the exception of the muscle of 1 animal.	Ivey *et al.*, 1978
			3,5,6-trichloro-2-pyridinol	kidney/0.037 ppm liver/.032 ppm fat/0.290 ppm[c]		
Dermal	Cow/Hereford (M&F)/12	1.2 g per plastic ear band single application to each ear/105 days	chlorpyrifos	fat/0.030 ppm[c]	Chlorpyrifos detected only in fatty tissues.	Ivey, 1979
			3,5,6-trichloro-2-pyridinol	kidney/0.032 ppm liver/.014 ppm fat/.024 ppm[c]		
Dermal	Cow/Hereford (NS)/11	0.05% Dursban emulsion single dip/35 days	chlorpyrifos	fat/0.456 ppm[b]	Averages chlorpyrifos residues in fat of cows treated by single dip ~ twice levels after a single spray (see below)	Clayborn *et al.*, 1968
Dermal	Cow/Hereford (NS)/9	0.05% Dursban emulsion 3 dips/49 days	chlorpyrifos	fat/2.31 ppm[b]	Average chlorpyrifos residues after multiple dip ~ six times levels found after a single dip (see above)	Clayborn *et al.*, 1968
Dermal	Cow/Hereford (NS)/2	0.05% Dursban emulsion single spray (3.78 l/animal)/35 days	chlorpyrifos	fat/0.202 ppm[b]	----	Clayborn *et al.*, 1968
Dermal	Cow/Hereford (NS)/2	0.25% Dursban emulsion single(1.8l/animal) spray/7 days	chlorpyrifos	fat/0.60 ppm[b]	----	Clayborn *et al.*, 1968
Dermal	Cow/beef cattle/(M)/57	0.023-0.027% solution 6 dips 21 days apart/196 days	chlorpyrifos	fat/2.01 ppm[b]	----	Ivey *et al.*, 1972

[a] omental, renal, and subcutaneous fat sample
[b] omental fat sample
[c] omental and renal fat samples

B. Acute/Subacute

1. Human Data

The acute effects of chlorpyrifos in humans are summarized below in Tables 7 and 8; Table 7 presents experimental data on acute chlorpyrifos exposure and Table 8 presents data obtained from case studies. The predominant effect of acute exposure to this compound was the inhibition of plasma and blood cholinesterase activities. In the majority of both the experimental and case studies, the changes in cholinesterase levels returned to normal 1-4 weeks after exposure was discontinued.

Table 7: Effects of Acute Exposure to Chlorpyrifos in Humans

Route	Number (sex)	Dose (formulation)	Duration	Effect[a]	Reference[b]
Oral	4/dose group (males)	0.014, 0.03, 0.10 mg/kg/day (Dowco® 179)	9- 28 days	blurred vision, runny nose, decreased plasma ChE[c](34%) after 9 days at 0.10 mg/kg[d]	Griffin *et al.*, 1976;DowElanco, date unspecified
Oral	6 (males)	0.5 mg/kg (pure)	single dose	decreased plasma ChE (15-29%)	Nolan *et al.*, 1984
Dermal	6 (males)	0.5 mg/kg (pure)[e]	single dose	decreased plasma ChE (13%)	Nolan *et al.*, 1984
Dermal	7 (NR)[f]	1.0, 1.5, 3.0, 5.0, 7.5 mg/kg	12 hours (single dose)	None	USEPA, 1990
Dermal	NR	up to 50 mg/kg (Dursban® 6); 31 mg/kg A.I.[g]	12 hours (single dose)	None	DowElanco, date unspecified
Dermal	7 (NR)	5 or 25 mg/kg	3, 12-hour exposures	decreased plasma ChE (30%)	USEPA, 1990
Dermal	2 (females)	25 mg/kg (Dursban® 6); 15 mg/kg A.I.	2 or 3, 12-hour exposures	None after 2 exposures; decreased plasma ChE (47.5-67%) after 3	DowElanco, date unspecified
Dermal	1 (female)	10 mg/kg (Dursban® 6); 6.2 mg/kg A.I.	4, 12-hour exposures	None	DowElanco, date unspecified
Inhalation	3 (males)	fog of 42.5 g/ gallon diesel oil (Dowco® 179)[h]	3-8 minutes	None	Ludwig *et al.*, 1970; DowElanco, date unspecified
Inhalation	3 (males)	fog of 170.1 g/ gallon diesel oil (Dowco® 179)[i]	1-4 minutes	None after 1 min.; decreased plasma ChE after 2 (85%) and 4 min (80-84%)	Ludwig *et al.*, 1970; DowElanco, date unspecified
Inhalation	4 (males)	108-167 mg/m^3	5 minutes	None	DowElanco, date unspecified
Inhalation	22 (NR)	up to 1181 µg/ 0.5 cfm	90 minutes	None; 0-7 days post-treatment	Lusk *et al.*, 1976

[a] The numbers in parentheses represent the difference from predose ChE levels.
[b] Results obtained from DowElanco, date unspecified and USEPA, 1990 were from unpublished studies
[c] Che = cholinesterase
[d] The no observable effect level for chlorpyrifos in humans was 0.03 mg/kg/day.
[e] Chlorpyrifos was dissolved in dipropylene glycol monomethyl ether or methylene chloride.
[f] NR = not reported
[g] A.I. = active ingredient (chlorpyrifos)
[h] DowElanco, date unspecified, reports that the subject exposed for 8 minutes received 1.1 mg chlorpyrifos/m^3.
[i] DowElanco, date unspecified, reports that the subjects received 79.1-132.6 mg chlorpyrifos/m^3.

Table 8: Case Studies Involving Acute Human Exposure to Chlorpyrifos Formulations

Route	Subject(s)	Formulation[a]	Symptoms	Reference
Oral	38-year-old male	25% solution	catatonia; hypersecretions in trachea/ bronchi; undetectable serum ChE[b]	Shemesh *et al.*, 1988
Oral	61-year-old male	8:1 mixture of chlorpyrifos and malathion	Death 24 hours after ingestion; decreased blood ChE	Lores *et al.*, 1978
Oral	42-year-old male	41% commercial formulation/300 mg	coma; severe cholinergic symptoms; inhibition of ChE and lymphocyte NTE;[c] parasthesia; polyneuropathy (axonal)	Lotti *et al.*, 1986
Oral	54-year-old male	NR[d](30 g chlorpyrifos)	increased plasma Che levels, and hormone levels (norepinephrine, epinephrine, ADH, and aldosterone)	Yao *et al.*, 1984
Oral	15-month-old female	Dursban®	miosis; tachycardia; areflexia; muscle weakness; decreased plasma ChE	McNabb *et al.*, 1988
Oral	5-year-old female	Rid-A-Bug®	paleness; diaphoresis; mitotic pupils; labored respiration; cyanosis;seizure-like motor activity; decreased plasma ChE	Seldan and Curry, 1987
Oral	23-year-old female	NR	stupor; pinpoint pupils, ankle clonus; episodic grimacing associated with choreoathetotic movement of limbs; respiratory alkalosis; decreased serum and erythrocyte ChE	Joubert *et al.*, 1984
Oral and Dermal	11-day-old male	Dursban®	cyanosis; lethargy; respiratory arrest; pin point pupils; excessive salivation; decreased erythrocyte ChE (50%)	Dunphy *et al.*, 1980
Dermal	8 termite control workers	NR	decreased plasma and blood ChE, and red and white blood cells; serum lipid and lipase abnormalities	Shimada, 1980
Inhalation and Dermal[e]	2 males (age NR)	Dursban®	peripheral neuropathy (distal axonopathy); diffuse dysautonomia with bladder and vasomotor disfunction	Kaplan *et al.*, 1986
Inhalation and Dermal[e]	26 students and teachers	low odor formulation	headaches; nausea; dizziness; diarrhea; vomiting	Maddy and Edmiston, 1989
Inhalation and Dermal[e]	7 spray workers	5% Dursban® M (201-527 gallons)	decreased plasma ChE levels (12-91%)	USEPA, 1990
Inhalation and Dermal[e]	68 pet care workers	Dursban®	blurred vision, flushed skin, decreased urination	Ames *et al.*, 1989
Unknown	52 pesticide workers	unknown	decreased ChE activity; anorexia, nausea muscle weakness	Pinem *et al.*, 1982

[a] The exposure dose was not reported or was unknown for all of these case reports except the one reported by Lotti *et al.*, 1986.

[b] ChE = cholinesterase levels; [c] NTE = neuropathy target esterase; [d] NR = not reported

[e] Exposure occured after application of the pesticide; the route of exposure was not specified, but could have potentially been dermal or by inhalation.

2. Animal Data

Acute LD_{50} and skin irritation data are presented below in Table 9. The effects of chlorpyrifos exposure observed in these studies included the following: soft stools, bloody nares, slight tremors, piloerection, exophthalmia, chromodacryorrhea (at 126-500 mg/kg in female rats and 500-2000 mg/kg in male rats), and diarrhea (at 200 mg/kg in male rats) [Dow Chemical, 1971].

In addition, a summary of the effects of acute exposure to chlorpyrifos in cats, cows, goats, and swine is presented at the end of this section in Table 10. As in humans, the predominant effect in these animals was a decrease in blood and plasma cholinesterase activity, which returned to normal within 1-4 weeks of dosing. In Table 10, the individual symptoms of toxicosis/clinical toxicity were not reported, and include the following; weakness, lethargy, ataxia, tremors, miosis, salivation, diarrhea, lateral recumbency [Scheidt *et al.*, 1987], anorexia, ptyalism, dyspnea, prostration [Palmer *et al.*, 1980], reduced responsiveness [Hooser *et al.*, 1988], restlessness, loss of appetite, urination and defecation, and convulsions [Mohamed *et al.*, 1990].

- ***oral, rats***

  As described in an abstract by Japanese authors, the toxic effects of chlorpyrifos in rats of unspecified strain were evaluated in a 28-day study. The test animals (N=5) were gavaged daily with concentrations of 0.0, 0.1, 0.78, 6.25, and 50.0 mg/kg chlorpyrifos in an unspecified solvent. Decreased serum cholinesterase (ChE) activity and degeneration of the kidney tubules were observed in the groups receiving doses of ≥0.78 mg/kg, while brain ChE activity decreased following doses of ≥6.25 mg/kg/day. Decreased total serum protein, triglycerides, total cholesterol, and weight gain were also observed in the high dose animals, while serum urea nitrogen and adrenal weight were increased. After a 14-day recovery period, all of these effects returned to normal with the exception of brain cholinesterase activity which remained depressed. The authors concluded that the primary adverse effect of chlorpyrifos is the depression of ChE activity [Ogawa *et al.*, 1988].

- ***oral, mice***

  Eighty male and female mice (strain unreported) were used in a 3 1/2-week study to examine the toxicity of chlorpyrifos at dietary levels. Test materials (Dursban®) were administered for 14 consecutive days at dietary concentrations of 40, 80, and 240 ppm Dursban®; the treatment period was followed by a 10-day recovery period. To measure plasma and erythrocyte cholinesterase(ChE) levels, blood samples were collected by cardiac puncture 24 hours and 1 and 2 weeks after the initial treatment, and after the 10-day recovery period.

  There were no significant treatment-related effects with regard to food consumption or mortality. However, after 2 weeks of treatment, weight losses of 9% (males) and 17% (females) were reported in the high dose group. Further, although plasma and erythrocyte ChE activities were significantly (no P value reported) inhibited at each dietary level, these activities returned to normal following cessation of chlorpyrifos treatment [Fakhr *et al.*, 1982].

- ***oral, monkeys***

  In an unpublished study conducted by Dow Chemical Company, the acute effects of a single, oral dose of chlorpyrifos were evaluated in Rhesus monkeys. Three monkeys (sex unreported) were given a 3.5 mg/kg dose of chlorpyrifos. Blood samples were collected before treatment and 4, 8, 24, and 48 hours after dosing to evaluate plasma and erythrocyte cholinesterase (ChE) activities.

  Erythrocyte ChE activities were approximately 60% lower than pretreatment values, 4 hours after treatment. However, they gradually increased to 66, 80, and 82% of the baseline values after 8, 24, and 48 hours, respectively. Plasma levels were more severely affected and were only 6, 8, 14, and 30% of the baseline values after 4, 8, 24, and 48 hours, respectively. No other signs of clinical toxicity were reported [USEPA, 1990].

- ***oral, monkeys***

  In an unpublished study conducted by the Dow Chemical Company, two Rhesus monkeys (sex not reported) given a single oral dose of chlorpyrifos (2 mg/kg) for 3 consecutive days, showed no clinical signs of toxicity. A sharp decrease (15 to 25% of control values) in plasma ChE activity was observed 24 hours after the initial dosing. An additional 5% reduction was observed after administration of the second and third doses. Erythrocyte ChE activity levels dropped only slightly during the first day; greater reductions (60- 65% of control levels) were observed on the second and third days of the study [USEPA, 1990].

- ***oral, dogs***

  In an unpublished range-finding study conducted by Dow Chemical Company (1972), pairs of beagle dogs were fed a diet containing 0.6 ppm chlorpyrifos (0.015 mg/kg/day) for 12 days. The animals showed no changes in either plasma or erythrocyte cholinesterase (ChE) activity. When the chemical was administered for 28 days at a dietary concentration of 2 ppm (0.1 mg/kg/day), the plasma ChE activity in one female was reduced by 50% after 7 days. In dogs fed 6, 20, or 60 ppm chlorpyrifos (0.15, 0.5, or 1.5 mg/kg/day) for 35 days, plasma ChE activity was reduced to 42%, 25%, and 17% of pretreatment values, respectively; however, erythrocyte and brain ChE activities did not change. From these two studies, it was concluded that the no observed adverse effect level (NOAEL) for dogs exposed orally to chlorpyrifos was 0.015 mg/kg/day [USEPA, 1990].

- ***inhalation, rats***

  The acute effects of chlorpyrifos were evaluated in an unpublished inhalation study conducted by the Dow Chemical Company in 1972. Groups of 10 male and 10 female Sprague-Dawley rats that inhaled an aerosol cloud containing 5 mg chlorpyrifos/L for an unspecified amount of time exhibited lacrimation, slight nasal discharge, and gasping during exposure. Animals appeared normal during the 14-day post-inhalation period, and post-mortem examination of tissues revealed no gross pathological changes [USEPA, 1990].

- ***intraperitoneal, rats***

  The acute effects of chlorpyrifos were studied in an unspecified number of male, Sprague Dawley rats. Chlorpyrifos (Dursban®) was diluted in water (1:20) and administered intraperitoneally at half the LD_{50} (dose not reported) for two consecutive days. The test animals were sacrificed and histopathological and histochemical evaluations of the liver, kidney, and testes were conducted. In addition, serum glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), alkaline phosphatase, and ChE activities were evaluated in blood samples taken from each animal.

  Two repeated doses of chlorpyrifos resulted in a significant ($P<0.05$) increases in serum GOT, GPT, and alkaline phosphate activities, as well as a significant ($P<0.05$) decrease in serum ChE levels. Histopathological examinations revealed damage to the gonads (necrosis of the seminiferous tubules), kidney (swelling of the convoluted tubules), and liver (midzonal necrosis). The necrotic part of the liver appeared pale with fatty changes at the periphery, and was characterized by mononuclear cell infiltrate, early formation of new bile ducts, and marked congestion of the central vein with dilated sinusoids. Histochemical evaluation of the liver revealed a depletion of glycogen especially around the central vein, and PAS (Periodic Acid-Shiff) positive material (carbohydrates) deposited at the side of the cell. Fatty infiltration of the liver was also observed in rats following liver damage. The authors concluded that chlorpyrifos is hepatotoxic in rats [Mikhail *et al.*, 1979].

- ***intraperitoneal, rats***

  Male Wistar strain rats were used to assess retinal damage following treatment with organophosphorus pesticides (OPs), including chlorpyrifos, and to compare these results to the effects of OPs on cholinesterase (ChE) activities. Groups of 5 test animals were administered intraperitoneal injections of chlorpyrifos at concentrations of 0.01 or 0.05 mmol/kg in olive oil. Control animals received injections of the vehicle only. Retinal damage was assessed by measuring electroretinographic (ERG) changes 5 hours and 2 days after injection; brain and retinochoroid ChE activities were determined 3 days after injection.

  ERG changes were only observed in animals dosed with 0.05 mmol/kg of chlorpyrifos. At this dose level, the amplitude of the alpha waves was significantly decreased after 5 hours ($P<0.001$) and 2 days ($P<0.05$), and the latency of the wave was significantly prolonged ($P<0.01$ and $P<0.001$ after 5 hours and 2 days, respectively). Amplitude of the beta waves was significantly decreased only after 5 hours ($P<0.001$), and the latency was significantly prolonged 5 hours ($P<0.01$) and 2 days ($P<0.001$) after injection. In the 0.05 mmol/kg dose group, ChE activities in the brain and retinochoroid were significantly decreased ($P<0.001$). Chlorpyrifos did not have a significant effect upon ERG measurement or ChE activity when administered at a concentration of 0.01 mg/kg. The authors of this study concluded that these decreases in amplitudes and increases in latencies observed in rats may be derived from the retinal degeneration caused by exposure to chlorpyrifos. They also concluded that there was not a consistent relationship between the changes in ChE and ERG; therefore a factor other than ChE inhibition contributes to the alteration of ERG induced by OPs [Yoshikawa *et al.*, 1990].

- *intraperitoneal, mice*

  In addition to studying the oral effects of chlorpyrifos in mice (see above), Fakhr *et al.*, evaluated the short term effects of chlorpyrifos (Dursban®) administered intraperitoneally. Groups of 10 male and 10 female mice of an unspecified strain received intraperitoneal injections of 5, 15, and 45 mg/kg Dursban® dissolved in 0.1 ml of dimethyl sulfoxide, twice weekly for 2 weeks. Dosing was followed by a 10-day recovery period. Blood samples were also collected 24 hours and 1 and 2 weeks after the initial treatment and after the recovery period plasma and erythrocyte cholinesterase (ChE) levels were determined.

  Intraperitoneal injection of chlorpyrifos were extremely toxic in mice. Twenty percent of the female mice died after receiving injections of 5 mg/kg Dursban® twice weekly for 2 weeks. This dose caused weight losses of 10% and 14% in the surviving males and females, respectively, compared to controls. Plasma and erythrocyte ChE activities were inhibited at all dose levels. Following administration with 5 mg/kg chlorpyrifos, plasma and erythrocyte cholinesterase activities were inhibited by 47% and 42% of the animals, respectively, 6 hours after dosing. However, a recovery trend was observed within 48 hours [Fakhr *et al.*, 1982].

- *dermal, mice*

  In conjunction with oral and intraperitoneal short-term toxicity tests described above, Fakhr *et al.*, evaluated the short-term effects of chlorpyrifos (Dursban®) on an unspecified number of mice treated dermally at concentrations of 11, 33, 66, and 99 mg/kg Dursban® dissolved in 0.1 ml of dimethyl sulfoxide. Applications to the shaved backs were made twice weekly for 2 weeks followed by a 10-day recovery period. Blood samples were collected by cardiac puncture 24 hours and 1 and 2 weeks after the initial treatment, then immediately after the 10-day recovery period.

