

CHLORPYRIFOS

Drinking Water Health Advisory
Office of Water
U.S. Environmental Protection Agency

I. INTRODUCTION

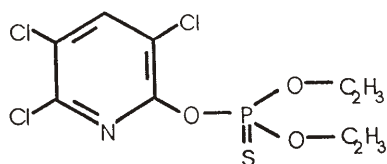
The Health Advisory (HA) Program, sponsored by the Office of Water (OW), provides information on the health effects, analytical methodology, and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State, and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime), and Lifetime exposures based on data describing noncarcinogenic endpoints of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifelong exposure and the ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit, or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 2921-88-2

Structural Formula

Chlorpyrifos

Synonyms

- Brodan; Chlorpyrifos; Chlorpyrifos-ethyl; Detmol U.A.; Dowco 179; Dursban; Dursban F; Ent 27311; Eradex; Ethion, dry; Lorsban; NA 2783 (Dot); OMS-0971; Phosphorothioic acid, O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) ester; Pyrinex.

Uses

- Chlorpyrifos is a broad-spectrum insecticide with many uses. An estimated 7 to 11 million pounds of chlorpyrifos are produced each year in the United States for domestic use. Of the total domestic chlorpyrifos usage, 57% is applied to corn and 5 to 6% to cotton. Commercial pest control and lawn and garden services consume 20 to 22% of the annual chlorpyrifos usage, followed by domestic household and lawn and garden application (9 to 13%).

Properties (Kenaga, 1980; Windholz et al., 1983; Worthing, 1987)

Chemical Formula	C ₉ H ₁₁ Cl ₃ NO ₃ PS
Molecular Weight	350.57
Physical State (25° C)	White, granular crystals
Boiling Point	--
Melting Point	41 to 43.5° C
Density	--
Vapor Pressure (25° C)	1.87 x 10 ⁻⁵ mm Hg
Water Solubility (25° C)	2 ppm
Specific Gravity	--
Log Octanol/Water Partition	4.99
Coefficient (log K _{ow})	--
Taste Threshold (water)	--
Odor Threshold (water)	--
Conversion Factor	--
(ppm air as mg/m ³)	--

Occurrence

- Based on a 3-year, 20-city nationwide study conducted by the Food and Drug Administration, Gartrell et al. (1985) estimated that the average daily intake of chlorpyrifos from food and beverages (including water) is approximately 0.001 to 0.005 µg/kg. Contaminated grain and cereal products and garden fruits were the food groups through which exposure occurred.

Environmental Fate

- Chlorpyrifos hydrolyzes readily in water; its rate of hydrolysis increases with temperature (Worthing, 1987). When mixed with distilled water (pH 6.5) or pasture water (pH 7 to 9), chlorpyrifos levels dropped an average of 25% at 24° C and 48% at 38° C within 8 hours (Schaefer and Dupras, Jr., 1969).
- Chlorpyrifos administered at a rate of 3.4 kg chlorpyrifos/hectare (ha) dissipated fairly rapidly in sand and organic muck soils with respective half-lives of 2 and 8 weeks in the top 15 cm of soil (Chapman and Harris, 1980). Low levels of chlorpyrifos (2 to 3% of the amount applied) remained in both soils for up to 2 years. 3,5,6-Trichloro-2-pyridinol was the primary degradation product, reaching maximum concentrations of 13 and 39% of the chlorpyrifos applied to the sand and muck soils, respectively. The concentrations of the oxygen analog of chlorpyrifos were ≤0.004 ppm in all samples. Chlorpyrifos (EC, emulsifiable concentrate), applied at 4 kg chlorpyrifos/ha to turf grass, dissipated rapidly with a half-life of <14 days in the soil and turf cover (Sears and Chapman, 1979). Movement of chlorpyrifos from the turf into the soil was minimal (<18% of the recovered chlorpyrifos at any time during the study).
- Breakdown of chlorpyrifos in soil primarily results from microbial metabolism (Miles et al., 1979). Chlorpyrifos (10 ppm) is degraded more rapidly in sandy loam soil (half-life, <1 week) than in organic soil (half-life, 2.5 weeks). In sterilized soils, the half-life for chlorpyrifos is > 17 weeks. Half-lives of 11 to 141 days were reported in another study in soils ranging in texture from loamy sand to clay

(Bidlack, 1979). 3,5,6-Trichloro-2-methoxy pyridine and two unidentified minor metabolites of chlorpyrifos were recovered after a 1-year incubation period; most of the radiocarbon, however, was recovered as $^{14}\text{CO}_2$ with small amounts incorporated into soil organic matter.

- After 30 days of aerobic aging of soil, ^{14}C -chlorpyrifos degraded with half-lives of 15 days in loam and 58 days in clay soils. The half-lives in treated and anaerobically incubated loam and clay were 39 and 51 days, respectively. The major degradation product formed was 3,5,6-trichloro-2-pyridinol. Degradation of this compound was very slow. Evolution of $^{14}\text{CO}_2$ was insignificant, and incorporation of ^{14}C into the soil organic matter was slow. Relatively low levels (<3%) of 3,5,6-trichloro-2-methoxy pyridine and two unidentified metabolites were present in small amounts of the samples (Bidlack, 1979).
- Chlorpyrifos was immobile in loamy sand and sandy loam soil; only 2 to 13% of the applied radioactivity leached out of the zone of application with 6 to 10 inches of water. Mobility in beach sand was low. After leaching with 10 inches of water, 78.9% of the surface-applied chlorpyrifos remained in the top inch of sand (Dow Chemical Company, 1972).
- Chlorpyrifos was not persistent in pond water treated at 0.05 lb active ingredient per acre (a.i./a) or in a polluted aquatic environment treated at 0.23 to 0.27 lb a.i./a (Schaefer and Dupras, 1970; Madder, 1977). The rates of decline were not determined, and losses to underlying segments were not investigated. Chlorpyrifos applied to pond or rice floodwater as a slow-release formulation (chlorinated polyethylene pellets) exhibited no patterns of decline in 22 weeks (Nelson and Evans, 1973). The concentration of chlorpyrifos was extremely variable in the top 1 inch of pond sediment and rice plot soil; however, there was a clear trend toward the partitioning of chlorpyrifos from water onto soil and sediments.
- ^{14}C -Chlorpyrifos residues found in wheat, soybeans and beets planted 119 days after treatment of loamy sand soil with ^{14}C -chlorpyrifos at 2 lb a.i./acre amounted to 0.31, 0.31 and 0.03 ppm chlorpyrifos equivalents, respectively. Chlorpyrifos was largely degraded in the soil before the crops were planted, however, and the plant residues consisted primarily of unidentified ^{14}C residues. Residues in wheat and soybeans concentrated in the vegetative portions of the plants (Bauriedel et al., 1976).