  Body weight decreases of 65% and 10-13% was reported in the animals receiving doses of 99 mg/kg and 66 mg/kg Dursban®, respectively. Unspecified body weight decreases were also observed in the other dose groups. In addition, in the high dose group (99 mg/kg), the plasma cholinesterase activities were inhibited by 14% following 1 week of treatment and erythrocyte activity was inhibited 21% after 24 hours. Although cholinesterase activities were inhibited for all dose levels tested, they recovered completely [Fakhr *et al.*, 1982].

- *percutaneous, rabbits*

  The acute effects of chlorpyrifos injected percutaneously were evaluated in an unpublished study conducted by Dow Chemical Company (1972). Groups of 4 albino rabbits (sex not reported) received percutaneous injections of 1.0, 2.0, or 3.98 g chlorpyrifos as a 25% solution. The rabbits were observed for clinical signs of toxicosis. Treatment with chlorpyrifos induced slight to moderate erythema, swelling, and necrosis. One rabbit from the 2.0 g dose group died 3 days after exposure, and 3 rabbits from the 3.98 g dose group died within 6 to 9 days of treatment. No other signs of toxicosis or mortalities were reported [USEPA, 1990].

- *dermal, rabbits*

  Groups of 3-6 albino New Zealand rabbits were used to examine the effects of dermal application of Dursban® 24E (23.7% chlorpyrifos). In one test, the skin on the backs of 6 animals was clipped, and 0.5 ml of the formulation was placed under secured patches on intact and abraded skin. After 24 hours of exposure, patches were removed and the reactions were evaluated. Application of chlorpyrifos resulted in moderate or severe erythema on all areas. Slight necrosis was seen on intact skin in four rabbits, and on abraded skin in five rabbits. The exposed areas also displayed moderate to severe edema.

  In a second test, 0.5 ml of the formulation was placed on the backs of 3 rabbits, and the reactions were observed periodically for 6.5 hours. Slight erythema was seen in 10 minutes on all exposed areas, slight edema was observed after 30-60 minutes, and slight necrosis was recorded after 1.5-3.5 hours. At the end of the exposure period, all areas showed moderate erythema, slight or moderate edema, and slight necrosis [Dow Chemical, 1971].

- *dermal, rabbits*

  In the study conducted above by Dow Chemical (1971), the effect of Dursban® 24E (23.7% chlorpyrifos) on the eyes was examined in albino New Zealand rabbits. Six rabbits were treated with 0.1 ml of the formulation into the conjunctival sac of the right eye. The left eye of each of the animals served as an untreated control. The eyes were examined 24, 48, 72 hours and 7 days after treatment. Application of this compound caused conjunctival redness and chemosis that left the eye lids half or completely closed in two animals, and partially everted in four animals. Iritis (5 animals) and moderate corneal injury (6 animals) were also observed [Dow Chemical, 1971].

- *dermal, dogs*

  The subacute clinical toxicity of chlorpyrifos was evaluated in dogs. Five beagle and mongrel dogs (2 female, 3 male) were dusted once daily, 5 days/week for two weeks (total of ten applications) with an aerosol containing 1.25% chlorpyrifos. The dust was applied at an unspecified rate, in excess (by at least 30 seconds) of that normally used in practice, until the skin and hair coat were thoroughly coated. A vehicle control group (N=3) was dusted in the same manner but without chlorpyrifos, and 2 other dogs served as the untreated control group. Body weights and appetite changes were monitored during the treatment period and during the first, second, and fourth weeks following treatment. Physical examinations including slit-lamp and indirect ophthalmoscopy were performed on each dog prior to treatment and at the 2-week and 8-week intervals. Blood samples were collected on days 1 and 3 prior to treatment and during weeks 1, 2, 4, and 8 of the study to evaluate the effects of chlorpyrifos exposure on hematology (erythrocyte count, packed cell volume, hemoglobin, and total and differential leucocyte counts). Separate blood samples were collected on

days 2 and 7 prior to the application of the spray and during weeks 1, 2, 4, and 8 of the study to evaluate blood chemistry (alkaline phosphatase, serum glutamic-pyruvic transaminase, serum glutamic-oxalacetic transaminase, blood urea nitrogen, and blood glucose). Finally, samples were collected for cholinesterase determinations on days 7, 14, 28, 56, and 88 of the study.

No clinical indications of toxicity were noted, and no mortalities were observed. One of the chlorpyrifos-treated dogs developed diarrhea one day after the last application of chlorpyrifos; however, its feces was normal the following day. The average weight gain was comparable between the chlorpyrifos or vehicle treatment groups and the untreated controls. There were no treatment related changes in either the hematology or blood chemistry parameters evaluated. While erythrocyte cholinesterase values fluctuated in treated and control animals, a gradual decrease was observed in the Dursban® treated group after 7 days of treatment, but no significant changes were reported. However, the plasma cholinesterase values in chlorpyrifos treated dogs were significantly decreased ($P<0.05$) following the first application of product, and remained significantly lower ($P<0.01$) up to 42 days after cessation of treatment. Similar increases were observed among dogs treated with the vehicle dust only. Plasma cholinesterase values in both groups began to return to pre-exposure levels 14 days (vehicle) or 28 days (Dursban®-treated) after treatment was discontinued. The authors could provide no explanation for the depression of plasma cholinesterase obtained with the vehicle dust alone [Dow Chemical, 1968].

Table 9: Acute LD_{50} Data for Chlorpyrifos in Animals

Species/Strain	Number/Sex	LD_{50} (mg/L)/LC_{50} (mg/L) (confidence limits)	Reference
ORAL			
Rats/albino	12/male	151 (179-252)	Hudson *et al.*, 1984
Rats/NS [a]	NS/Female	82	Pest Control, 1971
Rats/ albino Sprague Dawley	5/Male	713 (not calculable)[b]	Dow Chemical, 1971
	5/Female	356 (243-523)[b]	
Rats/Sprague Dawley	NS/Male & Female	82-163	Chambers and Chambers, 1989
Rats/NS	NS/Male	1173[c]	DowElanco, 1990
Rats/NS	NS/Female	766[c]	DowElanco, 1990
Rats/NS	NS/Female	599[d]	DowElanco, 1991a
Rats/NS	NS/Male	834[d]	DowElanco, 1991a
Rats/NS	NS/Male	226[e]	DowElanco, 1991b
Rats/NS	NS/Female	272[f]	Dow Elanco, 1991c
Rats/white	5/Male	60	Enan *et al.*, 1982
		25 (w/ ascorbic acid)	
Rats/albino Dow Wistar	5/Male	163 (97-276)	McCollister et al., 1974
Rats/albino Dow Wistar	5/Female	135 (97-188)	McCollister *et al.*, 1974
Rats/ albino Sherman	5/Male	118 (77-181)	McCollister *et al.*, 1974
Sherman	5/Female	155 (100-238)	
Rats/Sprague-Dawley	NS/Female	169 (146-196)[h]	Berteau and Deen, 1978
Mice/NAMRU	NS/Female	152 (143-162)[h]	Berteau and Deen, 1978
Mice/White	NS/NS	60[g]	El-Sebae *et al.*, 1978
		140	
Guinea pigs/NS	NS/NS	500	USDI, 1988; WHO, 1986
Guinea pigs/NS	4/Male	504 (299-850)	McCollister *et al.*, 1974
Rabbits/white New Zealand	1/Male	Not calculable	McCollister *et al.*, 1974
Rabbits/white New Zealand	NS/NS	1000-2000	USDI, 1988; Worthing, 1987
INHALATION			
Rats/NS	NS/Female	2.3 mg/L (4 hr)[c]	DowElanco, 1990
Rats/NS	NS/NS	>1.3 mg/L (4 hr)[d]	DowElanco, 1991a
Rats/NS	NS/NS	2.6-3.6 (4 hr)[e]	DowElanco, 1991b
Rats/Sprague-Dawley	8/Female	78 mg/L (57-108)[h]	Berteau and Deen, 1978
Mice/NAMRU	16/Female	94 mg/L (83-106)[h]	Berteau and Deen, 1978
INTRAPERITONEAL			
Mice/Charles River	NS/Male	192 (150-246)	Sultatos *et al.*, 1982
Mice/NS	NS/Male & Female	40	Fakhr *et al.*, 1982

Table 9: Acute LD_{50} Data for Chlorpyrifos in Animals (con't)

Species/Strain	Number/Sex	LD_{50} (mg/L)/LC_{50} (mg/L) (confidence limits)	Reference
DERMAL			
Rats/NS	NS/NS	202	Pest Control, 1971
Rabbits/NS	NS/NS	2000	Meister, 1990; WHO, 1986; Worthing, 1987
Rabbits/NS	NS/NS	694-1724[c]	DowElanco, 1990
Rabbits/NS	NS/NS	>2000[d]	DowElanco, 1991a
Rabbits/NS	NS/Male	1265[e]	DowElanco, 1991b
Rabbits/NS	NS/Female	930[e]	DowElanco, 1991b
Rabbits/NS	NS/NS	>2000[f]	DowElanco, 1991c
Rabbits/albino New Zealand	4/NS	3360 (2000-5650)	Dow Chemical, 1971

[a] NS = Not specified
[b] Applied as the commercial preparation Dursban® 24E (23.7% chlorpyrifos).
[c] Applied as the commercial preparation Dursban® 2E (24.1% chlorpyrifos).
[d] Applied as the commercial preparation Dursban® LO (41.5% chlorpyrifos).
[e] Applied as the commercial preparation Dursban® TC (42.8% chlorpyrifos).
[f] Applied as the commercial preparation Lorsban® 4E (40.7% chlorpyrifos).
[g] Applied as the commercial preparation Dursban® EC (40.8% chlorpyrifos).
[h] Applied as a 65% formulation in xylene.

Table 10: The Effects of Acute Exposure to Chlorpyrifos In Cats, Cows, Goats and Swine

Route	Species/ Strain	# Per Dose Group/Sex	Dose	Study duration (days/# of doses)	Effects[a]	References
Oral	Cat/Domestic shorthair	2/male	serial doses from 0.1-50.0 mg/kg (technical grade)[b]	1/5	reduced blood and plasma ChE; toxicosis and death (1 cat) at 50 mg/kg only	Hooser *et al.*, 1988
Oral	Cat/Domestic shorthair	6/male	40 mg/kg (technical grade)[b]	56/1	reduced blood and plasma ChE ($P<0.001$); toxicosis; reduced brain ChE and death (1 cat)	Hooser *et al.*, 1988
Oral	Goat/ Nubian	3/males and female	150 mg/kg (48% technical grade)[c]	7/1	clinical signs of toxicity; pulmonary, hepatic, intestinal, abomasal lesions; brain hemorrhage; changes in serum chemistry; death within 5 days	Mohamed *et al.*, 1990
Oral	Cow/Dairy Breed (new born)	5/NS	5, 10, or 25 mg/kg (technical grade)	7/1	dose-dependent reduction in blood ChE; severe toxicosis at 25 mg/kg	Palmer *et al.*, 1980
Dermal	Cow/Dairy Breed (new born)	5/NS	sprayed with 0.02-0.12% emulsion[d]	7/1	dose-dependent reduction in blood ChE; toxicosis at 0.06 and 0.12%; death (1 calf) at 0.12%	Palmer *et al.*, 1980
Dermal	Cow/Angus and Brahman cross breed (4-6 months old	5/NS	sprayed with 0.25-2.30% emulsion[d]	7/1	dose-dependent reduction in blood ChE; toxicosis (1 calf) at 2.30%	Palmer *et al.*, 1980
Dermal	Cow/Holstein	4/Bulls (pre treated with testosterone) and Steers	16 ml	86/2 (on days 28 and 56)	*Bulls*: decreased blood ChE ($P<0.01$); diarrhea, depression, anorexia after 2nd dose; *Steers*: None[e]	Haas *et al.*, 1983
Dermal	Cow/Brangus	1/bull	Not reported[f]	NR/1	decreased blood ChE; general signs of toxicity	Scarratt and Blodgett, 1986
Dermal	Cow/Limousin	1/Bull	Not reported (Dursban® 44)	NR/1	diarrhea, anorexia, weakness depression	Putnam and Edwards, 1984
Dermal	Swine/NS (piglets)	15/male and female	2.5% aerosol spray	20/1 (2 seconds)	decreased blood and brain ChE; toxicosis	Long *et al.*, 1986; Scheidt et al., 1987
Not specif.	Cat/Domestic shorthair	2/male and female	unknown (home sprayed)	18/6 applications	decreased ChE; general signs of toxicity	Jaggy and Oliver, 1990

[a] ChE = cholinesterase activity; symptoms of toxicosis and/or clinical toxicity are described at the beginning of section V.B.2. If P values were provided in the study, they were included in this table.

[b] Chlorpyrifos was dissolved in methylene chloride and mixed with olive oil.

[c] Chlorpyrifos was applied as the commercial preparation Dursban® 4 EC (48% active ingredient).

[d] Each calf was sprayed with 4 liters of an emulsifiable concentrate of Dursban® 24 E diluted to the specific concentrations (solvent unspecified).

[e] The authors of this study concluded that testosterone increases the toxicity of chloryrifos.

[f] The cow was treated with Dursban® 44 applied to the back.

C. Prechronic

1. Human Data

- Sharp and Warner evaluated the effects of repeated human exposure to dust and aerosol formulations of chlorpyrifos in 3 individuals (2 animal handlers and 1 technician). The test subjects treated dogs with chlorpyrifos (as either a dust or an aerosol) for 10 consecutive days. Protective equipment, including gas masks, rubber rain suits, gloves, and boots, was worn by the 2 dog handlers. One handler was exposed to chlorpyrifos for 3 days and the other was exposed for 7 days. The technician who was responsible for applying the test materials wore a paper mask, gloves, and long-sleeved coat, in addition to normal laboratory attire, and was exposed for 10 days. The erythrocyte and plasma ChE levels of all 3 individuals were measured on days 4 and 2 before treatment was initiated (to establish baseline values) and on post-exposure days 1, 7, 14, 28, and 56.

  At no time during the study were signs of illness reported. Plasma cholinesterase (ChE) values were found to be decreased following 14 days of exposure in each individual (no P value reported). Fourteen days after the final exposure, ChE levels had returned to the pre-exposure values in 2 of the 3 subjects (1 was not available for testing) and, for all three subjects, ChE activities had returned to normal by post-exposure day 56 [Dow Chemical Company, 1969].

- Plasma cholinesterase (ChE) activity was found to be significantly ($P<0.001$) inhibited in a group of 17 pest control operators who had been employed in the pest control industry for an average of 2 years. The operators were primarily exposed to 3 organophosphorus insecticides, including Dursban E-2, at a time-weighted average concentration of 7.54 mg/m^3 for 8 hours per day, 5 day per week. No effect on erythrocyte ChE activity was found. Most of the workers interviewed experienced headaches and complained of aggravated nasal or respiratory problems. However, general physical examinations were normal [Hayes *et al.*, 1980].

- As described in an abstract by Japanese authors, changes in the blood cholinesterase (ChE) activity have been observed among termite control workers who use chlorpyrifos. Plasma and erythrocyte ChE activity decreased in the busy season, during the months of May through September, and reportedly recovered during the off-season month of January. The ratio of the lowest level of plasma and erythrocyte ChE activities (from 6 workers exposed during the busy season) to the average levels of activity (from 6 workers exposed during the off-season) was found to be less than 50% and 70%, respectively. The negative correlation between exposure time and plasma and erythrocyte ChE activities were found to be significant (P value not specified) [Jitsunari *et al.*, 1989].

- In an unpublished study by Kenaga and Lembrant, 1967, it was reported that cholinesterase (ChE) levels of an individual responsible for the application of Dursban® to a mosquito breeding area on 23 days over a four month period were not affected. This man also inspected the sprayed areas on 72 occasions over approximately the same time period. The sprays were applied at the rate of 0.05 lb chlorpyrifos/acre in 2 gallons of water using a vehicle mounted mist blower. The worker reportedly did not wear gloves or a face mask [Dow, date unspecified].

2. Animal Data

- *oral, rats*

In an unpublished Dow Chemical Company study (1972), a no observed adverse effect level (NOAEL) of 0.5 mg/kg/day was determined, based upon reduced brain cholinesterase (ChE) activity in rats. Groups of 20 albino rats (10/sex/dose) were maintained on diets containing 10, 30, 100, or 300 ppm chlorpyrifos for 90 days. An additional group that received 1000 ppm daily was discontinued after 28 days because of the high mortality rate. The test animals were observed for signs of toxicosis, and blood samples were collected (at unreported intervals) to evaluate plasma and erythrocyte ChE activity. At the conclusion of the study, the animals were sacrificed and brain ChE activities were measured.

Plasma and erythrocyte ChE activities were depressed in a dose-dependent manner. Brain ChE activity was depressed by 10, 20, and 30% of the control levels in the animals dosed with 100, 300, and 1000 ppm, respectively. Brain ChE activities were depressed, but not significantly (P=0.05), in the 10 ppm (3-7%) and 30 ppm (19-22%) dose groups. The animals in the 1000 ppm dose group exhibited signs of severe ChE depression, including decreased food consumption, significant weight loss (no P values reported), tremors, bloody noses, circling and backing, ulceration of the cornea and nostrils, and death. Signs of illness were also reported in the 300 ppm dose group (tremors, slight diuresis, and slight growth retardation), but none were observed in the 10, 30, or 100 ppm dose groups [USEPA, 1990].

- *oral, rats*

The effects of chlorpyrifos were examined in an unpublished 91-day feeding study conducted by the Dow Chemical Company (1972). Groups of 20 albino rats (10/sex/dose) were fed 0.3, 1.0, 3.0, or 10.0 mg/kg chlorpyrifos for 91 consecutive days. At an unreported time point, plasma and erythrocyte cholinesterase (ChE) activities were depressed by 35-58% and 14-26% compared to control levels in the 3.0 and 10.0 mg/kg dose groups, respectively. Slight to severe signs of toxicity (hunched appearance, tremors and weight loss) were also reported at these dose levels. Rats receiving 0.3 and 1.0 mg/kg also had depressed plasma and erythrocyte ChE activities. Male rats in the 0.3 mg/kg dose group had reduced body weight gain. No signs of toxicity were observed at the 0.3 or 1.0 mg/kg dose levels. Survival was not effected at any dose level, and ChE activities returned to normal within 1 to 2 weeks after the test animals stopped receiving chlorpyrifos-supplemented diets [USEPA, 1990].

- ***oral, monkeys***

  In an unpublished study conducted by the Dow Chemical Company (1972), groups of 3 or 4 male and female rhesus monkeys were administered chlorpyrifos in an unspecified vehicle, by gavage, at concentrations of 0.08, 0.4, or 2.0 mg/kg/day for 6 months. Plasma and erythrocyte cholinesterase (ChE) levels were depressed in the 0.4 and 2.0 mg/kg dose groups. However, no changes in midbrain and cerebrum ChE activities were observed. In addition, no abnormalities were revealed upon histological examination. A NOAEL of 0.08 mg/kg/day was identified based on the absence of inhibition of plasma ChE at this dose [USEPA, 1990].