III. PHARMACOKINETICS

Absorption

- Chlorpyrifos (unlabeled, 99.8% pure) was readily absorbed from the gastrointestinal (GI) tract in six men given a single oral dose at 0.5 mg/kg (Nolan et al., 1984). Absorption was estimated to be approximately 70% over a 5-day period. Blood chlorpyrifos levels remained low (<30 ng/mL) throughout the study. Mean blood concentrations of the principal metabolite of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (3,5,6-TCP), peaked at 0.93 $\mu\text{g}/\text{mL}$ 6 hours after ingestion. There was a 1- to 2-hour delay in the absorption of the oral dose.
- Approximately 90% of a single oral dose of 50 mg ^{36}Cl -chlorpyrifos/kg (in corn oil) was absorbed from the GI tract of male Wistar rats within 2 to 3 days after dosing (Smith et al., 1967).
- A single oral dose of ^{14}C -chlorpyrifos (2,6-ring-labeled) (19.1 mg/kg, 23.5 $^\circ\text{Ci}/\text{mg}$; or 6.9 mg/kg, 48.4 $^\circ\text{Ci}/\text{mg}$) was absorbed rapidly by male Sprague-Dawley rats (Dow Chemical Company, 1972). At least 73% of the ^{14}C -chlorpyrifos was absorbed by the rats within 3 days after administration. Only 1.6 to 2.5% of the administered radioactivity remained in the tissues and carcass at 72 hours postdosing; blood ^{14}C levels peaked 1 to 3 hours after dosing, accounting for 3 to 6% of the ingested ^{14}C -chlorpyrifos. About 68 to 76%, 5 to 15%, and 0.15 to 0.63% of the administered ^{14}C was eliminated in the urine, feces and expired air, respectively, within 72 hours. The authors reported that absorption may have been slightly reduced in some animals as a result of predose starvation and frequent bleeding at 2-hour intervals.

- Less than 3% of single doses of analytical grade (unlabeled, 99.8% pure) chlorpyrifos (5.0 mg/kg, dissolved in dipropylene glycol methyl ether or methylene chloride) was absorbed 7 days after dermal application to six men (Nolan et al., 1984). Blood levels of 3,5,6-TCP, which were used to determine absorption and clearance rates of chlorpyrifos, peaked at 0.063 $\mu\text{g}/\text{mL}$ 24 hours post-dosing. The average half-life for the appearance of 3,5,6-TCP in the blood was 22.5 hours.

Distribution

- Because of the rapid elimination of chlorpyrifos and its metabolites following administration of a single oral dose of 0.5 mg/kg to six men (Nolan et al., 1984), they are not expected to accumulate to any appreciable extent in humans.
- The highest levels of radioactivity in male Wistar rats given a single oral dosage of ^{36}Cl -chlorpyrifos (50 mg/kg) were recovered at 4 hours post-dosing in the kidneys, liver, lung and fat (0.0924, 0.0690, 0.406 and 0.317 mmol radioactive equivalents/kg tissue, respectively) (Smith et al., 1967). Radioactivity was eliminated rapidly from the liver ($t_{1/2}$, 10 hours), kidney ($t_{1/2}$, 12 hours) and muscle ($t_{1/2}$, 16 hours) but was retained for a longer period of time by fat tissue ($t_{1/2}$, 62 hours).
- Tissue ^{14}C residue levels were low (< 1 ppm) 72 hours after male Sprague-Dawley rats were given a single oral dosage of [2,6- ^{14}C pyridyl]chlorpyrifos (19.1 mg/kg; 23.5 $^{\circ}\text{Ci}/\text{mg}$) (Dow Chemical Company, 1972). Fat and intestines contained the highest levels of radioactivity (approximately 0.757 and 0.363 ppm, respectively); brain ^{14}C residue concentrations were <0.010 ppm.

Metabolism

- Very low levels (<30 mg/mL) of unchanged chlorpyrifos were found in the blood and no parent compound was recovered in the urine during the 5 days after six men were given a single oral dose (0.5 mg/kg) of the pesticide (Nolan et al., 1984). Most of the chlorpyrifos was converted to 3,5,6-TCP; however, other metabolites were not identified.
- In studies of workers exposed occupationally to chlorpyrifos, several urinary metabolites of the insecticide were identified by gas chromatography. O,O-Diethyl phosphate was found in 96% of the urine specimens, and O,O-diethyl phosphorothionate was recovered from 28% of the samples (Hayes et al., 1980; Loes and Bradway, 1977). Hayes et al. (1980) reported that 8-hour exposure levels were <27.6 $\mu\text{g}/\text{m}^3$ for workers exposed to spray emulsions of Dursban E-2 containing 23.5% chlorpyrifos.
- Two major metabolites, ^{36}Cl -3,5,6-trichloro-2-pyridyl phosphate and ^{36}Cl -3,5,6-TCP were recovered from the urine and feces of male Wistar rats administered a single oral dose of 50 mg ^{36}Cl -chlorpyrifos/kg (in corn oil) (Smith et al., 1967).
- Male Sprague-Dawley rats given a single oral dose of ^{14}C -chlorpyrifos (19.1 mg/kg, 23.5 $^{\circ}\text{Ci}/\text{mg}$) excreted 3,5,6-TCP as the major metabolite and another unidentified compound in the urine (Dow Chemical Company, 1972). A total of 1% of the ^{14}C recovered in expired air, almost all of which was ^{14}C -CO₂, suggesting that some cleavage of the pyridyl ring had occurred.
- In an *in vitro* study using rat hepatic microsomes, ^{14}C -chlorpyrifos (10 mg/mL, 10.6 mCi/mmol) was readily metabolized to 3,5,6-TCP (Dow Chemical Company, 1972). No other metabolites were found. The reaction was NADPH-dependent, and binding of chlorpyrifos to microsomes occurred prior to catabolism. These findings were also noted in studies by Sultatos et al. (1981, 1982, 1985) and Sultatos and Murphy (1983). They indicated that chlorpyrifos may be metabolized by a glutathione-mediated process. Male Charles River Swiss mice injected with chlorpyrifos (70 mg/kg) displayed a “moderate but transient” depletion of hepatic glutathione (Sultatos et al., 1982).

- Mostafa et al. (1983) reported that the *in vivo* alkylating activities of 1-¹⁴C-ethyl- labeled chlorpyrifos were high following intraperitoneal injection of 5- or 15- mg/kg doses in male mice (strain not given). Labeled 7-ethylguanine found in hepatic RNA hydrolysates measured approximately $5.5 \times 10^{-3}\%$ of the administered radioactivity. The two major unidentified radioactive peaks associated with hepatic DNA hydrolysates corresponded to $3 \times 10^{-2}\%$ and $2.3 \times 10^{-3}\%$ of the applied ¹⁴C dose. The authors reported that the total incorporation of ¹⁴C into mouse liver nucleic acids was greater for RNA than for DNA. In addition, the degree of ¹⁴C-incorporation appeared to be dose related.

Excretion

- Within 5 days after ingesting single oral dose of chlorpyrifos (0.5 mg/kg), six men eliminated an average of 70% of the administered insecticide via the urine, with a urinary elimination half-life of 27 hours (Nolan et al., 1984). Fecal elimination of chlorpyrifos and/or its metabolites was not measured.
- Smith et al. (1967) reported that approximately 90% of a radioactive dose of ³⁶Cl- chlorpyrifos (50 mg/kg) administered orally to male Wistar rats was excreted in the urine within 2 to 3 days. The remaining 10% was eliminated in the feces.
- Approximately 68 to 70%, 14 to 15%, and 0.15 to 0.39% of a single oral dose of ¹⁴C-chlorpyrifos (19.1 mg/kg, 23.5 °Ci/mg) administered to two male Sprague- Dawley rats were eliminated in the urine, feces and exhaled air, respectively, within 72 hours after dosing (Dow Chemical Company, 1972). Thus, the urine provided the primary route of elimination for the insecticide and/or its metabolites.
- Essentially all of the 3% of a dermal dose (5.0 mg/kg) of chlorpyrifos absorbed by male volunteers was eliminated in the urine within 7 days post-administration (Nolan et al., 1984). An elimination half-life of 27 hours was reported.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- Plasma cholinesterase (ChE) activity was depressed to about 15% of predose levels following administration of a single oral dose of 0.5 mg chlorpyrifos/kg to six men (Nolan et al., 1984). Enzyme activity returned to near-normal (i.e., 80 to 90% of predose levels) within 4 weeks. No other signs or symptoms of toxicity were observed during the 30-day post- treatment period.
- In a study by Dow Chemical Company (1972), 16 human male volunteers (four/dose) received 0, 0.014, 0.03 or 0.10 mg chlorpyrifos/kg/day (in capsule form) for 28, 28, 21 or 9 days, respectively. The high-dose treatment (0.10 mg/kg/day) was discontinued after 9 days due to a runny nose and blurred vision in one individual. The authors did not state why administration of the 0.03 mg/kg dose was terminated on day 21. Mean plasma ChE activity in the high-dose (0.10 mg/kg) group was inhibited by about 30% when compared to the mean control value ($p < 0.05$) and by about 65% when compared to baseline (i.e., pretreatment) levels. In the group receiving 0.03 mg/kg/day doses, plasma ChE activity averaged about 70% of pretreatment levels and 87% of concurrent control values; however, these differences were not statistically significant. Plasma ChE activity was comparable for low-dose and control individuals. Plasma ChE activities of all affected persons returned to pretreatment levels within 4 weeks after administration of test material was terminated. No effect on erythrocyte ChE activity was observed at any dose. This study identified a No-Observed-Adverse-Effect Level (NOAEL) of 0.03 mg/kg/ day and a Lowest-Observed-Adverse-Effect Level. (LOAEL) of 0.1 mg/kg/day based on the absence or presence of decreased plasma ChE activity.