- ***inhalation, rats***

  A 13-week inhalation study was conducted to evaluate the prechronic effects of chlorpyrifos in rats. Groups of 20 Fischer 344 rats (10 male and 10 female) were exposed to targeted concentrations of 0, 5, 10, or 20 ppb (0, 72, 143, or 287 $\mu g/m^3$) chlorpyrifos for 6 hours/day, 5 days/week for 13 weeks using nose-only chambers. The animals were observed for any treatment-related effects after each exposure. Body weights were recorded weekly and urinalysis, hematology, and clinical chemistry parameters as well as brain, red blood cell (RBC), and plasma ChE activities were assessed. The animals were sacrificed and necropsied one day after the final dose was administered. Major organs such as the adrenals, brain, testes, liver, kidneys, and lungs were weighed, and complete sets of tissues from the high dose group and the control group were evaluated histologically.

  All of the rats, including the controls, had slight red staining around the eyes and nares during the first month of the study. No other abnormalities were observed in the exposed animals. There were no treatment-related differences observed in any of the following parameters evaluated: body weight, urinalysis, hematology, clinical chemistry, terminal body and organ weights, or pathology. In addition, chlorpyrifos treatment had no effect on either plasma, RBC, or brain ChE activities. The authors concluded that chlorpyrifos does not have a significant potential for subchronic toxicity in rats. Based on these results, a no-observed-effect level (NOEL) of 20.6 ppb was determined [Corley *et al.*, 1989].

D. Chronic/Carcinogenicity

1. Human Data

No data were found.

2. Animal Data

Chlorpyrifos has been found to be noncarcinogenic in long-term animal studies conducted by the Dow Chemical Company [DowElanco, 1990; DowElanco, 1991a; DowElanco, 1991b; DowElanco, 1991c]. Those Dow studies which are reported in the published literature (see McCollister *et al.*, 1974; McCollister *et al.*, 1973 below) or described in EPA documents are summarized below. Although Dow could not provide specific information on recent chronic/carcinogenicity testing on this compound, a DowElanco representative stated that carcinogenicity testing for chlorpyrifos is ongoing [DowElanco, 1992].

- ***oral, rats***

  In an unpublished study conducted by the Dow Chemical Company (1972), no clinical or histological signs of toxicity were observed in albino rats (20/sex/group) consuming dietary levels of 0.03, 0.15, or 0.75 mg chlorpyrifos/kg/day for 6 months. Plasma and erythrocyte cholinesterase (ChE) activities were reduced 35-60% and 50%, respectively, compared to controls in the high dose group. Brain ChE activity was not affected at any treatment level. Based on these results, a NOAEL of 0.15 mg/kg/day was determined. No other data were reported [USEPA, 1990].

- ***oral, rats***

  The chronic toxicity of chlorpyrifos was investigated by McCollister *et.al* in a 2-year study. Groups of 25 male and 25 female Sherman strain rats were fed doses of chlorpyrifos at concentrations of 0.0 (control), 0.01, 0.03, 0.1, 1.0, or 3.0 mg chlorpyrifos/kg/day. Additional groups of 5-7 rats of each sex at each dose level were set up to provide for interim pathological examination and cholinesterase (ChE) determinations. The animals were observed frequently and body weight, food consumption, and mortality were recorded. At 6-month intervals, blood and urine samples were collected from selected rats receiving 0.0, 1.0, or 3.0 mg/kg/day. The packed cell volume, hemoglobin, erythrocyte count, and total differential leucocyte counts were determined and urine samples were analyzed for total solids, pH, albumin, sugar, occult blood, and ketones. Plasma and red blood cell (RBC) ChE activity was determined for all rats in the groups killed after 1 week and 1, 3, 6, 9, 12, and 18 months, and for selected rats given each dose for 2 years. Brain ChE activity was determined in the animals on the test diets sacrificed at 6, 12, 18, and 24 months. To characterize the recovery of the ChE activity in the plasma, RBCs, and the brain, some rats were maintained on the various diets containing chlorpyrifos for 12 months, and then on the control diet for 7-8 weeks prior to sacrifice. In addition, blood urea nitrogen (BUN), serum alkaline phosphatase (AP), and serum glutamic-pyruvic transaminase (SGPT) were determined from blood samples collected from the animals sacrificed at 12, 18, and 24 months.

Autopsies were conducted on all of the animals sacrificed at 12, 18, and 24 months and those rats that received the control diet for 7-8 weeks after being fed diets containing chlorpyrifos for 12 months. Prior to decapitation, the animals were fasted for 16 hours and weighed. In addition, brain, heart, liver, kidneys, spleen, and testes were removed and weighed. Samples from these and the following organs or tissues were collected and preserved in 10% formalin: eye, pituitary, thyroid and parathyroid glands, trachea, esophagus, lungs, aorta, stomach, pancreas, small intestine, colon, mesenteric lymph nodes, urinary bladder, accessory sex glands, ovaries, uterus, skeletal muscle, sciatic nerve, spinal cord, sternum, sternal bone marrow, adrenal gland, and any nodules or masses suggestive of tumour development or other pathological processes. Histopathological examination was conducted on tissues of control rats and rats from the high dose group. Histopathological examination also was conducted on the tissues of all rats exhibiting grossly visible nodules or masses and on rats killed in a moribund state or dying spontaneously.

None of the rats displayed any signs of cholinergic response or other compound-related effects. There were no treatment related differences observed in body weight, mortality rate, food consumption, hematological studies, urinalysis, BUN, AP, or SGPT. Plasma ChE activity in the high dose males (3.0 mg/kg/day) was significantly ($P<0.05$) lower than control levels at the 1 week, and 3, 9, 12, 18, and 24 month sample intervals. Males in the 1.0 mg/kg dose group had ChE activities which were significantly depressed ($P<0.05$) after 9, 18, and 24 months of exposure. RBC ChE levels in these same dose groups were also significantly lower at each testing interval (except after 7 days in the 1 mg/kg/day dose group). The plasma and RBC ChE activities in the female rats given doses of 1.0 and 3.0 mg/kg were significantly ($P<0.05$) lower than the control group after 1 week (3.0 mg/kg RBC ChE only), and 1, 3, 6, 9, 12, 18, and 24 months. There were no significant ($P<0.05$) effects on either plasma or RBC ChE activity in animals receiving doses $\leq$ 0.1 mg/kg, except for the 0.1 mg/kg females whose RBC ChE activity was depressed ($P<0.05$) after the 1 and 12 month testing intervals. Brain ChE activity was significantly ($P<0.05$) depressed at all four sampling times in rats fed 3.0 mg/kg/day, with the overall means averaging 56% and 57% of the control value for males and females, respectively. The test animals given doses of 1.0 mg/kg/day showed no overall effect on brain ChE activity even though there were statistically significant differences at some of the sampling periods.

In both male and female rats, plasma, RBC, and brain ChE activities all returned to normal during the 7-8 week nontreatment period. Organ weights were not affected by treatment either on an absolute basis or as a percentage of body weight. Neither gross nor microscopic examination of tissues revealed changes attributable to ingestion of diets containing chlorpyrifos. The authors concluded that doses of 0.1 mg chlorpyrifos/kg/day or less produce no significant depression of ChE in plasma, RBC, or the brain and that concentrations of chlorpyrifos up to this level can be tolerated indefinitely by rats without toxicological effects [McCollister *et al.*, 1974; McCollister *et al.*, 1973].

oral, dogs

The chronic oral toxicity of chlorpyrifos in dogs was studied by McCollister *et. al* in two separate phases. In phase A, 6 groups consisting of 3 male and 3 female beagles were maintained on diets containing chlorpyrifos at doses of 0.0 (control), 0.01, 0.03, 0.1, 1.0, or 3.0 mg/kg/day. After 1 year, 1 male and 1 female from each dose group was sacrificed and autopsied. The remaining animals were maintained on control diets without chlorpyrifos for an additional 3 months prior to sacrifice. Plasma and red blood cell (RBC) cholinesterase (ChE) activities were determined in all the animals 3 times prior to receiving the test diet and after 1 week and 1, 3, 6, 9, and 12 months of testing. In addition, ChE activity was measured several times during the 3 month nontreatment period. In phase B, six groups of 4 male and 4 female beagles were maintained on the same diets described in phase A for 2 years before being sacrificed and autopsied. ChE activity was determined in these animals twice prior to testing and after 1 week and 1, 3, 6, 9, 12, 15, 18, and 24 months on the test diets. All of the dogs were observed daily for signs of toxicosis. Body weight and food consumption were recorded regularly. The animals (both phase A and B) in the 0.0, 1.0, and 3.0 mg/kg/day dose groups were subjected to complete hematological and serum chemical evaluations, and urinalyses. Prior to sacrifice (by exsanguination), the animals were given complete physical examinations which included routine ophthalmoscopic and neurological evaluations. The organs and tissues were evaluated in the same manner described above (McCollister *et al.*, 1973; MCCollister *et al.*, 1974) for rats. Tissues were microscopically examined from dogs receiving doses of 0.0, 1.0, and 3.0 mg/kg/day (phase A) and 0.0 and 3.0 mg/kg/day (phase B), and from any animals whose tissues displayed grossly visible lesions.

There were no signs of toxicity nor evidence of any increase in cholinergic activity in any of the dogs, at any time, during either phase. Also, there were no treatment-related differences in body weight, organ weight, organ-to body ratios, food consumption, hematological studies, urine analysis, or serum chemistry. However, the mean liver-to-body weight ratio was significantly ($P<0.05$) increased in the males fed 3.0 mg/kg/day. This was not observed in any other test group. The ChE activities in both male and female dogs (phases A and B) receiving doses of 0.1, 1.0, and 3.0 mg/kg/day showed significant ($P<0.05$) decreases in plasma ChE activity. There were also significant ($P<0.05$) differences in plasma ChE activity, at various sampling times, for the groups of male and female dogs in both phase A and phase B given the 0.03 mg/kg/day dose. RBC ChE activity was significantly ($P<0.05$) decreased in both male and female dogs (phase A and phase B) given doses of 1.0 and 3.0 mg/kg/day. RBC ChE activity was significantly decreased ($P<0.05$) at only 1 sampling period in females (phase B) dosed with 0.1 mg/kg/day. The ChE activity of plasma and RBCs of those dogs showing a significant depression while receiving test diets for 1 year returned to normal after the dogs were fed control rations for 2 weeks and 3 months, respectively.

There were no significant decreases in brain ChE activity, at any dose level, in the dogs sacrificed after 1 year (phase A). After 2 years of treatment, the brain ChE activities appeared to be slightly depressed in the 3.0 mg/kg/day group, although the mean values were not statistically different from the controls. Gross and microscopic examination of tissues revealed no alterations related to chronic chlorpyrifos exposure. The authors concluded that dogs can tolerate chlorpyrifos doses up to 0.03 mg/kg/day without experiencing significant toxicological effects [McCollister *et al.*, 1974; McCollister *et al.*, 1973].

E. Reproductive Effects and Teratogenicity

1. Human

- *in vitro, humans*

Chlorpyrifos was one of several environmental pollutants tested on human sperm to evaluate its reproductive effects. Normozoospermic semen samples (N=5) containing 10^6 spermatozoa resuspended in 1 ml medium were incubated with chlorpyrifos at concentrations of 0.1, 1.0, 10, 100, or 1000 ng. Chlorpyrifos showed a time- and dose-dependent effect on sperm motility (not significant), forward progression (not significant), hypoosmotic swelling(not significant), vitality($P<0.05$), and the induction of the acrosome reaction($P<0.05$). The authors concluded that under *in vitro* conditions, this compound can have an adverse effect on human sperm function and functional membrane integrity, and could possibly impair the process of fertilization [Roediger *et al.*, 1987].

2. Animal Data

Reproductive Effects

- *oral, rats*

The Dow Chemical Company (1972) conducted an unpublished three generation reproduction study to evaluate the reproductive and postnatal effects of dietary chlorpyrifos. Groups of 30 Sprague-Dawley albino rats (15 male and 15 female) were given feed supplemented with chlorpyrifos at concentrations of 0.1, 0.3, or 1.0 mg/kg/day. The fist generation rats received diets containing chlorpyrifos at concentrations of 0.03, 0.1, or 0.3 mg/kg/day and the second and third generations received dietary levels of 0.1, 0.3, or 1.0 mg chlorpyrifos/kg/day.

Chlorpyrifos exposure had no adverse reproductive effects in rats based on fertility, gestation, viability, and lactation indices. The litter size, pup weight, and sex ratios of offspring were also not affected by chlorpyrifos. In addition, ingestion of chlorpyrifos by first-, second- and third-generation rats had no adverse effects on survival, body weight gains, and food consumption of either male or female parents. Third generation male and female rats that consumed 1.0 mg/kg/day and third-generation females that consumed 0.3 mg kg/day had depressed plasma and erythrocyte ChE activities. The authors concluded that doses of chlorpyrifos up to 1.0 mg/kg/day have no detrimental reproductive effects in rats. A reproductive no observed adverse effect level (NOAEL) was determined to be 0.1 mg/kg/day [USEPA, 1990].

- *oral, mice*

  In a study described below (Deacon *et al.*, 1980) which was carried out to assess the developmental effects of chlorpyrifos in CF-1 mice, concentations of chlorpyrifos ranging from 0.1 - 25 mg/kg/day (administered on days 6-15 of gestation) were not found to affect any of the reproductive parameters evaluated. Specifically, the number of litters, and the average numbers of implantation sites/dam, live fetuses/litter, resorptions/litter, as well as the percentage of dead fetuses and the fetal sex ratio were comparable in the control and treatment groups [Deacon *et al.*, 1980].

- *dermal, dogs*

  The Dow Chemical Company (1972) reported the results of an unpublished reproductive study in dogs. Twelve dogs were dipped one to four times at 15- or 30-day intervals. Animals were either not pregnant, or up to 58 days pregnant, at the time of the first dip (average gestation period was 63±7 days). The report stated that multiple exposures to chlorpyrifos (0.025, 0.05, or 0.10% solutions) via dipping produced no maternal toxicity in mongrel dogs and had no effect on gestation or parturition [USEPA, 1990].

- *dermal, cattle*

  The effects of chlorpyrifos on semen production were studied in artificial insemination (AI) Holstein bulls. Chlorpyrifos (Dursban 44®) was applied to the backs of 185 young bulls (aged 9-52 months old). Seven bulls died and 27 more required medical attention including 6 bulls which were classified as very sick. Following recovery of the treated bulls, semen was collected and the effect of chlorpyrifos on semen characteristics, including volume of ejaculate, concentration of sperm, prefreeze percent motile sperm, total sperm per ejaculate, post-thaw motility, percent prefreeze discards, and percent post-thaw discards .

  Exposure to chlorpyrifos negatively influenced ejaculate volume, motility, total prefreeze discards, and percent post-thaw discards in the 6 sick bulls. The percentage of post-thaw discards was increased for up to six months in the chlorpyrifos treated bulls [Everett, 1982].

Developmental Effects

- *oral, rats*

  The Dow Chemical Company concluded that chlorpyrifos was not teratogenic in rats, as judged by external, skeletal, and visceral examination of second-litter fetuses from third-generation Sprague-Dawley female rats administered the compound by gavage at 1.0 mg/kg/day on days 6-15 of gestation. Parental females received chlorpyrifos in the diet at levels of 0.1, 0.3, or 1.0 mg/kg/day for the duration of their lives. Maternal weight gain and food consumption, corpora lutea, resorptions, fetus viability, pup weights, and sex ratios also appeared to be unaffected [USEPA, 1990].

oral, mice

The developmental effects of chlorpyrifos were studied by Deacon *et al.* in CF-1 mice. On days 6-15 of gestation, groups of pregnant mice (N=40-47) were gavaged with chlorpyrifos in cottonseed oil at concentrations of 1, 10, or 25 mg/kg/day. A control group (N=51) was administered an equivalent volume of cottonseed oil without test material. The dams were observed daily for signs of toxicity beginning on day 6 of gestation. Maternal body weights were recorded on days 6-16 and 18. On day 18 of the study, the animals were sacrificed and maternal body weight, the weight of maternal livers and gravid uteris including ovaries were recorded. The numbers and positions of live, dead, and resorbed fetuses were noted. The uteri of nonpregnant dams were examined for early resorption sites. The fetuses were weighed, measured (crown to rump), sexed, and examined for external alterations and cleft palate. One third of each litter was examined for soft tissue and skeletal alterations. To evaluate the clinical effects of chlorpyrifos on erythrocyte and plasma cholinesterase (ChE) activity, additional groups of 4-10 bred mice were dosed with 0, 0.1, 1, 10, or 25 mg/kg/day of chlorpyrifos on either day 6, day 6-10, or day 6-15 of gestation. Five hours after the final dosing (day 6, 10, and 15, respectively), blood was collected from the animals by cardiac puncture. A homogenate of fetuses from the litters of mice sacrificed on day 15 of gestation was prepared to measure total fetal ChE levels.

Severe maternal toxicity was observed in the high dose group (25 mg/kg). The incidence of maternal deaths increased significantly ($P<0.05$) in this dose group over the concurrent control value. One animal from each of the other 2 dose groups died on days 16 (10 mg/kg) and 10 (1 mg/kg) of gestation. In addition, the mean body weight of the mice in the high dose group was significantly decreased ($P<0.05$) compared to controls. Mean body weight gains among the dams in the other dose groups were comparable to the control values. Chlorpyrifos had no significant effect on maternal liver, gravid uterus, or adjusted body weights (maternal body weight minus gravid uterus) in any of the dose groups. The amount of food and water consumed was significantly decreased (no P value given) in the 25 mg/kg dose group only.

Symptoms indicative of severe ChE inhibition such as excessive salivation, tremors, urine-soaked coat, ataxia, and lethargy were observed in 32 of 47 animals given 25 mg/kg. Mild to moderate signs of ChE inhibition were observed in 9/44 animals in the 10 mg/kg/day dose group; and only 1/40 animals receiving 1 mg/kg chlorpyrifos was observed to salivate excessively. Both plasma and erythrocyte ChE levels in mice given 10 and 25 mg/kg chlorpyrifos on day 6, days 6-10, and days 6-15 of gestation were significantly decreased ($P<0.05$). Plasma ChE levels in mice receiving 1 mg/kg chlorpyrifos were significantly decreased ($P<0.05$) at the same interval. Administration of 1 mg/kg chlorpyrifos on days 6-10 of gestation also resulted in a significant reduction ($P<0.05$) in erythrocyte ChE. Fetal ChE levels were also significantly ($P<0.05$) decreased among the fetuses from dams given 10 or 25 mg/kg of chlorpyrifos on days 6 through 15 of gestation.

The average number of litters, implantation sites/dam, live fetuses/litter, and resorptions/litter were not affected by exposure to chlorpyrifos. Two dead fetuses were observed in the 10 mg/kg dose group but not in any of the other experimental groups. The fetal weight and crown to rump lengths were significantly decreased ($P<0.05$) in the litters from dams given 25 mg/kg chlorpyrifos.