- Five office workers exposed to chlorpyrifos in the air (levels not reported) for 5 to 21 hours over a 3-day period had significantly ($p < 0.01$) reduced erythrocyte ChE levels 1 month after exposure, when compared to values obtained 4 months post-exposure (Hodgson et al., 1986). Erythrocyte ChE activity measured on the first day after exposure was estimated to be approximately 33% of the 4-month value. Physical examinations, nerve conduction studies, and routine blood and urine tests were normal for all but one worker, who developed numbness and tingling in the fingertips of both hands 3 weeks after exposure. Most of the individuals complained of fatigue, weakness and anxiety and experienced diarrhea, abdominal pain and nausea within hours and also during the first 3 weeks after exposure to chlorpyrifos. Symptoms were resolved by 4 weeks, and no chlorpyrifos was detected in the office air 2 weeks after the initial exposure period.
- A 42-year-old man who ingested approximately 300 mg chlorpyrifos/kg was comatose and showed acute signs of cholinergic toxicity through day 17. Longer term neurological effects (leg weakness, reduced or abolished tendon reflex, reduced or lost vibration sense, and muscle denervation) were present from day 40 and became progressively worse with time (Lotti et al., 1986). Blood concentration of chlorpyrifos dropped in an exponential manner from 680 nmol/L on day 3 to 49 nmol/L on day 10; none was detected 13 days after ingestion. Blood ChE, plasma butylcholinesterase and lymphocyte neuropathy target esterase (NTE) activity levels were markedly depressed on day 30 but began to increase thereafter, through day 90. Inhibition of NTE preceded the development of polyneuropathy.
- An 11-day-old boy, exposed to chlorpyrifos in the home, became lethargic and cyanotic prior to respiratory arrest (Dunphy et al., 1980). The infant was resuscitated but remained limp and relatively unresponsive to stimuli. His red blood cell ChE activity level was about 50% below normal. After 8 days, the infant appeared well but ChE activity was not measured. Exposure was probably via both the oral and cutaneous routes, since chlorpyrifos residues were found on dish towels, food preparation surfaces and the infant's clothing. Direct inhalation exposure may also have occurred since the house reportedly smelled strongly of insecticides when the baby was taken to the hospital.
- Insecticide-related signs or symptoms of toxicity were not observed in any of six men who received a single dermal application of 5.0 mg chlorpyrifos/kg (Nolan et al., 1984). Mean plasma ChE activity was depressed slightly (to about 13% of predose levels) but did not exhibit a consistent pattern among the individual volunteers.
- Seven human adults (sex not reported) were exposed dermally, by patch tests, to 1.0, 1.5, 3.0, 5.0 or 7.5 mg chlorpyrifos/kg; the total exposure areas ranged from 2.25 to 1350 in², and the length of exposure was 12 hours (Dow Chemical Company, 1972). No skin irritation was observed in any of the subjects, and both erythrocyte and plasma ChE levels remained unchanged throughout the experimental period. In addition, no morphological alterations were observed in lymphocytes obtained from exposed sites. The data indicate that low levels of chlorpyrifos do not present a significant toxicity hazard from acute skin exposure.
- Plasma ChE activities in a group of seven adult humans (sex not reported) decreased by about 30% following multiple 12-hour dermal exposures to chlorpyrifos (Dow Chemical Company, 1972). During the first test period, individuals received three applications of 25 mg chlorpyrifos/kg, and in the second experiment, each subject received applications of 5 mg chlorpyrifos/kg. No other effects, including dermal irritation, were observed. ChE activity levels returned to normal within 7 to 9 days after the final exposure.
- Spray workers exposed to 0.5% chlorpyrifos emulsion in field trials for malaria control showed decreased plasma and erythrocyte ChE activity levels (Eliason et al., 1969). In this study, five of seven sprayers showed more than a 50% reduction in ChE within 2 weeks after spraying began.
- In a study by Ludwig et al. (1970), groups of two to three human volunteers were exposed to one of several thermal aerosols containing chlorpyrifos. Exposures of 3 to 8 minutes at concentrations of about

0.8 μm^3 produced no significant changes in ChE levels. This concentration is similar to the application rate recommended in thermal fogging.

Long-term Exposure

- Plasma ChE was significantly ($p < 0.001$) inhibited in a group of 17 workers exposed occupationally to a Time-Weighted Average (TWA) of 7.54 mg chlorpyrifos/ m^3 for 8 hours/day, 5 days/week, for 2 years, when compared to age- and sex-matched controls (Hayes et al., 1980). Most workers experienced headaches and complained of aggravated nasal or respiratory problems. General physical examinations were normal, however as were erythrocyte ChE activity levels.
- Two groups of machine-operating farm workers (numbers not reported) exposed daily to a granular insecticide containing 5% chlorpyrifos were examined over a 2-year period (Majczakowa et al., 1985). These tractor drivers and feeder operators were in contact with insecticide concentrations not exceeding 0.015 and 0.040 mg/m^3 , respectively, based on samples periodically analyzed from breathing areas of workers. The authors reported that up to 2 mg chlorpyrifos were recovered from the workers' hands at various sampling intervals. Average potential exposure at work to chlorpyrifos was estimated to be 0.373 mg/hour for the first year of the study and 0.034 mg/hour for the second year. No signs of toxicity or changes in blood ChE activity were observed.