The incidence of total major malformations were slightly increased ($P=0.0566$) in the 1 mg/kg dose group, but not in the 10 or 25 mg/kg dose groups. Litters from the 1 mg/kg dose group had a significantly ($P<0.05$) increased incidence of exencephaly compared to control values. In addition, a significant increase ($P<0.05$) in the incidence of unfused sternebrae and a significant decrease ($P<0.05$) in the incidence of fused sternebrae were observed among litters from the 1 mg/kg dose group. Significant increases in the occurrence of several minor skeletal variants were seen in litters of mice from the 25 mg/kg dose group. Table 11 summarizes the incidences of fetal alterations in each group.

These results were not repeatable when Deacon *et al.*, tested additional groups of 35-41 bred mice dosed with 0, 0.1, 1, or 10 mg/kg/day chlorpyrifos on days 6-15 of gestation using the same experimental design. At these dose levels, no evidence of maternal toxicity was observed with the exception of significantly ($P<0.05$) decreased plasma ChE levels among dams administered 1 or 10 mg/kg chlorpyrifos on day 6, days 6-10, and days 6-15. Erythrocyte ChE levels were also significantly ($P<0.05$) decreased from control values among mice given 10 mg/kg chlorpyrifos at the same time intervals and in mice administered 1 mg/kg test compound on days 6-10 or days 6-15 of gestation. No effect on the plasma or erythrocyte ChE levels was observed at the 0.1 mg/kg dose level. The fetal ChE levels were slightly less (not significant) than control values among litters from the 10 mg/kg dose group; no effects on fetal ChE levels were observed in the other dose groups.

No effects were observed at any dose level with respect to the average number of litters, implantation sites/dam, live fetuses/litter, and resorptions/litter or fetal measurements. In addition, no single malformation occurred at an incidence which was significantly greater than the control group. When considered collectively, the incidence of total malformations was not significantly different from the controls. The incidence of exencephaly was not altered in this phase of the study. In the 10 mg/kg dose group, significant decreases ($P<0.05$) in the incidence of delayed ossification of the skull bones and in delayed ossification of the sternebrae were observed. A nonsignificant decrease in delayed ossification of the skull bones was also observed in the 1 mg/kg dose group, these occurrences are not considered to be indicitive of fetotoxicity, or to have toxicological significance.

The authors concluded that chlorpyrifos was not teratogenic in mice dosed at concentrations up to 25 mg/kg/day. They further report that fetotoxicity, as evidenced by the increased occurrence of severe skeletal variants and decreased fetal body measurements observed during the first phase of the study, was a result of a dosage that was toxic to the mother [Deacon *et al.*, 1980].

- ***dermal, dogs***

  In conjunction with the reproductive study by the Dow Chemical Company (USEPA, 1990) described previously, it was reported that 58 of the 85 (68%) pups born to the dogs repeatedly dipped in chlorpyrifos (0.025, 0.05, or 0.10% solutions) died before 8 weeks of age. It was reported that only one of the mortalities was directly related to the chlorpyrifos exposure [USEPA, 1990].

Table 11. Incidence of Fetal Alterations Among Mice Administered Chlorpyrifos

	Chlorpyrifos (mg/kg/day)			
	0	1	10	25
	No. of fetuses examined/No. of litters examined			
External and skeletal examination	408/36	347/29	359/30	326/29
Soft tissue examination	142/36	115/29	122/30	111/29
Bones of the skull	226/34	232/29	237/30	215/28
External No. fetuses (litters) affected				
Exencephaly	1 (1)	5 (5)[a]	1 (1)	4 (3)
Ablepharia	1(1)	1 (1)[b]	1 (1)[b]	2 (2)[b]
Cleft palate	0	2 (2)	1 (1)	2 (1)
Soft tissue examination				
Small cerebral hemisphere	1 (1)	1 (1)	1 (1)	0
Skeletal examination				
Multiple defects[c]	0	0	1 (1)	0
Ribs, fused (1)01 (1)0				
Skull, delayed ossification[d]	5 (5)	9 (5)	10 (6)	34 (10)[a]
Sternebrae, delayed ossification[d]	37 (17)	24 (11)	19 (11)	78 (22)[a]
Sternebrae, unfused[d]	2 (2)	7 (6)[a]	3 (3)	8 (7)[a]
Sternebrae, fused[d]	24 (16)	9 (6)[a]	23 (12)	6 (5)[a]
Total major malformations	4 (4)	8 (8)[e]	5 (5)	6 (4)

a – Significantly different from the control value, P<0.05.

b – Ablepharia was observed in fetuses exhibiting exencephaly.

c – This fetus exhibited occipital bone one-half normal size; fused cervical vertebrae; elongated thoracic vertebrae; bilobed, misshapen, fused and misaligned thoracic centra; and misshapen and misaligned ribs.

d – This alteration was considered to be a skeletal variant and was not included in the calculation of the total malformed fetuses.

e – P=0.0566

Deacon *et al.*, 1980

F. Genetic Toxicology

1. Human Data

No data were found .

2. Prokaryotic and Eukaryotic Data

The genotoxic effects of chlorpyrifos in prokaryotic and eukaryotic organisms are summarized below in Tables 12 and 13, respectively. Table 14 presents the data on *in vivo* genotoxicity and Table 15 summarizes the genotoxicity of this compound in plants.

Table 12: The Genotoxicity of Chlorpyrifos in Prokaryotic Organisms

Test organism (strain)	Genetic endpoint	Dose	Test Conditions[a]	Response	Reference
Salmonella typhimurium (TA97, TA98, TA100, TA1530, TA1535)	reverse gene mutations	0-200 µg/plate	- metabolic activition	negative	Vishwanath and Jamil, 1986
S. typhimurium (TA98, TA100, TA102, TA1535, TA1538)	reverse gene mutations	0.1 ml[b]	+ rat liver S9 activation	negative	Choi *et al.*, 1985
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	reverse gene mutations	0-5,000 µg/plate[b]	+ rat liver S9 activation	negative	Moriya *et al.*, 1983
S. typhimurium (SL4525, SL4700)	DNA damage	NR[c]	- metabolic activation	negative	Sandhu *et al.*, 1985
S. typhimurium (TA100, TA1535, TA1537, TA1538)	reverse gene mutations	1-1,000 µg/plate	+/- rat liver S9 activation	negative	USEPA, 1977
S. typhimurium (TA92, TA98, TA100, TA1535, TA1537, TA2637)	reverse and forward (TA98, TA100) gene mutations	0-1 mg/plate	-/+ rat, mouse and hamster liver S9 activation	negative	Remondelli *et al.*, 1986
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	reverse gene mutations	NR	+/- rat liver S9 activation	negative	Gentile *et al.*, 1982
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	reverse gene mutations	extracts of treated *Zea mays* (B37) exposed (NR concentration)	+ plant activation	negative	Gentile *et al.*, 1982
S. typhimurium (TA98, TA100)	reverse gene mutations	NR	+ metabolic activation	negative	Kawachi *et al.*, 1980a; 1980b
S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)	reverse gene mutations	NR	+/- rat liver S9 activation	negative	Gollapudi *et al.*, 1989
S. typhimurium (TA98, TA100)	reverse gene mutations	NR	+/- metabolic activation	negative	Shirasu *et al.*, 1982
Bacillus subtilis (NR)	rec assay	NR	+/- metabolic activation	negative	Kawachi *et al.*, 1980a; 1980b
Bacillus subtilis (H17 and M45)	rec assay (DNA damage)	2.5 mg	- metabolic activation	positive (one out of four assay procedures)	USEPA, 1977

Table 12: The Genotoxicity of Chlorpyrifos in Prokaryotic Organisms (Continued)

Test organism (strain)	Genetic endpoint	Dose	Test Conditions [a]	Response	Reference
Escherica coli (PQ37, PQ3703)	SOS induction	0-500 µg/ml	UV irradiated	negative	Ohta *et al.*, 1986
E. coli (WP2 hcr)	reverse gene mutations	0-5,000 µg/plate [b]	+/- rat liver S9 activation	negative	Moriya *et al.*, 1983
E. coli (WP2)	reverse gene mutation	1-1,000 µg/plate	+/- rat liver S9 activation	negative	USEPA, 1977
E. coli (NR)	SOS induction	NR	+/- rat liver S9 activation	negative	Xu and Schurr, 1990
E. coli (W3110 and P3478)	DNA damage	2.5 mg	- metabolic activation	positive (one out of four assay procedures)	USEPA, 1977

[a] Liver S9 fractions are from Arochlor-induced animals unless otherwise noted; + = with; - = without
[b] Applied as the commercial formulation Dursban®
[c] NR = Not reported

Table 13: The (*In vitro*) Genotoxicity of Chlorpyrifos in Eukaryotic Organisms

Test Organism (strain)	Genetic endpoint	Dose	Test Conditions[a]	Response	Reference
Human Lymphocyte	SCE[b] and chromosomal abberations	0.02-20.0 µg/ml	- metabolic activation	negative	Nelson *et al.*, 1990
Human Lymphocyte (LAZ-007)	SCE	0.02-20.0 µg/ml[c]	+/- rat liver S9 activation[d]	positive at 2 and 20 µg/ml (P<0.01)	Sobti *et al.*, 1982
Human Lymphocyte (LAZ-007)	- SCE	0.024-2.4 µg/ml[c]	NR[e]	positive (35-128% increase)	Sobti *et al.*, 1981
	- chromosomal aberrations			positive at 2.4 µg/ml	
	- cell cycle traverse			negative	
Human lung fibroblasts (WI-38)	unscheduled DNA synthesis	$0\text{-}10^{-3}$ M	+/- mouse liver S9 activation	negative	USEPA, 1977
Rat hepatocytes (Fisher 344)	unscheduled DNA synthesis	NR	NR	negative	Gollapudi *et al.*, 1989
Chinese hamster ovary cells (K_1-BH_4)	forward mutations	NR	+/- rat liver S9 activation	negative	Gollapudi *et al.*, 1989
Chinese hamster ovary cells (K_1-BH_4)	SCE and chromosomal aberrations	1.0-100 µg/ml	- metabolic activation	negative	Muscarella *et al.*, 1984
Hamster lung fibroblasts (NR)	chromosomal aberrations	NR	+ metabolic activation	positive (P value NR)	Kawachi *et al.*, 1980a; 1980b
Silkworm (NR)	mutations	NR	NR	negative	Kawachi *et al.*, 1980a; 1980b
Saccharomyces cerevisiae (D4)	mitotic gene conversion	NR	+/- rat liver S9 activation	negative	Gentile *et al.*, 1982
Saccharomyces cerevisiae (D4)	mitotic gene conversion	extracts of treated *Zea mays* (B37) (concentration NR)	+ plant activation	negative	Gentile *et al.*, 1982
Saccharomyces cerevisiae (D3)	mitotic recombination	5% w/v	+/- rat liver S9 activation	negative	USEPA, 1977

[a] Liver S9 fractions are from Arochlor-induced animals unless otherwise noted; + = with; - = without
[b] SCE = sister chromatid exchanges
[c] Applied as the commercial preparation Dursban®
[d] Liver S9 fractions were obtained from phenobarbitol-incuced rats
[e] NR = Not Reported

Table 14 The *In Vivo* Genotoxicity of Chlorpyrifos in Eukaryotic Organisms

Test Organism (strain and sex)	Genetic Endpoint	Dose and Route	Response	Reference
Drosophila melanogaster (Canton-S males)	sex-linked recessive lethals	0.1 ppm by feeding [a]	negative	USEPA, 1981
D. melanogaster (NR)	partial and complete chromosome loss	50 ppb by feeding NR[b]	positive (P<0.05) for complete loss	Woodruff et al., 1983
Rat (NR)	chromosomal aberrations in bone marrow cells	NR	negative	Kawachi *et al.*, 1980a; 1980b
Mouse (NR)	micronucleus test in bone marrow cells	30.5 mg/kg orally [a]	positive (P value NR)	Benova *et al.*, 1989a; 1989b
Mouse (Swiss, sex NR)	micronucleus test in bone marrow cells	intraperitoneal: 5-30 mg/kg 2x/week for 1-3 weeks dermal: 99 ppm 2x/week for 1-2 weeks oral: 80 and 240 ppm for 1-14 days, and 120 ppm for 2-10 weeks	positive (P<0.01) negative positive (P<0.01 and 0.05)	Amer and Fahmy, 1982
Mouse (CD-1, sex NR)	micronucleus test in bone marrow cells	NR (oral)	negative	Gollapudi *et al.*, 1989

[a] Chlorpyrifos applied as the commercial preparation Dursban®
[b] NR = Not reported

Table 15: The Genotoxicity of Chlorpyrifos in Plants

Test Organism (strain)	Genetic endpoint	Concentration	Results	Reference
Zea mays (W22)	reverse and forward gene mutations in gametophytes	*in situ* treatment with 2.24 kg/hectare	negative	Plewa, 1985; Plewa and Wagner, 1981, Gentile *et al.*, 1982
Allium cepa L. (NR)	chromosomal aberrations	1-hour pulse exposure of roots to 50-150 ppm	positive (P value NR)	Rao *et al.*, 1988
Hordeum vulgare L. (NR)	chromosomal aberrations and chlorophyll mutations in M2 generation	0.2-1.0%	positive (P value NR)	Grover and Kaur, 1981
Barley root tips (NR)	chromosomal aberrations	soil treated with 5.70 mg/kg	positive (P value NR)	Grover *et al.*, 1990
Vicia faba (V. Giza I)	abnormal pollen mother cells	- seedlings sprayed for 4 consecutive days - sprayed once as seedlings at flowering stage - flowering plants sprayed once and for 2-4 consecutive days	positive ($P<0.05$) positive ($P<0.01$) positive ($P<0.01$ and 0.05)	Amer and Farah, 1983

NR = Not reported

G. Other Toxicological Effects

3. Biochemistry

- ***oral, rats***

  Chlorpyrifos was found to inhibit liver esterase activity in female Sprague-Dawley rats following oral administration at unspecified concentrations for 15 days. The inhibitory effect on liver carboxyesterase was observed at lower concentrations than were required to inhibit ChE and carboxyesterase activities in red cells, plasma, and brain [Killeen and Griffen, 1972].

- ***oral, rats***

  The ability of chlorpyrifos to inhibit hormone-sensitive lipase (HSL) and lipoprotein lipase (LPL) of rat adipose tissue was evaluated in four groups of male and female Sprague-Dawley rats maintained on a fat enriched or normal diet supplemented with 100 ppm chlorpyrifos (Dursban®) for one year. Chlorpyrifos was not found to have an effect on HSL, the enzyme responsible for fatty acid mobilization formadipose tissue triglyceride or LPL, the enzyme involved in the uptake of circulating triglyceride fatty acids [Buchet *et al.*, 1977].

- ***oral, rabbits***

  The effect of chlorpyrifos on aminotransferase was studied by administering a single oral dose of 100 ppm chlorpyrifos to 4 male and 4 female rabbits *(oryctolagus cuniculus)* and measuring blood plasma glutamic oxaloacetic transaminase (GOT-ase) and glutamic pyruvic transaminase (GPT-ase) activities. Increasing levels of GOT-ase activity were recorded on days 5 and 37, and on days 6, 15, 27, and 41 following administration in males and females, respectively. These peaks were followed by considerable depressions in enzyme activity in both sexes. GOT-ase activities in treated males and females did not return to normal levels and significantly (P value not specified) lower enzyme levels compared to controls were observed after 47 days. With GPT-ase, two sharp increases in the level of activity were followed by significant depressions in both males and females. By the end of the experiment, GPT-ase activity was lower in test males than control males, but higher in chlorpyrifos-treated females than controls [Afifi and Zidan, 1986].

- ***inhalation, rats***

  The effect of chlorpyrifos on rat whole blood serotonin concentrations was assessed by exposing rats to aerosols containing a particulate chlorpyrifos concentration of 38 mg/kg. Serotonin levels, which have been reported to be elevated in animals under stress, were not found to be elevated following exposure to chlorpyrifos [Berteau and Deen, 1976].

- ***intraperitoneal, rats***

  The effect of chlorpyrifos on serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) activities following intraperitoneal administration of Dursban® in male Sprague-Dawley rats has been described. Significant ($P \geq 0.05$) increases compared to controls in the activities of both GOT and GPT were observed [Mikhail *et al.*, 1979].

- ***intraperitoneal, mice***

  The inductive effect of chlorpyrifos on the hepatic cytochrome P-450 dependent monoxygenase system was investigated in 4 ICR-Dublin male mice intraperitoneally injected with 25 mg chlorpyrifos/kg in 50 µl of corn oil for 3 consecutive days. Based on significant ($P \leq 0.05$) increases in p-nitroanisole relative to liver and protein weights in treated animals compared to controls, chlorpyrifos was determined to induce mixed function oxidases [Fabacher *et al.*, 1980].

- ***intraperitoneal, mice***

  Male mice of unspecified strain were used to study the alkylating properties of chlorpyrifos on guanine (N-7 position) in nucleic acids prepared from mouse livers. An unspecified number of mice were injected interperitoneally with 5 or 15 mg/kg ^{14}C-chlorpyrifos and sacrificed 6, 24, 48, or 192 hours after dosing. The incorporation of ^{14}C increased in a dose-dependent manner and was found to be greater in RNA than DNA, with the amount of radioactivity in both nucleic acids decreasing rapidly with time. Chlorpyrifos was concluded to be a potent alkylating compound compared to other organophosphates (with methyl esters) previously studied by these authors [Mostafa *et al.*, 1983].

- ***intraperitoneal, mice***

  The extent of glutathione (GSH)-dependent detoxification of chlorpyrifos and chlorpyrifos oxon was studied in 4 male Charles River albino mice following intraperitoneal injection with 70 mg/kg chlorpyrifos in dimethyl sulfoxide. The addition of a GSH to incubation mixtures was found to significantly ($P < 0.05$) increase the degradation of chlorpyrifos oxon. The authors noted that since incubation of chlorpyrifos oxon with GSH-fortified boiled supernatant fraction did not result in any significant loss of substrate, the degradative activity was the result of enzymatic processes. Chlorpyrifos did not appear to be a substrate for GSH- transferases; this pesticide was found to produce only a transient, moderate reduction in the GSH content after a 16- hour incubation [Sultatos *et al.*, 1982].

- ***intraperitoneal/oral, mice***

  The effect of intraperitoneal and oral pretreatment with chlorpyrifos ($\geq$ 100 mg/kg for 3 days) on male ICR mouse hepatic glutathione (GSH) S-epoxide S-aryl, or S-aralkyl transferase activities was evaluated. Chlorpyrifos was found to cause a small depression in GSH S-epoxide transferase activity, while GSH S-aralkyl activity was slightly elevated. A significant ($P \leq 0.05$) increase in GSH-aryl activity compared to the control was observed [Kulkarni *et al.*, 1980; Kulkarni *et al.*, 1978].

- ***in vitro, human***

  The effect of slow-release insecticide strips containing chlorpyrifos (Dursban®) on the inhibition of monocyte esterase activity was evaluated using human monocytes. Chlorpyrifos was found to marginally inhibit human monocyte esterase based on its fifty percent inhibition value ($ID_{50} = 1.8 \times 10^{-2}$ g/liter blood) [Lee and Waters, 1977].

- ***in vitro, rats***

  Chlorpyrifos was one of several organophosphorus anticholinesterase compounds studied to determine its effect on rat cardiac muscarinic receptors. The hearts from male Sprague-Dawley rats were removed and the M_2 subtype of muscarinic receptor was isolated and incubated with 5 nM (+)-[^{3}H] *cis*-methyldioxolane {[^{3}H]CD) and either 0.1 or 1.0 µM chlorpyrifos to determine its ability to inhibit [^{3}H]CD binding. The authors found that chlorpyrifos significantly inhibited (no P value given) [^{3}H]CD binding at 1.0 µM, however, it was the least potent [^{3}H]CD binding inhibitor tested. Thus, it was concluded that chlorpyrifos does not greatly influence cardiac function [Silveira *et al.*, 1990].

- ***in vitro, rats***

  The effect of chlorpyrifos on adrenal corticosterone formation was studied on adrenal cells from male Sprague-Dawley rats which were incubated with Dursban® at concentrations ranging from 10^{-7} to 10^{-4}M in the presence of adrenocorticotropic hormone (ACTH), adenosine 3', 5'-monophosphate (cAMP), and it was determined that chlorpyrifos depressed endogenous corticosterone synthesis at concentrations ranging from 5.7×10^{-6} to 1×10^{-4}M ($P < 0.05$) and blocked corticosteroidogenesis in response to CTH and cAMP stimulation at a concentration of 10^{-4}M ($P < 0.05$) [Ciren and Brown, 1974].

- *in vitro, rats*

The oxidative desulfuration of chlorpyrifos was studied in rat brain and liver to assess whether monooxygenase activity (*i.e.*, activation to an oxon metabolite) is a major determinant of the level of acute toxicity of chlorpyrifos. Microsomal fractions were prepared from brain and liver samples collected from adult male and female Sprague-Dawley rats, and were incubated with 50 μM chlorpyrifos in an NADPH-generating system for 30 (brain) or 2 (liver) minutes. Thirty-two milligrams of a bovine brain particulate preparation was also present throughout the incubation as an exogenous source of acetylcholinesterase (AChE). Hepatic microsomal desulfuration activity was observed to be significantly ($P<0.05$) higher in males compared to females. Chlorpyrifos was activated by brain microsomal and crude mitochondrial fractions, but to a very low extent with no differences between the sexes. The desulfuration activity observed for the liver microsomes was approximately 2100-fold greater than the combined activity of the brain mitochondria and brain microsomes. From the data, the authors state that brain oxidative desulfuration correlates well with the acute toxicity of chlorpyrifos (relative to other phosphorothionate insecticides), and it may prove to be an important factor in determining overall acute toxicity levels of phosphorothionate insecticides [Chambers and Chambers, 1989].

- *in vitro, rats*

As described in an abstract by a Japanese author, the effect of chlorpyrifos on mitochondrial oxidative phosphorylation in the rat liver was investigated. Chlorpyrifos was found to decrease respiration (States 3 and 4) in a dose-dependent manner and was also observed to stimulate latent ATPase activity. However, DNP-stimulated ATPase activity was not affected. Sakai concluded that this compound impedes mitochondrial oxidative phosphorylation [Sakai, 1990].

- *in vitro, mice*

The hepatic microsomal activation and detoxification of chlorpyrifos were evaluated *in vitro* using microsomal fractions from male albino mice incubated with chlorpyrifos at concentrations of 7.95-170 μM. The incubation of mouse hepatic microsomes in the presence of chlorpyrifos resulted in the activation of this compound to chlorpyrifos oxon and its detoxification to 3, 5, 6-trichloro-2-pyridinol. From kinetic parameters using direct linear plots, the appKms describing microsomal production of chlorpyrifos oxon and 3, 5, 6-trichloro-2-pyridinol were 20.90±3.24 and 16.12±3.40 μM, respectively. The appVmaxs for the same reactions were 3.91±0.16 nmols/100 mg liver/min and 8.13±0.29 nmols/100 mg/liver, respectively. The cytochrome P-450 monooxygenase system was implicated in these reactions, as evidenced by the requirement for NADPH and inhibition by carbon monoxide [Sultatos and Murphy, 1983].

H. Aquatic Toxicity

The acute toxicity of chlorpyrifos in aquatic organisms is summarized below in Table 15, which reports on LC_{50} (96-hour) values in fresh and salt water invertebrates and fish. Additional effects of chlorpyrifos exposure on these organisms are detailed in the bullets that follow.

- Fathead minnow larvae (*Pimephales promelas*) exposed to approximately 2.10 µg/L of chlorpyrifos continuously for 30 days, or to 317 µg/L for 1 hour, developed significantly more (P value not reported) deformities than control larvae. In addition, growth was significantly inhibited in larvae exposed to ≥272 ± 43.84 µg/L for 3 hours or ≥411 ± 2.8 µg/L for 5 hours. Fish exposed to 7.08 ± 0.09 µg/L for 30 days had a 34.7% lower survival rate than control larvae [Jarvinen *et al.*, 1988].

- In a life-cycle test with fathead minnows, 35 newly hatched larvae were grown in chambers with chlorpyrifos concentrations ranging from 0.12-2.68 µg/L for 60-200 days. A second generation of larvae was exposed to these concentrations for 30 days. In the first generation, survival was significantly decreased at the two highest doses (1.21 and 2.68 mg/L), and deformities (constriction of body, fattening of the body behind constriction, and a shortening of the caudal peduncle) occurred in the 2.68 µg/L dose group after only 30 days of exposure. Brain acetylcholinesterase activities of the first generation were significantly inhibited at doses ≥0.27 µg/L. Chlorpyrifos exposure also affected the maturity and reproductive processes of the fish, by reducing the number of sexually mature adults, the number of spawns, egg production (at doses ≥0.63 µg/L), and embryo hatchability (in the 2.68 µg/L dose group). Chlorpyrifos was more toxic to second generation fish, inhibiting growth at every dose level, and inducing deformities at 1.21 and 2.68 µg/L [Jarvinen *et al.*, 1983].

- In the 28-day life-cycle test with the mysid (*Mysidopsis bahia*), survival and reproduction were reduced at a chlorpyrifos concentration of 42 µg/L, and growth was significantly reduced (P value not reported) at only 0.004 µg/L. Of six other saltwater fish exposed to chlorpyrifos in early life-stage toxicity tests (details not reported), the California grunion was the most sensitive, with decreased weight as the most sensitive endpoint [USEPA, 1986].

- Many species of aquatic organisms have been found to bioaccumulate chlorpyrifos. In the fathead minnow, the mean bioconcentration factor (BCF) was 1,673 after 60 days [Jarvinen *et al.*, 1983]. In an experimental outdoor stream, the reported average BCFs for a fathead minnow and a bluegill were 590 and 100, respectively after exposures of 18-33 days. The BCF has been found to depend on the availability of food and the concentration of chlorpyrifos in the water [USEPA, 1986].

- Sublethal effects of chlorpyrifos on aquatic organisms include inhibition of ChE activities in brain and hematopoietic tissues, sluggishness, motor incoordination, delayed maturity and growth, reproductive abnormalities, and reduced feed intake. In addition, a loss of equilibrium was documented in 50% of brown shrimp (*Penaeus aztecus*) exposed to 0.32 µg chlorpyrifos/L for 24 hours [USDI, 1988].

Table 15: Acute 96-Hour LC_{50} Data for Chlorpyrifos in Aquatic Organisims

Organism	LC_{50} (µg/L)	Reference
Fresh Water Vertebrates		
Cutthroat trout (*Salmo clarkil*)	18	USEPA, 1986
Rainbow trout (*Salmo gairdner*)	7.1-51.0	USEPA, 1986; USDI, 1988
Lake tout (*Salvelinus namaycush*)	98	USEPA, 1986; USDI, 1988
Goldfish (*Carassius auratus*)	>806	USEPA, 1986
Fathead minow (*Pimephales promelas*)	170-542	USEPA, 1986
Channel catfish (*Ictalurus punctatus*)	280-806	USEPA, 1986; USDI, 1988
Bluegill (*Lepomis marochirus*)	1.1-10	USEPA, 1986; USDI, 1988
Inland silverside (*Menidia beryllina*)	4.2	USDI, 1988
Salt Water Fish		
Sheepshead minnow (*Cyprinodon variegatus*)	136-270	USEPA, 1986; USDI, 1988
Mummichog (*Fundulus heterociltus*)	4.65	USEPA, 1986
Longnose killifish (*Fundulus similis*)	4.1	Schimmel *et al.*, 1983
California grunion (*Leuresthes tenuis*)	1.0-5.5	USEPA, 1986; USDI, 1988
Atlantic silverside (*Menidia menidia*)	0.5-4.5	USEPA, 1986; USDI, 1988
Tidewater silverside (*Menidia peninsulae*)	0.4-4.2	USEPA, 1986; USDI, 1988
Striped bass (*Morone saxatilis*)	0.58	USEPA, 1986
Striped mullet (*Mugil cephalus*)	5.4	Schimmel *et al.*, 1983
Gulf toadfish (*Opsanus beta*)	520	USEPA, 1986; USDI, 1988
Fresh Water Invertebrates		
Snail (*Aplexa hypnorum*)	>806	USEPA, 1986
Amphipod (*Gammarus lacustris*)	0.11-0.32	USEPA, 1986
Amphipod (*Gammarus pseudolimnaeus*)	0.18	USEPA, 1986
Crayfish (*Orconectes immunis*)	6	USEPA, 1986
Stonfly (*Pteronarcella badia*)	0.38-10.0	USEPA, 1986
Stonefly (*Claassenia sabulosa*)	0.57	USDI, 1988
Pygmy backswimmer (*Neopiea striola*)	1.22-1.56	USEPA, 1986
Crawling water beetle (*Peitodytes*)	0.8	USEPA, 1986
Salt Water Invertebrates		
Eastern oyster (*Crassostrea virginica*)	1,991	USEPA, 1986
Mysid (*Mysidopsis bahia*)	0.035-0.056	USEPA, 1986; Shimmel *et al.*, 1988
Amphipod (*Ampelisca abdita*)	0.16	USEPA, 1986
Amphipod (*Rhepoxynius abronius*)	0.14	USEPA, 1986
Korean shrimp (*Palaemon macrodactylus*)	0.01-0.25	USEPA, 1986

I. Avian Toxicity

The acute avian toxicity (LD_{50}) of chlorpyrifos is presented below in Table 16. prechronic/chronic and reproductive/teratogenic effects of this compound in birds are summarized in Tables 17 and 18, respectively.

Table 16: Acute Toxicity of Chlorpyrifos in Avian Species

Organism	LD_{50} (mg/kg)	Reference
Chickens/White, Leghorn	34.8 (29.3-40.4)	Miyazaki and Hodgson, 1972; McCollister *et al.*, 1974
European Starling	5	USDI, 1988
Ring-necked pheasant	8.41-17.1	Hudson *et al.*, 1984
Common grackle	13	USDI, 1988
House sparrow	10-21	USDI, 1988; Hudson *et al.*, 1984
Japanese quail	13.7-15.9	USDI, 1988; Hudson *et al.*, 1984
Sandhill crane	25-50	USDI, 1988; Hudson *et al.*, 1984
Rock dove	26.9	Hudson *et al.*, 1984
Crow	>32	USDI, 1988
Canadian goose	40-80	Hudson *et al.*, 1984
Chukar	60.7-61.1	Hudson *et al.*, 1984
Northern bobwhite	32-108	USDI, 1988
Mallard	14.5-83.3	USDI, 1988
Ringed turtle dove	157	USDI, 1988

Table 17: Effects of Acute, Prechronic and Chronic Exposure to Chlorpyrifos in Avian Species

Route	Species (Strain/sex)	Dose	Effect	Reference
Oral	Duck (Mallard NR[a])	56-562 ppm for 11 days	decreased food consumption, decreased body weight	Kenega *et al.*, 1979
Oral	Quail (Bobwhite/ NR)	single dose of 0.1-2.5 mg/kg	decreased brain ChE[b] ($P<0.01$) at 1.0, 1.5 and 2.0 mg/kg; 10-50% mortality ≥1.5 mg/kg	Cairns *et al.*, 1991
Oral	Chicken (White Leghorn/cockerel)	0.32-1280 ppm for 3 weeks	decreased weight gain, food consumption; death at 80-1280 ppm; brain lesions	Brust *et al.*, 1971
Oral	Chicken (White Leghorn/cockerel)	0.08-80 ppm for 4 weeks	decreased weight gain and blood ChE levels, and death at 80 ppm	Brust *et al.*, 1971
Oral	Chicken (Fayoumi/ female)	single dose of 32 mg/kg	ataxia, respiratory problems; decreased ChE, body weight, food consumption, egg production	Abbassy *et al.*, 1981
Oral	Chicken (White Leghorn/NR)	25-100 ppm for 4 weeks	decreased ChE activity	Schlinke, 1970
Oral	Chicken (White Leghorn/cockerel)	1 mg/kg, 3x/week for 30 weeks	decreased ChE levels	Miyazaki and Hodgson, 1972
Oral	Chicken (White Longhorn/hens)	25-200 ppm for 52 weeks	decreased ChE levels	Sherman and Herrick, 1973
Oral	Duck (Mallard/NS)	8 or 80 ppm for 3 months	decreased weight gain ($P<0.01$), ChE levels at 80 ppm	Meyers and Gile,1986; Gile, and Meyers 1986
Oral	Chicken (*gallus-gallus domesticus*/ femle)	60-150 mg/kg 2x/day for 5-6 days	delayed polyneuropathy	Capodicasa *et al.*, 1990

[a] NR = Not reported
[b] ChE = Cholinesterase

Table 18: Reproductive and Teratogic Effects of Chlorpyrifos in Avian Species

Route	Species (Strain)	Dose	Effect	Reference
REPRODUCTIVE				
Oral	Duck (Mallard)	8 or 80 ppm in diet	decrease ($P<0.05$) in number of hatchlings, and duckling survival in 80 ppm dose group	Meyers and Gile, 1986
Oral	Duck (Mallard)	80 ppm	decrease ($P<0.05$) in egg production and weight, and duckling size	Gile and Meyers, 1986
Oral	Chicken (NS)	100 ppm	decrease in fertility (15%), hatchability (17%)	Schom *et al.*, 1973
Oral	Chukar (NS)	100 ppm	increase in hatchability	Schom *et al.*, 1973
Oral	Quail (NS)	100 ppm	None	Schom *et al.*, 1973
TERATOGENIC				
Injection	Chicken (NS)	1.0 mg/egg	twisted necks, indented backs; edema	Schom *et al.*, 1973
Injection	Chukar (NS)	0.47 mg/egg	twisted backs and necks	Schom *et al.*, 1973
Injection	Quail (Bobwhite)	0.35 mg/egg	twisted necks and amuscular legs	Schom *et al.*, 1973
Immersion	Quail (Japanese)	30 seconds in 210-840 g/hectare	higher incidence ($P<0.04$) of deformities, longer hatching time ($P<0.05$) at 840 g/ha	Martin, 1990

VI. STRUCTURE ACTIVITY RELATIONSHIPS

Organophosphorus insecticides exert their toxic effects by inhibiting acetylcholinesterase. A variety of behavioral changes have been attributed to organophosphate short-term or long-term dosing, and in nearly all of the cases reported, there was a concomitant inhibition of acetylcholinesterase. Some organophosphorus compounds have been found to affect tissue carboxyesterases at doses below those affecting acetylcholinesterase [WHO, 1986].

Many organophosphorus insecticides are embryotoxic at doses that are toxic to the mother. Teratogenic effects (cerebellar hypoplasia) have been reported for trichlorophon in pigs [WHO, 1986]. In addition, teratogenic and embryotoxic effects associated with fenchlorphos have been observed in blue foxes; teratogenic effects caused by fenchlorphos were also reported for rabbits (increase in major skeletal malformations and cerebellar hypoplasia) [Fikes, 1990].

Various organophosphorus pesticides have been reported to show positive responses in *in vitro* mutagenicity tests and, according to the World Health Organization, it can be concluded that some organophosphorus pesticides are weakly mutagenic [WHO, 1986]. Specifically, dichlorvos has been found to be positive in *Salmonella*, in mouse lymphoma cells, and in *in vitro* cytogenetics assays. In addition, both dioxathion and dimethoate were positive in *Salmonella* and gave inconclusive results in cytogenetics assays. Diazinon was found be negative in *Salmonella*, mouse lymphoma cells, and *in vitro* cytogenetics assays [NTP, 1991].

Several organophosphorus pesticides have been evaluated for carcinogenic potential by the International Agency for Research on Cancer (IARC). In several cases, the conclusion was that acceptable tests had been performed with no evidence of carcinogenic potential, while in others, IARC reports that there was "limited evidence consisting of very small effects above the control background levels in lifetime studies [WHO, 1986]." For instance, dichlorvos is listed as a Group 3 carcinogen by IARC based on inadequate animal data and the absence of human data. This compound was found to cause a nonsignificant increase in esophagal tumors in male and female B6C3F1 mice fed dichlorvos in their diet at concentrations of 300 mg/kg and 600 mg/kg. However, when tested in the diet of male and female Osborne-Mendel rats at concentrations of 150 mg/kg and 300 mg/kg, no increase in tumor formation was observed [IARC, 1979]. In studies conducted by the National Toxicology Program (NTP), it was determined that there was some evidence of carcinogenic activity in male rats administered dichlorvos by gavage and equivocal evidence of carcinogenicity in female rats. In male and female mice that received this compound by gavage, some evidence (males) or clear evidence (females) of carcinogenicity was reported. In addition, diazinon, dioxathion, and dimethoate have been tested in 2-year bioassays by oral administration using male and female rats and mice and were found to exhibit no evidence of carcinogenicity [NTP, 1991].

Some of the chlorinated organophosphates are suspected of being capable of producing liver and kidney damage; however there is limited data to support the supposition [Clayton and Clayton, 1982]. One such chlorinated organophosphate, chlorpyrifos-methyl, was not found to be carcinogenic (or to produce liver and kidney damage) in rats or mice at dietary dose levels up to 3.0 mg/kg/day and 9.0 mg/kg/day, respectively [USEPA, 1985].

VII. REFERENCES

Abbassy, M.A., El-Nawawy, A.S. and El-Din, M.T., "Toxicity and Residues from Feeding Single Oral Doses of Chlorpyrifos and Pirimifos-Methyl to Fayoumi Laying Hens." Mededeligen van de Faculteit Landbouwwetenchappen, Rijksuniversiteit Gent, Vol. 46, No. 1 (1981), pp. 377-386.

Afifi, F.A. and Zidan, A.A., "Aminotranamiases Activity in Relation to the Oral Administration of a Single Dose of Chlorpyrifos Insecticide." Egyptian Journal of Physiological Sciences, Vol. 13, No. 1, 2 (1986), pp. 145-152.