Animals

Short-term Exposure

- An oral LD_{50} of 152 mg/kg was reported for female mice and 169 mg/kg for female rats given chlorpyrifos by intubation in soy bean oil (details of the chlorpyrifos formulation were not provided) (Berteau and Deen, 1978). Oral LD_{50} values for male and female rats ranged from 118 to 245 mg/kg ; no significant sex-related differences were observed (Gaines, 1969; McCollister et al., 1974). The acute oral LD_{50} for male guinea pigs was 504 mg/kg , and no deaths were noted in male and female rabbits dosed with 1,000 mg/kg (McCollister et al., 1974).
- In a study conducted by Dow Chemical Company (1972), each of three rhesus monkeys (sex not specified) was given a single oral dose of 3.5 mg chlorpyrifos/ kg . Erythrocyte ChE levels were 60% below pretreatment levels at 4 hours post-dosing but increased to 66, 80 and 82% of baseline values at 8, 24 and 48 hours, respectively. Plasma ChE levels were more severely affected and were only 6, 8, 14 and 30% of baseline values at the respective sampling times tested above.
- Two rhesus monkeys (sex not reported) given a single oral dose of 2 $\text{mg}/\text{kg}/\text{day}$ chlorpyrifos for 3 consecutive days showed no clinical signs of toxicity (Dow Chemical Company, 1972). 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 (to 60 to 65% of control levels) were observed on the second and third days of the study.
- In a range-finding study conducted by Dow Chemical Company (1972), pairs of beagle dogs consuming a diet containing 0.6 ppm (0.015 $\text{mg}/\text{kg}/\text{day}$, based on Lehman, 1959) chlorpyrifos for 12 days showed no changes in either plasma or erythrocyte ChE activity. When the chemical was administered for 28 days at a dietary concentration of 2 ppm (0.1 $\text{mg}/\text{kg}/\text{day}$), the plasma ChE activity in one female was reduced by 50% within 7 days after the study began. In another study, dogs fed 6, 20 or 60 ppm (0.15, 0.5 and 1.5 $\text{mg}/\text{kg}/\text{day}$) chlorpyrifos for 35 days showed reduced plasma ChE activity 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 NOAEL was 0.015 $\text{mg}/\text{kg}/\text{day}$ for dogs exposed orally to chlorpyrifos.

- Symptoms of severe ChE inhibition developed in beagle dogs (two/sex/ group) fed 2,000 (50 mg/kg/day) or 600 (15 mg/kg/day) ppm chlorpyrifos in the diet for 5 and 16 days, respectively (Dow Chemical Company, 1972; conversions based on Lehman, 1959). These dogs were taken off their respective diets and placed on a 200-ppm diet. Additional groups of dogs consumed a 200-ppm (5-mg/kg/day) diet for up to 45 days or a 20- or 60- ppm (0.5 or 1.5 mg/kg/day) diet for up to 88 days. Slowed growth was observed in all males and in females consuming 200 ppm chlorpyrifos. Plasma and erythrocyte ChEs were depressed in all groups of animals. Brain ChE activity was decreased in both sexes receiving 200 ppm but only in females consuming the 60-ppm diet. Gross and histological examination of tissues was normal in all dogs. This study indentified a brain ChE-depression NOAEL of 0.5 mg/kg/day and a LOAEL of 1.5 mg/kg/day for beagles of both sexes.
- Acute dermal and inhalation exposures to chlorpyrifos (in 65% xylene) were as toxic to mice and rats as were oral exposures. A dermal LD₅₀ value of 202 mg/kg for rats was reported by Gaines (1969), and inhalation LC₅₀ values of 152 and 169 mg/kg were reported for female mice and rats, respectively, by Berteau and Deen (1978).
- In a study by Berteau and Dean (1978), groups of 16 mature female NAMRU mice (30 to 35 g) inhaled a 65% xylene aerosol cloud containing the equivalent of 0.1 to 50 mg chlorpyrifos/kg for 27 to 50 minutes. Dose-related decreases in plasma acetylcholinesterase were observed; enzyme activity was 55% of predosing activity following exposure to 0.2 mg/kg and less than 10% after exposure to 50 mg/kg.
- 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 lachrymation, slight nasal discharge and gasping during exposure (Dow Chemical Company, 1972). Animals appeared normal during the 14-day post-inhalation period, and postmortem examination of tissues revealed no gross pathological changes.

Dermal/Ocular Effects

- Chlorpyrifos (0.5 mL of a 24% solution) was applied to the intact and abraded skin of six New Zealand albino rabbits (sex and age not reported) (Dow Chemical Company, 1972). Animals were exposed to the test material for 24 hours. Moderate to severe erythema developed on all exposed areas; slight necrosis was observed on four of the intact areas and five of the abraded areas. All exposed skin areas had some degree of edema. Reactions of intact and abraded skin of three additional rabbits exposed to chlorpyrifos (24% in solution) for 6 hours included slight erythema, slight edema and slight necrosis within 10, 30 to 60, and 90 to 210 minutes, respectively.
- Instillation of chlorpyrifos (0.1 mL of a 24% solution) into the conjunctival sac of the right eye of six New Zealand albino rabbits (sex and age not reported) produced conjunctival redness, iritis and corneal injury in all treated eyes (Dow Chemical Company, 1972).
- No skin or eye irritation developed in any of the 40 adult male and female mongrel dogs (number/sex not reported) or 85 puppies dipped repeatedly in 0.0125, 0.025, 0.05 or 0.10% chlorpyrifos solutions (Dow Chemical Company, 1972). Adults were dipped three to six times at 15- or 30-day intervals; puppies (6 to 8 weeks old) were dipped up to three times in the 0.025% solution but only once in the 0.05% solution.
- Percutaneous injections of 1.0, 2.0 or 3.98 g chlorpyrifos (as a 25% solution) into groups of four albino rabbits (sex not reported) induced slight to moderate erythema, swelling, and necrosis (Dow Chemical Company, 1972). On mid-dose rabbit died 3 days after exposure, and three high-dose animals died within 6 to 9 days post-dosing.