Ahdaya, S. and Guthrie, F.E., "Stomach Absorption of Intubated Insecticides in Fasted Mice." Toxicology, Vol. 22 (1982a), pp. 311-317.

Ahdaya, S.M. and Guthrie, F.E., "Uptake of Insecticides by Intestinal Epithelial Cell Suspensions Isolated from Mice." Bulletin of Environmental Contamination and Toxicology, Vol. 29 (1982b), pp.76-83.

Ahdaya, S.M., Monroe, R.J. and Guthrie, F.E., "Absorption and Distribution of Intubated Insecticides in Fasted Mice." Pesticide Biochemistry and Physiology, Vol. 16 (1981), pp. 38-46.

Al-Samariee, A.I., Shaker, K.A.M. and Al-Bassomy, M.A., "Residue Levels of Three Organophosphorus Insecticides in Sweet Pepper Grown in Commercial Greenhouses." Pesticide Science, Vol. 22 (1988), pp. 189-194.

Amer, S.M. and Farah, O.R., "Cytological Effects of Pesticides. XIII. "Meiotic effects of the insecticide 'Dursban'." Cytologia, Vol. 48 (1983), pp. 557-563.

Amer, S.M. and Fahmy, M.A., "Cytogenetic Effects of Pesticides. I. Induction of Micronuclei in Bone Marrow by the Insecticide Dursban." Mutation Research, Vol. 101 (1982), pp. 247-255.

American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices, Fifth Edition. Cincinnati: ACGIH, 1986, p. 138.

American Conference of Governmental Industrial Hygienists, Inc (ACGIH). Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices for 1990-1991. Cincinnati: ACGIH, 1990, pp. 16-17.

Ames, R.G., Brown, S.K., Rosenberg, J., Jackson, R.J., Stratton, J.W. and Quenon, S.G., "Health Symptoms and Occupational Exposure to Flea Control Products among California Pet Handlers." American Industrial Hygiene Association Journal, Vol. 50, No. 9 (1989), pp. 466-472.

Anderson, D.J. and Hites, R.A., "Chlorinated Pesticides in Indoor Air." Environmental Science and Technology, Vol. 22, No. 6 (1988), pp. 717-720.

Asakawa, F., Jitsunari, F., Suna, S., Shiraishi, H., Manabe, Y., Gotoh, A. and Nakajima, T., "The Actual State of Occupational Exposure to Chlorpyrifos of Termite Control Workers." Nippon Eiseigaku Zasshi, Vol. 44, No. 4 (1989), pp. 921-928.

Benova, D.K., Roupova, I., Yagova, A., Vuglenov, A. and Bineva, M., "Mutagenicity Studies on Six Pesticides in Mice." Environmental and Molecular Mutagenesis, Vol. 14, Suppl. 15 (1989a), p. 19.

Benova, D.K., Ropova, I.M., Yagova, A.K.H. and Bineva, M.V., "The In Vivo Mutagenic Effects of the Pesticides Vastak and Dursban Studied by the Micronucleus Test in Mouse Bone Marrow." Genetika, Vol. 25, No. 12 (1989b), pp. 2266-2268.

Berteau, P.E. and Deen, W.A., "A Comparison of Oral and Inhalation Toxicities of Four Insecticides to Mice and Rats." Bulletin of Environmental Contamination and Toxicology, (1978), pp. 113-120.

Berteau, P.E. and Deen, W.A., "Changes in Whole Blood Serotonin Concentrations in Rats Exposed to Insecticide Aerosols." Toxicology Applied Pharmacology, Vol. 37, No. 1 (1976), p. 134.

Berteau, P.E., Knaak, J.B., Mengle, D.C. and Schreider, J.B., "Insecticide Absorption From Indoor Surfaces, Hazard Assessment and Regulatory Requirements." Biological Monitoring for Pesticide Exposure: Measurement, Estimation, and Risk Reduction, ACS Symposium Series, No. 382, Wang et al., *eds.*, Washington, D.C., 1989, pp. 315-326.

Brady, U.E., Tippins, R., Perry, J., Young, J.R. and Wauchope, R.D., "Chlorpyrifos Exposure of Workers Entering Sweet Corn after Chemigation." Bulletin of Environmental Contamination and Toxicology, Vol. 46 (1991), pp. 343-350.

Brenner, F.E., Bond, G.G., McLaren, E.A., Greene, S. and Cook, R.R., "Morbidity Among Employees Engaged in the Manufacture or Formulation of Chlorpyrifos." British Journal of Industrial Medicine, Vol. 46 (1989), pp. 133-137.

BRS Information Technologies, On-Line Database, June, 1991.

Brust, R.A., Miyazaki, S. and Hodgson, G.C., "Effect of Dursban in the Drinking Water of Chicks." Journal of Economic Entomology, Vol. 64, No. 5 (1971), pp. 1179-1183.

Buchet, J.P., Lauwerys, R. and Roels, H., "Long Term Exposure to Organophosphorus Pesticides and Lipid Metabolism in the Rat." Bulletin of Environmental Contamination and Toxicology, Vol. 17, No. 2 (1977), pp. 175-183.

Budavari, S., *et al.*, eds., The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals, Eleventh Edition. Rahway, New Jersey: Merck, 1989, p. 339.

Capodicasa, E., Scapellato, M.L., Moretto, A., Caroldi, S. and Lotti, M., "Chlorpyrifos-Induced Delayed Polyneuropathy." Archives of Toxicology, Vol. 65 (1991), pp. 150-155.

Cairns, M.A., Maguire, C.C., Williams, B.A. and Bennett, J.K., "Environmental Toxicology. Brain Cholinesterase Activity of Bobwhite Acutely Exposed to Chlorpyrifos." Environmental Toxicology and Chemistry, Vol. 10 (1991), pp. 657-664.

Cancerlit, On-Line database, August 1991.

Chambers, J.E. and Chambers, H.W., "Oxidative Desulfuration of Chlorpyrifos, Chlorpyrifos-Methyl, and Leptophos by Rat Brain and Liver." Journal of Biochemical Toxicology, Vol. 4, No. 3 (1989), pp. 201-203.

Cheng, T., Bodden, R.M., Puhl, R.J. and Bauriedel, W.R., "Absorption, Distribution, and Metabolism of [^{14}C]Chlorpyrifos Applied Dermally to Goats." Journal of Agricultural and Food Chemistry, Vol. 37 (1989), pp. 1108-1111.

Choi, E.J., Kim, Y.K. and Roh, J.K., "Genetic Toxicity of Pesticides Used in Korea on *Salmonella typhimurium* and *Saccharomyces cerevisiae*." Environmental Mutagens and Carcinogens, Vol. 5-1 (1985), pp. 11-18.

Citizens Against Pesticide Misuse (CAPM), 1989, Letter from Helen Auten, Director for Citizens Against Pesticide Misuse, to Dr. D. Rall, Director, National Toxicology Program, May, 1989.

Civen, M. and Brown, C.B., "The Effect of Organophosphate Insecticides on Adrenal Corticosterone Formation." Pesticide Biochemistry and Physiology, Vol. 4 (1974), pp. 254-259.

Clayborn, H.V., Hoffman, R.A., Mann, H.D. and Oehler, D.D., "Residues of Dursban and Its Oxygen Analog in the Body Tissues of Treated Cattle." Journal of Economic Entomology, Vol. 61, No. 4 (1968), pp. 983-986.

Clansky, J.B., Suspect Chemicals Sourcebook. California: Roytech Publications, 1989.

Clayton, G.D., and Clayton, F.E., Patty's Industrial Hygiene and Toxicology, Third Edition, Volume 2C. New York: John Wlley and Sons, 1982.

Corley, R.A., Calhoun, L.L., Dittenber, D.A., Lomax, L.G. and Landry, T.D., "Chlorpyrifos: A 13-Week Nose-Only Vapor Inhalation Study in Fischer 344 Rats." Fundamental and Applied Toxicology, Vol. 13 (1989), pp. 616-618.

Cowgill, U.M., Gowland, R.T., Ramirez, C.A. and Fernandez, V., "The History of a Chlorpyrifos Spill: Cartagena, Colombia." Environment International, Vol. 17 (1991), pp. 61-71.

Currie, K.L., McDonald, E.C., Chung, L.T.K. and Higgs, A.R., "Concentrations of Diazinon, Chlorpyrifos, and Bendiocarb after Application in Offices."American Industrial Hygiene Association Journal, Vol. 51, No. 1 (1990), pp. 23-27.

Davies, J.E., Enos, H.F., Barquet, A., Morgade, C. and Danauskas, J.X., "Pesticide Monitoring Studies. The Epidemiologic and Toxicologic Potential of Urinary Metabolites." Developments in Toxicology and Environmental Science, Vol. 4 (1979), pp. 369-378.

Deacon, M.M., Murray, J.S., Pilny, M.K., Rao, K.S., Dittenber, D.A., Hanley, T.R. and John, J.A., "Embryotoxicity and Fetoxicity of Orally Administered Chlorpyrifos in Mice." Toxicology and Applied Pharmacology, Vol. 54 (1980), pp. 31-40.

Dishburger, H.J., McKellar, R.L., Pennington, J.Y. and Rice, J.R., "Determination of Residues of Chlorpyrifos, Its Oxygen Analogue, and 3, 5, 6-Trichloro-2-pyridinol in Tissues of Cattle Fed Chlorpyrifos." Journal of Agricultural and Food Chemistry, Vol. 25, No. 6 (1977), pp. 1325-1329.

Dow Chemical Company, Acute Toxicological Properties of Dursban® 24 E Insecticide. Submitted by Norris, J.M. and Leong, B.K., Department of Pathology and Toxicology Human Health Research and Development Laboratories, Zionsville, Indiana, December, 1971.

Dow Chemical Company, The Clinical Toxicity of Dursban® in the Dog After Multiple Applications of a Dust Formulation. Submitted by Sharp, L.D. and Warner, S.D., Department of Pathology and Toxicology Human Health Research and Development Laboratories, Zionsville, Indiana, October, 1968.

Dow Chemical Company, Repeated Simultaneous Human Exposure to Aerosol and Dust Formulations of Dursban®. Submitted by Sharp, L.D. and Warner, D.D., Department of Pathology and Toxicology Human Health Research and Development Laboritories, Zionsville, Indiana, February, 1969.

DowElanco, Human Studies on Exposure to Chlorpyrifos: Technical Data Sheet, Date Unspecified.

DowElanco, Material Safety Data Sheet for Dursban® 2E Insecticide. May 1990. Indianapolis, Indiana.

DowElanco, Material Safety Data Sheet for Dursban® LO Insecticide. April 1991a. Indianapolis, Indiana.

DowElanco, Material Safety Data Sheet for Dursban® TC Termiticide Concentrate. January 1991b. Indianapolis, Indiana.

DowElanco, Material Safety Data Sheet for Lorsban® 4E Insecticide. August 1991c. Indianapolis, Indiana.

DowElanco, Telephone conversation with DowElanco representative, October 15, 1991d.

Dunphy, J., Kesselbrenner, M., Stevens, A., Vlec, B. and Jackson, R.J., "Pesticide Poisoning in an Infant — California." Morbidity and Mortality Weekly Report, Vol. 29, No. 33 (1980), pp. 254-255.

Edmiston, S. and Maddy, K.T., "Summary of Illnesses and Injuries Reported in California by Physicians in 1986 as Potentially Related to Pesticides." Veterinary and Human Toxicology, Vol. 29, No. 5 (1987), pp. 391-397.

El-Sebae, A.H., Ahmed, N.S. and Soliman, S.A., "Effect of Pre-Exposure on Acute Toxicity of Organophoshorus Insecticides to White mice." Journal of Environmental Science and Health, Vol., B13, No. 1 (1978), pp. 11-24.

Enan, E.E., El-Sebae, A.H., Enan, O.H. and El-Fiki, S., "*In-Vivo* Interaction of Some Organophosphorus Insecticides with Different Biochemical Targets in White Rats." Journal of Environmental Science and Health, Vol. B17, No. 5 (1982), pp. 549-570.

Everett, R.W., "Effect of Dursban 44 on Semen Output of Holstein Bulls." Journal of Dairy Science, Vol. 65 (1982), pp. 1781-1794.

Fabacher, D.L., Kulkarni, A.P. and Hodgson, E., "Pesticides as Inducers of Hepatic Drug-Metabolizing Enzymes-I. Mixed Function Oxidase Activity." General Pharmacology, Vol. 11 (1980), pp. 429-435.

Fakhr, I.M.I., El-Dardery, M., Mostafa, I.Y. and Zayed, S.M.A.D., "Short Term Toxicity Studies of Dursban and Gardona in Mice." Journal of the Egyptian Medical Association, Vol. 65 (1982), pp. 71-83.

Fenske, R.A., Black, K.G., Elkner, K.P., Lee, C., Methner, M.M. and Soto, R., "Potential Exposure and Health Risks of Infants Following Indoor Residential Pesticide Applications." American Journal of Public Health, Vol. 80, No. 6 (1990), pp. 689-693.

Fenske, R.A. and Elkner, K.P., "Multi-Route Exposure Assessment and Biological Monitoring of Urban Pesticide Applicators During Structural Control Treatments with Chlorpyrifos." Toxicology and Industrial Health, Vol. 6, No. 3/4 (1990), pp. 349-371.

Fikes, J.D., "Organophoshorus and Carbamate Insecticides." Veterinary Clinics of North America: Small Animal Practice, Volume 20, No. 2 (March, 1990) pp. 353-367.

Food and Drug Administration Pestcide Program, "Food and Drug Administration Pestcide Program: Residues in Foods-1987." Journal of the Association of Official Analytical Chemists, Vol. 71, No. 6 (1988), pp. 156A-174A.

Francis, B.M., Metcalf, R.L. and Hansen, L.G., "Toxicity of Organophosphorus Esters to Laying Hens after Oral and Dermal Administration." Journal of Environmental Science and Health, Vol. B20, No. 1 (1985), pp. 73-95.

Freedman, H.H., Process for Preparing Phosphorothioates and Phenylphosponothioates, (United States), 586, 441, August 3, 1976.

Gartrell, M.J., Craun, J.C., Podrebarac, D.S. and Gunderson, E.L., "Pesticides, Selected Elements, and Other Chemicals in Adult Total Diet Samples, October 1978-September 1979." Journal of the Association of Official Analytical Chemists, Vol. 68, No. 6 (1985a), pp. 1184-1197.

Gartrell, M.J., Craun, J.C., Podrebarac, D.S. and Gunderson, E.L., "Pesticides, Selected Elements, and Other Chemicals in Infant and Toddler Total Diet Samples, October 1979-September 1980." Journal of the Association of Official Analytical Chemists, Vol. 68, No. 5 (1985b), pp. 842-861.

Gentile, J.M., Gentile, G.J., Bultman, J., Sechriest, R., Wagner, E.D. and Plewa, M.J., "An Evaluation of the Genotoxic Properties of Insecticides Following Plant and Animal Activation." Mutation Research, Vol. 101 (1982), pp. 19-29.

Gile, J.D. and Meyers, S.M., "Effect of Adult Mallard Age on Avian Reproductive Tests." Archives of Environmental Contamination and Toxicology, Vol. 15 (1986), pp. 751-755.

Gollapudi, B.B., Zempel, J.A., Mendrala, A.L., Linscombe, V.A., McClintock, M.L. and Sinha, A.K., "Genetic Toxicity Testing of Chlorpyrifos and Its Major Metabolite." 1989 Environmental and Molecular Mutagenesis, EMS Abstracts, Vol. 14, Suppl. 15 (1989), p. 72.

Gosselin, R.E., *et al.*, Clinical Toxicology of Commerical Products, Fifth Edition. Baltimore: Williams and Wilkins, 1984, p. II-293, III 336-343.

Griffin, T.B., Coulstan, F. and McCollister, D.D., "Studies of the Relative Toxicities of Chlorpyrifos and Chlorpyrifosmethyl in Man." Toxicology Applied Pharmacology, Vol. 37, No. 1 (1976), p. 105.

Grover, I.S., Dhingra, A.K., Adhikari, N. and Ladhar, S.S., "Genotoxicity of Pesticides and Plant Systems." Progress in Clinical and Biological Research, Mutation and the Environment, Part E (1990), pp. 91-106.

Grover, I.S. and Kaur, P., "Mutagenicity of Some Organophosphate Pesticides in Barley." Genetics, Vol. 97, No. 51 (1981), pp. s45-s46.

Haas, P.J., Buck, W.B., Hixon, J.E., Shanks, R.D., Wagner, W.C., Weston, P.G. and Whitmore, H.L., "Effect of Chlorpyrifos on Holstein Steers and Testosterone-Treated Holstein Bulls." American Journal of Veterinary Research, Vol. 44, No. 5 (1983), pp. 879-881.

Hall, L.L., Fisher, H.L., Sumler, M.R., Monroe, R.J., Chernoff, N. and Shah, P.V., "Dose Response of Skin Absorption in Young and Adult Rats." Performance of Protective Clothing: Second Symposium, ASTM STP 989, Mansdorf, S.Z., Sager, R. and Nielsen, A.P., eds., American Society for Testing and Materials, Philadelphia, Pennsylvania, 1988, pp. 177-194.

Hayes, A.L., Wise, R.A. and Weir, F.W., "Assessment of Occupational Exposure to Organophosphates in Pest Control Operators." American Industrial Hygiene Association Journal, Vol. 41 (1980), pp. 568-575.

Hooser, S.B., Beasley, V.R., Sundberg, J.P. and Harlin, K., "Toxicologic Evaluation of Chlorpyrifos in Cats." American Journal of Veterinary Research, Vol. 49, No. 8 (1988), pp. 1371-1375.

Howard, P.H., *et al.*, eds., Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Vol. 3. Lewis Publishers, 1991, pp. 132-144.

Hudson, R.H., Tucker, R.K. and Haegele, M.A., Handbook of Toxicity of Pesticides to Wildlife, United States Department of the Interior Fish and Wildlife Service, Second Edition, Washington, D.C.: Resource Publication 153, 1984, pp. 1-7, 23-24, 86-90.

Hughes, D.N., Boyer, M.G., Papst, M.H. and Fowle, C.D., "Persistence of Three Organophosphorus Insecticides in Artificial Ponds and Some Biological Implications." Archives of Environmental Contamination and Toxicology, Vol. 9 (1980), pp. 269-279.

International Agency for Research on Cancer (IARC), IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 20, 1979.

Ivey, M.C., "Chlorpyrifos and 3, 5, 6-Trichloro-2-Pyridinol: Residues in the Body Tissues of Cattle Wearing Chlorpyrifos-Impregnated Plastic Ear Tags." Journal of Economic Entomology, Vol. 72, No. 6 (1979), pp. 909-911.

Ivey, M.C., Mann, H.D., Oehler, D.D., Claborn, H.V., Eschle, J.L. and Hogan, B.F., "Chlorpyrifos and its Oxygen Analogue: Residues in the Body Tissues of Dipped Cattle." Journal of Economic Entomology, Vol. 65, No. 6 (1972), pp. 1647-1649.

Ivey, M.C. and Palmer, J.S., "Chlorpyrifos and 3, 5, 6-Trichloro-2-Pyridinol: Residues in Body Tissues of Swine Treated with Chlorpyrifos for Hog Louse and Itch Mite Control." Journal of Economic Entomology, Vol. 72, No. 6 (1979), pp. 837-838.

Ivey, M.C., and Palmer, J.S., "Chlorpyrifos and 3, 5, 6- Trichloro-2-Pyridinol: Residues in ths Body Tissues of Sheep Treated with Chlorpyrifos for Sheet Ked Control." Journal of Economic Entomology, Vol. 74, No.2, (1981) pp. 136-137.

Ivey, M.C., Palmer, J.S. and Hooten, E.C., "Chlorpyrifos and 3, 5, 6-Trichloro-2-Pyridinol: Residues in the Body Tissues of Cattle Wearing Chlorpyrifos-Impregnated Plastic Ear Bands." Journal of Economic Entomology, Vol. 71, No. 4 (1978), pp. 697-700.

Jackson, M.D. and Lewis, R.G., "Insecticide Concentrations in Air after Application of Pest Control Strips." Bulletin of Environmental Contamination and Toxicology, Vol. 27 (1981), pp. 122-125.

Jackson, M.D. and Wright, C.G., "Diazinon and Chlorpyrifos Residues in Food after Insecticidal Treatment in Rooms." Bulletin of Environmental Contamination and Toxicology, Vol. 13, No. 5 (1975), pp. 593-595.

Jaggy, A. and Oliver, J.E., "Chlorpyrifos Toxicosis in Two Cats." Journal of Veterinary Internal Medicine, Vol. 4 (1990), pp. 135-139.

Jarvinen, A.W., Nordling, B.R. and Henry, M.E., "Chronic Toxicity of Dursban (Chlorpyrifos) to the Fathead Minnow (*Pimephales promelas*) and the Resultant Acetylcholinesterase Inhibition." Ecotoxicology and Environmental Safety, Vol. 7 (1983), pp. 423-434.

Jarvinen, A.W., Tanner, D.K. and Kline, E.R., "Toxicity of Chlorpyrifos, Endrin, or Fenvalerate to Fathead Minnows Following Episodic or Continuous Exposure." Ecotoxicology and Environmental Safety, Vol. 15 (1988), pp. 78-95.

Jitsunari, F., Asakawa, F., Nakajima, T., Shimada, J. and Ogata, M., "Variations in Blood Cholinesterase Activity Levels in Termite Control Worklers using Chlorpyrifos." Okayama Igakkai Zasshi, Vol. 101 (1989), pp. 843-852.

Jitsunari, F., Asakawa, F., Shiraishi, H., Suna, S., Manabe, Y., Gotoh, A. Nakajima, T., and Shimada, J., "Variations in Blood Cholinesterase Activity and Exposure to Chlorpyrifos in Termite-Control Workers." Nippon Eiseigaku Zasshi, Vol. 44, No. 6 (1990), pp. 1049-1058.

Joubert, J., Joubert, P.H., van der Spuy, M. and van Graan, E., "Acute Organophosphate Poisoning Presenting with Choreo-Athetosis." Clinical Toxicology, Vol. 22, No. 2 (1984), pp. 187-191.

Kaplan, J.G., Kessler, J., Pack, D.R. and Schaumburg, H.H., "Dursban Causes Peripheral Neuropathy." Neurology, Vol. 36, Suppl. 1 (1986), p. 176.

Kaur, P. and Grover, I.S., "Cytological Effects of Some Organophosphorus Pesticides. I. Mitotic Effects." Cytologia, Vol. 50 (1985), pp. 187-197.

Kawachi, T., Komatsu, T., Kada, T., Ishidate, M., Sasaki, M., Sugiyama, T. and Tazima, Y., "Results of Recent Studies on the Relevance of Various Short-Term Screening Tests in Japan." The Predictive Value of Short-Term Screening Tests in Carcinogenicity Evaluation, Vol. 3 (1980a), pp. 253-267.

Kawachi, T., Yahagi, T., Kada, T., Tazima, Y., Ishidate, M., Sasaki, M. and Sugiyama, T., "Cooperative Program on Short-Term Assays for Carcinogenicity in Japan." International Agency for Research on Cancer (IARC) Publication Scientific, No. 27 (1980b), pp. 323-330.

Kenaga, E.E, Fink, R.J. and Beavers, J.B. "Dietary Toxicity Tests with Mallards, Simulating Residue Decline of Chlorpyrifos and Avoidance of Treated Food." Avian and Mammalian Wildlife Toxicology, ASTM STP, American Society for Testing and Materials, 1979, pp. 36-44.

Killeen, J.C. and Griffin, T.B., "Inhibition Studies of Carboxyesterase Activity." Toxicology Applied Pharmacology, Vol. 22, No. 2 (1972), p. 329.

Kirk-Othmer, Encyclopedia of Chemical Technology, Third Edition, Vol. 13, New York: Wiley-Interscience, 1981, pp. 413-419, 437-453, 483-485.

Kirk-Othmer, Encyclopedia of Chemical Technology, Third Edition, Vol. 19, New York: Wiley-Interscience, 1982, p. 470.

Kulkarni, A.P., Fabacher, D.L. and Hodgson, E., "Induction of Hepatic Xenobiotic Metabolizing Enzymes by Pesticides. II. Glutathione S-Transferase." Toxicology Applied Pharmacology, Vol. 45, No. 1 (1978), p. 321.

Kulkarni, A.P., Fabacher, D.L. and Hodgson, E., "Pesticides as Inducers of Hepatic Drug-Metabolizing Enzymes-II. Glutathione S-Transferases." General Pharmacology, Vol. 11 (1980), pp. 437-441.

Lee, M.J. and Waters, H.C., "Inhibition of Monocyte Esterase Activity by Organophosphate Insecticides." Blood, Vol. 50, No. 5 (1977), pp. 947-951.

Leidy, R.B. and Wright, C.G., "Airborne Residues of a Termiticide Formulation of Chlorpyrifos in Homes." American Chemical Society Agrochemicals, 193rd ACS National Meeting, Denver, Colorado, 1987.

Leidy, R.B., Wright, C.G. and Dupree, H.E., "Applicator Exposure to Airborne Concentrations of a Termiticide Formulation of Chlorpyrifos." Bulletin of Environmental Contamination and Toxicology, Vol. 47 (1991), pp.177-183.

Lewis, R.G., Bond, A.E., Johnson, D.E. and Hsu, J.P., "Measurement of Atmospheric Concentrations of Common Household Pesticides: A Pilot Study." Environmental Monitoring and Assessment, Vol. 10 (1988), pp. 59-73.

Long, G.G., Scheidt, A.B., Everson, R.J. and Oehme, F.W., "Age Related Susceptibility of Newborn Pigs to the Cutaneous Application of Chlorpyrifos." Veterinary and Human Toxicology, Vol. 28, No. 4 (1986), pp. 297-299.

Lores, E.M., Sovocool, G.W., Harless, R.L., Wilson, N.K. and Moseman, R.F., "A New Metabolite of Chlorpyrifos: Isolation and Identification." Journal of Agricultural Food Chemistry, Vol. 26, No. 1 (1978a), pp. 118-122.

Lores, E.M., Bradway, D.E. and Moseman, R.F., "Organophoshorus Pesticide Poisonings in Humans: Determination of Residues and Metabolites in Tissue and Urine." Archives of Environmental Health, Vol. 33, No. 5 (1978b), pp. 270-276.

Lotti, M., Moretto, A., Zoppellari, R., Dainese, R., Rizzuto, N. and Barusco, G., "Inhibition of Lymphocytic Neuropathy Target Esterase Predicts the Development of Organophosphate-Induced Delayed Polyneuropathy." Archives of Toxicology, Vol. 59 (1986), pp. 176-179.

Ludwig, P.D., Kilian, D.J., Dishburger, H.J. and Edwards, H.N., "Results of Human Exposure to Thermal Aerosols Containing Dursban® Insecticide." Mosquito News, Vol. 30, No. 3 (1970), pp. 346-354.

Lusk, E.E., Womeldorf, D.J., Washino, R.K., Akesson, N.B. and Whitesell, K.G., "Effects of Nonthermal Aerosol Applications of Chlorpyrifos on Non-Target Arthropods, and People in an Urban Area." Proceedings and Papers of the Annual Conference of the California Mosquito Control Association, Vol. 44 (1976), pp. 78-85.

Maddy, K.T. and Edmiston, S., "Selected Incidents of Illnesses and Injuries Related to Exposure to Pesticides Reported by Physicians in California in 1986." Veterinary and Human Toxicology, Vol. 30, No. 3 (1988), pp. 246-254.

Maddy, K.T., Edmiston, S. and Richmond, D., "Illness, Injuries, and Deaths from Pesticide Exposures in California 1949-1988." Reviews of Environmental Contamination and Toxicology, Vol. 114 (1990), pp. 57-123.

Martin, P.A., "Effects of Carbofuran, Chlorpyrifos and Deltamethrin on Hatchability, Deformity, Chick Size and Incubation Time of Japanese Quail (*Coturnix Japonica*) Eggs." Environmental Toxicology and Chemistry, Vol. 9 (1990), pp. 529-534.

Marquis, J.K., "Contemporary Issues in Pesticide Toxicology and Pharmacology." Concepts in Toxicology, Vol. 2. Karger, 1986, pp. 22, 28-37.

McCollister, S.B., Kociba, R.J. and Gehring, P.J., "Studies on the Acute and Chronic Oral Toxicity of O, O-Diethyl-O-(3, 5, 6-Trichloro-2-Pyridyl) Phosphorothioate." The Pharmacologist, Vol. 15, No. 2 (1973), p.226.

McCollister, S.B., Kociba, R.J., Humiston, C.G., McCollister, D.D. and Gehring, P.J., "Studies of the Acute and Long-Term Oral Toxicity of Chlorpyrifos (O, O-Diethyl-O-(3, 5, 6-Trichloro-2-Pyridyl) Phosphorothioate)." Food and Cosmetic Toxicology, Vol. 12 (1974), pp. 45-61.

McConnell, R., Anton, A.F.P. and Magnotti, R., "Crop Duster Aviation Mechanics: High Risk for Pesticide Poisoning." American Journal of Public Health, Vol. 80, No. 10 (1990), pp. 1236-1239.

McKellar, R.I., Dishburger, H.J., Rice, J.R., Craig, L.F. and Pennington, J., "Residues of Chlorpyrifos, its Oxygen Analogue, and 3, 5, 6-Trichloro-2-pyridinol in Milk and Cream from Cows Fed Chlorpyrifos." Journal of Agricultural and Food Chemistry, Vol. 24, No. 2 (1976), pp 283-286.

McNabb, S.D., Kearns, G.L. and Fiser, D.H., "Continuous Infusion Pralidoxime (CIP) for Treatment of Organophosphate Poisoning." Clinical Research, Vol. 36, No. 1 (1988), p. 56A.

Meister, R.T., ed., 1990 Farm Chemicals Handbook. Willoughby, Ohio: Meister Publishing Company, 1990, p. C 70.

Meyers, S.M. and Gile, J.D., "Mallard Reproductive Testing in a Pond Environment: A Preliminary Study." Archives of Environmental Contamination and Toxicology, Vol. 15 (1986), pp. 757-761.

Mikhail, T.H., Aggour, N., Awadallah, R., Boulos, M.N., El-Dessoukey, E.A. and Karima, A.I., "Acute Toxicity of Organophosphorus and Organochlorine Insecticides in Laboratory Animals." Zeitschrift für Ernährungswiss, Vol. 18 (1979), pp. 258-268.

Mix, J., "Termiticide Market Stabilizes." Pest Control, Vol. 55, No. 2 (1987), pp. 22-23.

Mix, J., "Leading Today's Termiticide Parade." Pest Control, Vol. 56, No. 3 (1988), pp. 40-41.

Miyazaki, S. and Hodgson, G.C., "Chronic Toxicity of Dursban and Its Metabolite, 3, 5, 6-Trichloro-2-Pyridinol in Chickens." Toxicology and Applied Pharmacology, Vol. 23, (1972), pp. 391-398.

Mohamed, O.S.A., Adam, S.E.I. and El Dirdira, N.I., "The Combined Effect of Dursban and Reldan on Nubian Goats." Veterinary and Human Toxicology, Vol. 32, No. 1 (1990), pp. 47-48.

Moriya, M., Ohta, T., Watanabe, K., Miyazawa, T., Kato, K. and Shirasu, Y., "Further Mutagenicity Studies on Pesticides in Bacterial Reversion Assay Systems." Mutation Research, Vol. 116 (1983), pp. 185-216.

Mostafa, I.Y., Adam, Y.M. and Zayed, S.M.A.D., "Bioalkylation of Nucleic Acids in Mice by Insecticides. I. Alkylation of Liver RNA and DNA by Chlorpyrifos." Z. Naturforsch, Vol. 38c (1983), pp. 461-464.

Moye, H.A. and Malagodi, M.H., "Levels of Airborne Chlordane and Chlorpyrifos in Two Plenum Houses: Saranex S-15 as a Vapor Barrier." Bulletin of Environmental Contamination and Toxicology, Vol. 39 (1987), pp. 533-540.

Muscarella, D.E., Keown, J.F. and Bloom, S.E., "Evaluation of the Genotoxic and Embryotoxic Potential of Chlorpyrifos and Its Metabolites *In Vivo* and *In Vitro*." Environmental Mutagenesis, Vol. 6 (1984), pp. 13-23.

National Institute for Occupational Safety and Health (NIOSH), National Occupational Exposure Survey (NOES), data communicated by Joseph A. Seta, Acting Section Chief, Division of Surveillance, Hazard Evaluations and Field Studies. February 1991.

National Toxicology Program (NTP), NTP Results Report - Results and Status Information on all NTP Chemicals Produced from NTP Chemtrak System. FTS 541-3419, October, 1991.

Nelson, M.C., Jalal, S.M. and Larson, O.R., "Genotoxicity of the Organophoshorus Insecticide Chlorpyrifos Based on Human Lymphocyte Culture." Cytologia, Vol. 55 (1990), pp. 589-592.

Nolan, R.J., Rick, D.L., Freshour, N.L. and Saunders, J.H., "Chlorpyrifos: Pharmacokinetics in Human Volunteers." Toxicology and Applied Pharmacology, Vol. 73 (1984), pp. 8-15.

Office of the Federal Register, National Archives and Records Administration. Code of Federal Regulations, Title 29, Labor, Part 1910. U.S. Government Printing Office. Washington, D.C. January 19, 1989, pp. 2335, 2340, 2644-2645, 2648-2649, 2652-2653, 2661.

Office of the Federal Register, Code of Federal Regulations, Title 40, Environmental Protection Agency, Subpart B, Part 185.1000. U.S. Government Printing Office. Washington, D.C. July 1, 1991a, pp. 440-445, 464-469.

Office of the Federal Register, Notices: Intent to Suspend Certain Pesticides, Part III, Environmental Protection Agency, U.S. Government Printing Office. Washington, D.C., Vol. 56, No. 64 (April 3, 1991b), pp. 13720-13721, 13723.

Ogawa, Y., Suzuki, S., Uchida, O., Kamata, E., Saito, M., Umemura, T., Wakana, M., Kaneko, T., Kurokawa, Y. and Tobe, M., "28-Day Repeated Dose Toxicity Test for Chlorpyrifos in Wistar Rat." Eisei Shikensho Hokoko - Bulletin of the National Institute of Hygienic Sciences (Tokyo), Vol. 0, No. 106 (1988), pp. 48-54.

Ohta, T., Watanabe, M., Tsukamoto, R., Shirasu, Y. and Kada, T., "Antimutagenic Effects of 5-Fluorouracil and 5-Flourodeoxyuridine on UV-Induced Mutagenesis in *Escherichia coli*." Mutation Research, Vol. 173 (1986), pp. 19-24.

Palmer, J.S., Rowe, L.D. and Crookshank, H.R., "Effect of Age on Tolerance of Calves to Chlorpyrifos." American Journal of Veterinary Research, Vol. 41, No. 8 (1980), pp. 1323-1325.

Pest Control, "Public Health Pesticides." Pest Control, Vol. 39, No. 3, (1971) pp. 13-16, 19-22, 24, 26, 28-30, 32, 34, 36, 38, 40, 42, 44-47, 50-51.

Pesticide and Toxic Chemical News, "Chlorpyrifos" Pesticide and Toxic Chemical News, January 1, 1992, p. 2.

Piers Imports Database, Searched August, 1991

Pinem, M., Kasiman, S., Panjaitan, T.B. and Lubis, H.R., "Decreasing Cholinesterase Activity of Labourers Exposed to Pesticides." Proceedings of the Tenth Asian Conference on Occupational Health (Singapore), Vol. 1 (1982), pp. 197-198.

Plewa, M.J., "Plant Genetic Assays and Their Use In Studies on Environmental Mutagenesis In Developing Countries." Basic Life Sciences, Vol. 34 (1985), pp. 249-268.

Plewa, M.J. and Wagner, E.D., "Germinal Cell Mutagenesis in Specially Designed Maize Genotypes." Environmental Health Perspectives, Vol. 37 (1981), pp. 61-73.

Polymers, Paint, Colour Journal, "Latex Coating is Useful as Insecticide." Polymers, Paint, Colour Journal, Vol. 176, No. 4166 (1986), p. 348.

Putnam, M.R. and Edwards, W.C., "Treatment of Chronic Chlorpyrifos Poisonine in a Limousin Bull." The Bovine Practitioner, No. 19 (1984), pp. 204-207.

Rao, B.V., Rao, B.G.S. and Sharma, C.B.S.R., "Cytological Effects of Herbicides and Insecticides on *Allium cepa* Root Meristems." Cytologia, Vol. 53 (1988), pp. 255-261.

Remondelli, P., Mugnoz, B., Della Morte, R., Belisario, M.A., Staiano, N. and De Lorenzo, F., "Evaluation of the Mutagenic Potential of Thirteen Pesticides by Measuring both His+ and HGPRT-Deficient Mutants in *Salmonella typhimurium*." Medecine Biologie Environnement, Vol. 14 (1986), pp. 377-386.

Reynolds, J.E.F., ed., Martindale: The Extra Pharmacopoeia, Twenty-ninth Edition. London: The Pharmaceutical Press, 1989, pp. 1344, 1346.

Roediger, B., van der Ven, H., Al-Hasani, S., Reinecke, A., Hartje, M., Weber, U., Diedrich, K. and Krebs, D., "The Effect of Environmental Pollutants on Human Sperm Function *In Vitro*." Human Reproduction (OXF), Vol. 2, Suppl. 1 (1987), pp. 12-13.

Ross, J., Thongsinthusak, T., Fong, H.R., Margetich, S. and Krieger, R., "Measuring Potential Dermal Transfer of Surface Pesticide Residue Generated from Indoor Fogger Use: An Interim Report." Chemosphere, Vol. 20, Nos. 3/4 (1990), pp. 349-360.