Long-term Exposure

- Groups of 20 albino rats (10/sex/dose) were maintained on diets containing 10, 30, 100 or 300 ppm chlorpyrifos (approximately 0.5, 1.5, 5 or 15 mg/kg, respectively, based on Lehman, 1959) for 90 days (Dow Chemical Company, 1972). Another group of rats that received 1,000 ppm (50 mg/kg) chlorpyrifos in the feed was included in this study, but due to high mortality, this group was terminated after 28 days. Plasma and erythrocyte ChE activity levels were depressed in a dose-related manner, at 1,000 ppm the average plasma ChE activity for both sexes was less than 1% of the control value. Brain ChE activity also was reduced to about 30%, 20% and 10% of control values in animals consuming 100, 300 and 1,000 ppm chlorpyrifos, respectively. Exposure to 0.5 mg/kg/day for 90 days caused a 3 to 7% reduction in brain ChE activity, and 1.5- mg/kg/day doses reduced brain ChE activity by 19 to 22% after 90 days (neither was significantly different from control values at $p = 0.05$). The animals dosed at 1,000 ppm exhibited signs of severe ChE depression (e.g., tremors, bloody noses, circling and backing, ulceration of the cornea and nostrils), decreased food consumption, significant weight loss and increased mortality. Rats consuming the 300-ppm feed experienced tremors, slight diuresis and slight growth retardation. Consumption of the three lowest doses produced no signs of toxicity. The NOAEL based on reduced brain ChE activity was 0.5 mg/kg/day.
- In a 91-day study conducted by Dow Chemical Company (1972), groups of 20 albino rats (10/sex/dose) fed 3.0 or 10.0 mg chlorpyrifos/kg/day exhibited reduced plasma and erythrocyte ChE activities (35 to 58% and 14 to 26% of control values, respectively) and showed slight to severe signs of ChE inhibition and toxicity (e.g., hunched appearance, tremors, weight loss). Rats consuming a 0.3- or 1.0- mg/kg/day diet had depressed plasma and erythrocyte ChE levels. Male rats given 0.3 mg chlorpyrifos/kg/day had reduced body weight gains. No adverse effects were observed at the 0.03- or 0.1- mg/kg/day dose levels. Survival was not affected at any exposure level, and ChE activities returned to normal within 1 to 2 weeks after withdrawal of the test compound from the diet. This study identified a NOAEL of 0.1 mg/kg/day and a LOAEL of 0.3 mg/kg/day (for male rats).
- Albino rats (20/sex/group) consuming dietary levels of 0.03, 0.15 or 0.75 mg chlorpyrifos/kg/day for 6 months showed no significant clinical or histological signs or symptoms of organophosphate poisoning (Dow Chemical Company, 1972). Animals ingesting the high-dose feed exhibited reduced plasma and erythrocyte ChE activities (i.e., 35 to 60% and 50% of control values, respectively). Brain ChE activity was not affected at any treatment level. This study identified a NOAEL of 0.15 mg chlorpyrifos/kg/day.
- A group of 20 Sprague-Dawley rats (4 weeks old, sexes combined) were fed diets containing 100 ppm chlorpyrifos (5 mg/kg/day) for 1 year. Seventeen animals also consumed a diet supplemented with both chlorpyrifos (100 ppm) and corn oil (final concentration, 20%) (Buchet et al., 1977; conversions based on Lehman, 1959). Control animals consumed nonsupplemented or corn oil-only supplemented diets (19 and 18, respectively). All rats grew normally and had normal levels of hormone sensitive lipase, lipoprotein lipase, serum fatty acids (free and total), serum glycerol and serum cholesterol (total). Total glycerol and cholesterol content of the aorta in test animals were also comparable to controls, but total aortic fatty acids were increased in animals consuming both chlorpyrifos and 20% oil in the diet. Total blood ChE activity was reduced by 40% in the chlorpyrifos-exposed group on the normal feed and by 60% in those animals on the fat-enriched regimen. A LOAEL of 5 mg/kg/day, based on reduced ChE activity and increased total aortic fatty acids, was identified in this study.
- In a study conducted by McCollister et al. (1974), groups of 7-week-old Sherman rats (25/sex/dose) fed a diet containing 1.0 or 3.0 mg chlorpyrifos/kg/day for 2 years exhibited significantly ($p < 0.05$) depressed plasma ChE activity levels. Erythrocyte ChE activities were depressed ($p < 0.05$) by approximately 67% and 85% of control values in rats fed the 1.0- and 3.0-mg/kg/day diets, respectively; brain ChE activity was significantly ($p < 0.05$) reduced (to about 57% of controls) in the high-dose animals only. Effects on ChE activity were reversible when consumption of a chlorpyrifos-free diet was resumed. ChE activity in animals fed 0.1 mg/kg/day was comparable to control values. No clinical signs of toxicity

were observed at any dose. A NOAEL of 0.1 mg chlorpyrifos/kg/day based on plasma ChE activity, and a NOAEL of 3.0 mg/kg/day based on systemic effects were established in this study.

- Groups of three or four rhesus monkeys (males and females combined) that received chlorpyrifos by gavage at doses of 0.08, 0.4 or 2.0 mg/kg/day for 6 months showed no significant compound-related clinical effects compared to control animals (Dow Chemical Company, 1972). The only evidence of exposure to chlorpyrifos was reduced plasma and erythrocyte ChE activities in the mid- and high-dose monkeys (significance levels not reported). Midbrain and cerebrum ChE values were not affected in any group. Histological examination revealed that the liver and kidney showed no abnormalities in any of the animals. A NOAEL of 0.08 mg/kg/day was identified, based on the absence of inhibition of ChE at this dose.
- Plasma ChE activity was depressed by 40 to 75% of pretest or control values in groups of three or four male and female beagle dogs (aged 10 to 11 months) given 0.1, 1.0 or 3.0 mg chlorpyrifos/kg/day in the diet for 1 to 2 years (McCollister et al., 1974). Brain ChE activity was slightly depressed (by 8 to 21% of the control value) at the highest dose level; however, these decreases were not statistically significant ($p < 0.05$). Both plasma and brain ChE activities returned to normal when dosed animals were placed on the control diet. No significant health effects were observed at any dose. (0.01 and 0.03 mg/kg/day) using the following criteria: mortality, body weight, food intake, hematological and clinical chemistry parameters, organ weight, tumor incidence, and gross and histopathological examination of tissues. The only notable difference was a statistically significant ($p < 0.05$) increase in the mean liver-to-body weight ratio of high-dose males administered chlorpyrifos for 2 years. The NOAEL for dogs identified in this study was 0.03 mg chlorpyrifos/kg/day based on plasma ChE activity levels and was 3.0 mg/kg/day based on systemic effects.