Sakai, R., "Toxicity of Organic Phosphates and Chloronaphthalenes. Part 1. The Effect on Mitochondrial Oxidative Phosphorylation in the Rat Liver." Okayama Igakkai Zasshi, Vol. 102, Nos. 7-8 (1990), pp. 989-996.

Sandu, S.S., Waters, M.D., Simmon, V.F., Mortelmans, K.E., Mitchell, A.D., Jorgenson, T., Jones, D.C.L., Valencia, R. and Stack, F., "Evaluation of the Genotoxic Potential of Certain Pesticides Used in Pakistan." Basic Life Sciences, Vol. 34 (1985), pp. 185-219.

Sax, N.I. and Lewis, R.J. Sr., Dangerous Properties of Industrial Materials, Volume II. Seventh Edition. New York: Van Nostrand Reinhold, 1989, pp. 1524-1525.

Scarratt, W.K. and Blodgett, D.J., "Chlorpyrifos Intoxication in a Bull." Journal of the American Veterinary Medical Association, Vol. 188, No. 12 (1986), pp. 1444-1446.

Scheidt, A.B., Long, G.G., Knox, K. and Hubbard, S.E., "Toxicosis in Newborn Pigs Associated with Cutaneous Application of an Aerosol Spray Containing Chlorpyrifos." Journal of the American Veterinary Medical Association (JAVMA), Vol. 191, No. 11 (1987), pp. 1410-1412.

Schimmel, S.C., Garnas, R.L., Patrick, J.M. and Moore, J.C., "Acute Toxicity, Bioconcentration, and Persistence of AC 222, 705, Benthiocarb, Chlorpyrifos, Fenvalerate, Methyl Parathion, and Permethrin in the Estuarine Environment." Journal of Agricultural Food Chemistry, Vol. 31 (1983), pp. 104-113.

Schlinke, J.C., "Chronic Toxicity of Dursban in Chickens, 1969." Journal of Economic Entomology, Vol. 63, No. 1 (1970), p. 319.

Schom, C.B., Abbott, U.K. and Walker, N., "Organophosphorus Pesticide Effects on Domestic and Game Bird Species: Dursban®." Poultry Science, Vol. 52, No. 5 (1973), p. 2083.

Selden, B.S. and Curry, S.C., "Prolonged Succinylcholine-Induced Paralysis in Organophosphate Insecticide Poisoning." Annals of Emergency Medicine, Vol. 16, No. 2 (1987), pp. 215-217.

Shah, P.V., Fisher, H.L., Sumler, M.R., Monroe, R.J., Chernoff, N. and Hall, L.L., "Comparison of the Penetration of 14 Pesticides Through the Skin of Young and Adult Rats." Journal of Toxicology and Environmental Health, Vol. 21 (1987), pp. 353-366.

Shah, P.V., Monroe, R.J. and Guthrie, F.E., "Comparative Rates of Dermal Penetration of Insecticides in Mice." Toxicology and Applied Pharmacology, Vol. 59 (1981), pp. 414-423.

Shemesh, I., Bourvin, A., Gold, D. and Kutscherowsky, M., "Chlorpyrifos Poisoning Treated with Ipratropium and Dantrolene: A Case Report." Clinical Toxicology, Vol. 26, No. 7 (1988), pp. 495-498.

Sherman, M. and Herrick, R.B., "Fly Control and Chronic Toxicity from Feeding Dursban® (*O,O*-Diethyl *O*-3, 5, 6-Trichloro-2-Pyridyl Phosphorothioate) to Laying Hens." Poultry Science, Vol. 52 (1973), pp. 741-747.

Silveira, C.L., Eldefrawi, A.T. and Eldefrawi, M.E., "Putative M_2 Muscarinic Receptors of Rat Heart Have High Affinity for Organophosphorus Anticholinesterases." Toxicology and Applied Pharmacology, Vol. 103 (1990), pp. 474-481.

Smith, G.N., Watson, B.S. and Fischer, F.S., "Investigations on Dursban Insecticide. Metabolism of [^{36}Cl]O,O-Diethyl O-3, 5, 6-Trichloro-2-pyridyl Phosphorothioate in Rats." Metabolism, Vol. 15, No. 1 (1967), pp. 132-138.

Smith, D.A. and Wiseman, J.S., "Pesticide Poisoning." Texas Medicine, Vol. 67, No. 2 (1971), pp. 56-59.

Sobti, R.C., Krishan, A. and Pfaffenberger, C.D., "Cytokinetic and Cytogenetic Effects of Some Agricultural Chemicals on Human Lymphoid Cells *In Vitro*: Organophosphates." Mutation Research, Vol. 102 (1982), pp. 89-102.

Sobti, R.C., Krishan, A., Pfaffenberger, C., Mansell, P.W.A. and Davies, J., "Cytogenetic Monitoring of Environmental Pollutants in South Florida." Proceedings of the American Association for Cancer Research, Vol. 22 (1981), p. 110.

SRI International, 1991 Directory of Chemical Producers, United States of America, Menlo Park, California, 1991a, pp. 117-119, 841.

SRI International, 1991 Directory of Chemical Producers, Western Europe, Volume 2, Menlo Park, California, 1991b, pp. 798, 1617.

SRI, Chemical Economics Handbook Online, database available from SRI, Menlo Park California, March, 1991c.

Stimmann, M.W. and Ferguson, M.P., "Potential Pesticide Use Cancellations in California." California Agriculture, Vol. 44, No. 4 (1990), pp. 12-16.

Sultatos, L.G., "Factors Affecting the Hepatic Biotransformation of the Phosphorothioate Pesticide Chlorpyrifos." Toxicology, Vol. 51 (1988), pp. 191-200.

Sultatos, L.G., Costa, L.G. and Murphy, S.D., "Factors Involved in the Differential Acute Toxicity of the Incecticides Chlorpyrifos and Methyl Chlorpyrifos in Mice." Toxicology and Applied Pharmacology, Vol. 65 (1982), pp. 144-152.

Sultatos, L.G., Minor, L.D. and Murphy, S.D., "Metabolic Activation of Phosphorothioate Pesticides: Role of the Liver." The Journal of Pharmacology and Experimental Therapeutics, Vol. 232, No. (1985), pp. 624-628.

Sultatos, L.G. and Murphy, S.D., "Kinetic Analyses of the Microsomal Biotransformation of the Phosphorothioate Insecticides Chlorpyrifos and Parathion." Fundamental and Applied Toxicology, Vol. 3 (1983), pp. 16-21.

Sunaga, M., Yoshida, M., Ueda, T., Kosaka, M. and Hara, I., "Relationship Between Exposure to Chlorpyrifos and Concentration of Urinary Alkylphosphates in Termite Control Workers." Japanese Journal of Industrial Health, Vol. 31 (1989a), pp. 142-149.

Sunaga, M., Yoshida, M. and Hara, I., "Metabolism and Urinary Excretion of Chlorpyrifos in Rats." Japanese Journal of Hygiene (Nippon Eiseigaku Zasshi), Vol. 43, No. 6 (1989b), pp. 1124-1129.

United States Coast Guard (USCG), Chemical Hazards Response Information System (CHRIS), Hazardous Chemical Data. U.S. Coast Guard Publication No. CG-446-1. U.S. Coast Guard. Washington, D.C. 1985.

United States Department of the Interior (USDI), Chlorpyrifos Hazards to Fish, Wildlife, and Invertebrates: A Synoptic Review. Submited by Paxuent Wildlife Research Center, Laurel, Maryland to USDI, Fish and Wildlife Service, 1988, pp. 1-36.

United States Environmental Protection Agency (USEPA), Evaluation of Selected Pesticides as Chemical Mutagens *In Vitro* and *In Vivo* Studies. Submited by Stanford Research Institute, Menlo Park, California to USEPA, Office of Research and Development, Research Triangle Park, North Carolina, 1977, pp. 1-238.

United States Environmental Protection Agency (USEPA), Mutagenesis Screening of Pesticides using *Drosophila*. Submited by WARF Institute, Inc., Madison, Wisconsin to USEPA, Office of Research and Development, Research Triangle Park, North Carolina, 1981, pp. 71.

United States Environmental Protection Agency (USEPA), Pesticide Fact Sheet Number 37: Chlorpyrifos. United States Environmental Protection Agency, Office of Pesticides and Toxic Substances, Washington, D.C., 1984a, pp. 1-8.

United States Environmental Protection Agency (USEPA), Guidance for the Reregistration of Pesticide Products Containing Chlorpyrifos as the Active Ingredient. USEPA, Office of Pesticide Programs, Washington D.C., 1984b, pp. 1-17.

United States Environmental Protection Agency (USEPA), Pesticide Fact Sheet Number 57: Chlorpyrifos-Methyl. United States Environmental Protection Agency, Office of Pesticides and Toxic Substances, Washington, D.C., 1985, pp. 1-4.

United States Environmental Protection Agency (USEPA), Ambient Water Quality Criteria for Chlorpyrifos-1986. Submited by the Office of Research and Development Environmental Research Laboratories, Duluth, Minnosota and Narragansett, Rhode Island to USEPA, Office of Water Regulations and Standards Division, Washington, D.C., 1986, pp. 1-64.

United States Environmental Protection Agency (USEPA), Pesticide Exposure to Florida Greenhouse Applicators. Submited by Florida Pesticide Hazard Assessment Project, University of Florida, Lake Alfred, Florida to USEPA, Office of Research and Development, Cincinnati, Ohio, 1988, pp. 1-98.

United States Environmental Protection Agency (USEPA), Chlorpyrifos. Drinking Water Health Advisory, Office of Water, USEPA, September 1990, pp. 1-23.

United States Environmental Protection Agency (USEPA), Telephone conversation with D. Lott, USEPA-FIFRA Section, Philadelphia, Pa., October, 11, 1991.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1985. U.S. Government Printing Office. Publication No. 1892. Washington, D. C., 1986.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1986. U.S. Government Printing Office. Publication No. 2009. Washington, D. C., 1987.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1987. U.S. Government Printing Office. Publication No. 2118. Washington, D. C., 1988.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1988. U.S. Government Printing Office. Publication No. 2219. Washington, D. C., 1989.

United States International Trade Commission (USITC), Synthetic Organic Chemicals, United States Production and Sales, 1989. U.S. Government Printing Office. Publication No. 2338. Washington, D. C., 1990.

Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Second Edition. New York: Van Nostrand Reinhold, 1983, pp. 391-392.

Vishwanath, R. and Jamil, K., "Mutagenic and Genotoxic Activities of Certain Organophosphorus Compounds, Using Ames Salmonella Assay, With and Without Microsomal Induction." Indian Journal of Experimental Biology, Vol. 24 (1986), pp. 305-308.

Woodruff, R.C., Phillips, J.P. and Irwin, D., "Pesticide-Induced Complete and Partial Chromosome Loss in Screens with Repair-Defective Females of *Drosophila melanogaster*." Environmental Mutagenesis, Vol. 5 (1983), pp. 835-846.

World Health Organization (WHO), Environmental Health Criteria 63: Organophosphorus Insecticides: A general Introduction. World Health Organization, Geneva, 1986, pp. 13-23, 176.

Worthing, C.R., ed., The Pesticide Manual: A World Compendium, Eighth Edition. Croydon: The British Crop Protection Council, 1987, pp. 179-180.

Worthy, W., "Household Pesticide Hazards Examined." Chemical and Engineering News, 1991, p. 50.

Wright, C.G. and Leidy, R.B., "Chlorpyrifos Residues in Air After Application to Crevices in Rooms." Bulletin of Environmental Contamination and Toxicology, Vol. 19 (1978), pp. 340-344.

Wright, C.G. and Leidy, R.B., "Insecticide Residues in Air of Buildings and Pest Control Vehicles." Bulletin of Environmental Contamination and Toxicology, Vol. 24 (1980), pp. 582-589.

Wright, C.G., Leidy, R.B. and Dupree, H.E., "Chlorpyrifos and Diazinon Detection on Surfaces in Dormitory Rooms." Bulletin of Environmental Contamination and Toxicology, Vol. 32 (1984), pp. 259-264.

Wright, C.G., Leidy, R.B. and Dupree, H.E., "Chlorpyrifos in the Ambient Air of Houses Treated for Termites." Bulletin of Environmental Contamination and Toxicology, Vol. 40 (1988), pp. 561-568.

Wright, C.G., Leidy, R.B. and Dupree, H.E., "Diazinon and Chlorpyrifos in the Air of Moving and Stationary Pest Control Vehicles." Bulletin of Environmental Contamination and Toxicology, Vol. 28 (1982), pp. 119-121.

Wright, C.G., Leidy, R.B. and Dupree, H.E., "Insecticides in the Ambient Air of Rooms Following Their Application for Control of Pests." Bulletin of Environmental Contamination and Toxicology, Vol. 26 (1981), pp. 548-553.

Xu, H.H. and Schurr, K.M., "Genotoxicity of 22 Pesticides in Microtitration SOS Chromotest." Toxicity Assessment: An International Journal, Vol. 5 (1990), pp. 1-14.

Yao, M., Kudo, T., Kudo, M., Sakai, T., Matsuki, A., Oyama, T., Okitsu, K. and Fukuda, S., "A Case of Acute Intoxification with Chlorpyrifos." Masui, Vol. 33, No. 2 (1984), pp. 204-211.

Yoshikawa, H., Yoshida, M. and Hara, I., "Electroretinographic Changes Induced by Organophosphorus Pesticides in Rats." The Journal of Toxicological Sciences, Vol. 15 (1990), pp. 87-95.

APPENDIX I. On-Line Databases Searched

Date of Search: August 1991

BRS:
HZDB

CIS:
TSCATS

DIALOG:
Aquatic Science Abstracts
Biobusiness
Cancerlit
Chem Bus Newsbase
Chemical Exposure
Chemical Industry Notes
Chem Saf Newsbase
Chem Regs and Guidelines
CRIS
Environmental Bibliography
Enviroline
Federal Register
Fed. Res. in Progress
Occup Health/Safety
Oceanic Abstract
PTS Newsletter
PTS Prompt
Piers Exports
Piers Imports
Pollution Abstracts
Trade and Industry
Toxline
Water Resources Abstract

MEAD:
Gen Fed; CFR
Lexis Bnaenv

NLM:
Chemid
Chemline
Dart
Eticback
Emicback
HSDB
IRIS
RTECS
Toxline 65
Toxline

STN:
Beilstein
CA
CApreviews
Chemlist
CSCHEM
Registry

Others:
NOES: National Occupational Exposure Survey (NIOSH)

APPENDIX II. SAFETY INFORMATION

- **HANDLING AND STORAGE**

  Chlorpyrifos is stable at temperatures less than 50°C. This compound will undergo exothermic decomposition at approximately 130°C [DowElanco, 1990] and emit toxic fumes of chlorine, nitrous oxides, phosphorous oxides, and sulfer oxides [Sax and Lewis, 1989].

  See sections II.C., Chemical and Physical Properties, and IV.D., Regulatory Status, for additional information.

- **EMERGENCY FIRST AID PROCEDURES**

  Eye: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. Immediately transport the victim to a hospital even if no symptoms (such as redness or irritation) develop.

  Skin: IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently was affected skin areas thoroughly with soap and water. If symptoms such as inflammation or irritation develop, IMMEDIATELY call a physician or go to a hospital for treatment.

Inhalation: IMMEDIATELY leave the contaminated area and take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital.

Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used.

Ingestion: CHOLINESTERASE INHIBITORS ARE EXTREMELY TOXIC AND FAST ACTING POISONS. Atropine is an antidote for cholinesterase inhibitors but should only be administered by properly trained personnel. In the absence of this option and if the victim is conscious and not convulsing, it may be worth considering the risk of inducing vomiting, even though the induction of vomiting is not usually recommended outside of a physician's care. Ipecac syrup or salt water may be used to induce vomiting in such an emergency. IMMEDIATELY call a hospital or poison control center and transport the victim to a hospital.

If the victim is convulsing or unconscious, do not give anything by mouth, assure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY transport the victim to a hospital.

- **PROTECTIVE EQUIPMENT**

  Eye: Safety goggles

  Gloves: Two pairs of dissimilar protective gloves shall be worn when handling the neat chemical, otherwise one pair. When contact with this chemical has been known to occur, change gloves immediately.

  Clothing: Minimally, a disposable laboratory suit (e.g. Tyvek ®) shall be worn, as specified in the most current NTP Statement of Work or the NTP Health and Safety Minimum Requirements.

  Respiratory Protection: A NIOSH-approved chemical cartridge respirator with an organic vapor and high-efficiency particulate filter cartridge.

- **EXTINGUISHANT**

  Dry chemical, carbon dioxide or halon extinguisher.

- **MONITORING PROCEDURES**

  There is no NIOSH analytical method reported in the NIOSH Manual of Analytical Methods for chlorpyrifos.

- **SPILLS AND LEAKAGE**

  Persons not wearing the appropriate protective equipment and clothing shall be restricted from areas of spills until cleanup has been completed. When exposure to unknown concentrations may occur, air-purifying respirators may not be used. Chemical cartridge respirators with organic vapor cartridges may not be used when airborne concentrations exceed 1000 ppm.

  If chlorpyrifos is spilled the following steps shall be taken:

  1. In order to prevent dust formation, use moistened paper towels to clean up a solid spill. Avoid dry sweeping.

  2. If a liquid solution is spilled, use vermiculite, sodium bicarbonate, sand, or paper towels to contain and absorb the spill.

  3. Clean the spill area with dilute alcohol (approximately 60-70%) followed by a strong soap and warm water washing.

  4. Dispose of all absorbed material as hazardous waste.

- **DECONTAMINATION OF LABORATORY EQUIPMENT**

  TDMS Terminal: Whenever feasible, a protective covering (e.g.,plastic wrap) shall be placed over the keyboard when in use.

  General Equipment: Before removing general laboratory equipment (i.e., lab carts, portable hoods and balances) from animal dosing rooms and/or chemical preparation areas, a decontamination process shall be conducted in addition to routine housekeeping procedures.

- **WASTE MANAGEMENT AND DISPOSAL PROCEDURES**

  Waste Management: If an inhalation study is to be conducted, all exhaust air from the inhalation chamber must be cleaned with appropriate air cleaning devices unless the laboratory has informed local and state air pollution regulatory agencies of both the laboratory's operating practices and the potential hazards of the chemical's in use. Compliance with all federal, state and local air pollution laws and regulations is required. A specific air cleaning system design must consider the specific conditions of the laboratory (eg., air flow rates and volumes, mixing of exhaust streams, size of inhalation chamber, etc.) and the dosing regimen selected. Air cleaning systems designs must be described by the laboratory and approved by the NTP Office of Laboratory Health and Safety.

  Waste Disposal: Securely package and label, in double bags, all waste material. All potentially contaminated material (i.e., carcasses, bedding, disposable cages, labware) shall be disposed of by incineration in a manner consistent with federal (EPA), state, and local regulations or disposed of in a licensed hazardous waste landfill.