Reproductive Effects

- In a three-generation reproduction study, groups of 15 male and 15 female Sprague-Dawley albino rats that received up to 1.0 mg chlorpyrifos/kg/day in the feed showed no adverse reproductive or postnatal effects, as judged by fertility, gestation, viability and lactation indices (Dow Chemical Company, 1972). Litter size, pup weight and sex ratios of offspring from treated rats also were unaffected by exposure to the test compound. In addition, ingestion of chlorpyrifos (0.03, 0.1 or 0.3 mg/kg/day by the first-generation rats and 0.1, 0.3 or 1.0 mg/kg/day by the 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 rats (both sexes) consuming the 1.0-mg/kg/day diet had depressed plasma and erythrocyte ChE activities, as did females given feed containing 0.3 mg chlorpyrifos/kg/day. It was concluded that the reproductive NOAEL from this study is 0.1 mg/kg/day.
- Dow Chemical Company (1972) reported 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. 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, 63 ± 7 days).
- Everett (1982) studied the effects of dermal applications of a test material consisting of 43.2% chlorpyrifos on 185 Holstein bulls. No other dosing information was provided. In the 172 bulls that did not exhibit severe toxic effects, semen production initially was depressed but returned to normal within 6 months post-treatment. Normal semen production was measured for at least 12 months post-treatment. Six bulls became very sick following exposure to chlorpyrifos, and their semen production did not return to normal within 12 months. The remaining seven bulls died after being treated with the insecticide.

Developmental Effects

- In a developmental study conducted by Deacon et al. (1980), 40 to 47 pregnant CF-1 mice were dosed, by gavage, with 1, 10 or 25 mg chlorpyrifos/kg/day on gestation days 6 through 15. Fifty-one

animals were used in the control group. Severe maternal toxicity, including mortality, clinical signs of ChE inhibition, and significant ($p < 0.05$) decreases in maternal body weight gains and food and water consumption were reported at 25 mg/kg/day. Plasma and erythrocyte ChE levels were significantly ($p < 0.05$) reduced at all dose levels tested when compared with controls. Developmental toxic effects were reported at 25 mg/kg/day. The findings included significant reductions in fetal body weight and crown-rump lengths. Exencephaly was noted in four fetuses from three litters of mice dosed with 25 mg/kg/day (nonsignificant) and in five fetuses from five litters in the 1-mg/kg/day dose group (significant at $p < 0.05$). Significant increases ($p < 0.05$) in the incidences of delayed ossification of the skull and sternebrae were also reported at the highest dose level. The incidence of sternebrae abnormalities was high ($p < 0.05$) among fetuses born to dams in the lowest dose group (1 mg/kg/day). These results were not repeatable, however, when additional groups of 35 to 41 CF-1 mice were given 0, 0.1, 1 or 10 mg chlorpyrifos/kg by gavage on gestation days 6 through 15 (Deacon et al., 1980). Thus, although the first study suggests a fetal LOAEL of 1 mg/kg/day based on reduced ChE activity and adverse developmental effects, the data are equivocal due to the lack of any significant response in the second group of test animals. From both studies combined, the NOAEL appears to be 0.1 mg/kg/day.

- 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 insecticide by gavage at 1.0 mg/kg/day on gestation days 6 through 15 (Dow Chemical Company, 1972). Parental females received chlorpyrifos in the diet at levels of 0.1, 0.3 or 1.0 mg/kg/day for the rest of their lives. Maternal weight gains and food consumption, corpora lutea, resorptions, fetus viability, pup weights and sex ratios also appeared to be unaffected.
- In the dog reproduction study by Dow Chemical Company (1972), 58 of 85 (68%) pups born to mongrel dogs that had been dipped repeatedly in chlorpyrifos (0.025, 0.05 or 0.10% solutions) died before 8 weeks of age. Only one puppy death was attributed to chlorpyrifos (due to symptoms suggestive of organophosphate toxicity). No other details were given.

Mutagenicity

- Chlorpyrifos was not mutagenic in *Salmonella typhimurium* or *Escherichia coli* either in the absence or presence of both mammalian and plant microsomes (Gentile et al., 1982; Moriya et al., 1983; Shirasu et al., 1976, Waters et al., 1982). Similarly, chlorpyrifos did not induce reverse mutations in *Zea mays* (Gentile et al., 1982; Seehy et al., 1984) or cause sex-linked recessive lethal mutations in *Drosophila melanogaster* (Waters et al., 1982).
- Evidence of *in vivo* induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells following intraperitoneal or oral administration of chlorpyrifos have been reported (Amer and Fahmy, 1982). Chlorpyrifos induced mitotic suppression and increased the frequency of chromosome aberrations in *Vicia faba* (Abdou and Abdei-Wahab, 1985). It produced clastogenic effects in barley (Kaur and Grover, 1985).
- Chlorpyrifos, without exogenous metabolic activation, was genotoxic in DNA polymerase I-deficient *E. coli* and recombination-deficient *S. typhimurium* (Waters et al., 1982). However, inconsistent results have been seen in the *Bacillus subtilis* rec-assay. Waters et al. (1982) reported a positive response, but Shirasu et al. (1976) and Kada et al. (1980) found no genotoxic activity. Chlorpyrifos was not recombinogenic in *Saccharomyces cerevisiae* D₃ either with or without rat liver microsomes (Waters et al., 1982) or in *S. cerevisiae* D₄ with or without mammalian and plant microsomes (Gentile et al., 1982). Unscheduled DNA synthesis was not increased in chlorpyrifos-treated human lung fibroblast (Waters et al., 1982). Chlorpyrifos was judged negative for the induction of sister chromatid exchanges in Chinese hamster ovary cells, chick embryos (Muscarella et al., 1984), and the LAZ-007 human lymphoid cell line (Sobti et al., 1982).

Carcinogenicity

- Chlorpyrifos was not tumorigenic in a chronic feeding study in which 7-week-old Sherman rats were administered up to 3.0 mg chlorpyrifos/kg/ day for 2 years (McCollister et al., 1974). Thirty rats/sex/dose were used; an additional five to seven rats/sex/group killed for interim gross and microscopic pathological examinations were normal throughout the experimental period. In this study too few animals were included to fully assess the carcinogenicity of chlorpyrifos in rats. Since there was no evidence of toxicity at tested doses, a minimal toxic dose (MID) may not have been used.
- No excess tumors developed in groups of 10- to 11-month-old beagle dogs (three or four/sex/group) fed 0.01, 0.03, 0.1, 1.0 or 3.0 mg chlorpyrifos/kg in the diet for 1 to 2 years (McCollister et al., 1974). In addition, gross and microscopic examination of tissues was normal for all dose levels throughout the experimental period. However, this study is considered of limited usefulness in providing data to assess the carcinogenic potential of chlorpyrifos: the study was relatively short (i.e., less-than-lifetime for dogs), and the animals may not have been tested at MID.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term, and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) (\text{BW})}{(\text{UF}) (\text{___ L/day})} = \text{___ mg/L (___ } \mu\text{g/L)}$$

where:

- NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.
- BW = assumed body weight of a child (10 kg) or an adult (70 kg).
- UF = uncertainty factors (10, 100, 1,000, or 10,000), in accordance with EPA or NAS/OW guidelines.
- ___ L/day = assumed daily water consumption of a child (1 L/day) or an adult 2 U day).

One-day Health Advisory

No suitable information was found in the available literature for determining the One-day Health Advisory (HA) for chlorpyrifos. The Ten-day HA for a child, 30 $\mu\text{g/L}$, calculated below, is recommended for use as a conservative estimate for a 1-day exposure to chlorpyrifos.

Ten-day Health Advisory

The human oral-exposure study by Dow Chemical Company (1972) has been selected to serve as the basis for the Ten-day HA because it contains adequate human data of appropriate length. In this study, groups of four healthy adult men were administered chlorpyrifos in capsule form at doses of 0, 0.014, 0.03 or 0.10 mg/kg for 28, 28, 21 or 9 days, respectively. Adverse health effects were observed only in the high-dose (0.10 mg/kg) group; at this exposure level, plasma ChE activity was reduced by approximately 65% when compared to control values. One individual in this group also experienced a runny nose and blurred vision. A NOAEL of 0.03 mg/kg/day was identified from this study.

Another study by Dow Chemical Company (1972), in which a NOAEL of 0.015 mg/kg was reported for beagle dogs consuming chlorpyrifos in the feed for 12 days, was also considered for the calculation of the Ten-day HA. However, this value was not used because the available human data were within one order of

magnitude of the animal data. Therefore, the results of this dog study support the human data used to calculate the Ten-day HA but are not the most appropriate for the derivation of this HA.

The Ten-day HA for the 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.03 \text{ mg/kg/day}) (10 \text{ kg})}{(1 \text{ L/day}) (100)} = 0.03 \text{ mg/L (rounded to } 30 \text{ } \mu\text{g/L)}$$

where:

- 0.03 mg/kg/day = NOAEL, based on the absence of decreased plasma ChE activity in male human subjects exposed to chlorpyrifos via the oral route for 21 days (Dow Chemical Company, 1972).
- 10 kg = assumed weight of child.
- 10 = uncertainty factor, chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from a human study is employed.
- 1 L/day = assumed water consumption of 10-kg child.

Longer-term Health Advisory

The study by Dow Chemical Company (1972) in which humans received daily oral doses of chlorpyrifos for up to 28 consecutive days has been selected to serve as the basis for the Longer-term HA because it contains human data that identify a NOAEL and a LOAEL. Although several adequate subchronic animal studies were available, data from these studies indicate that humans are more sensitive to chlorpyrifos following oral administration than other species. Using human data would, therefore, allow for a more conservative estimate of a Longer-term HA for a 10 kg child. The following studies used plasma and erythrocyte ChE activity levels as the basis for NOAEL and LOAEL values. Two 3-month feeding studies with rats identified NOAELs of 0.1 and 1.5 mg/kg/day; respective LOAELs were 0.3 and 5 mg/kg/day (Dow Chemical Company, 1972). A 6-month study in which rats received chlorpyrifos in the diet identified a NOAEL of 0.15 mg/kg/day and a LOAEL of 0.75 mg/kg/day (Dow Chemical Company, 1972). Finally, monkeys exposed via oral gavage to chlorpyrifos for 6 months showed no adverse effects at 0.08 mg/kg/day doses but had reduced ChE activities at 0.4 mg/kg/day (Dow Chemical Company, 1972). The human study, also conducted by Dow Chemical Company (1972), identified a NOAEL of 0.03 mg/kg/day and a LOAEL of 0.1 mg/kg/day based on the absence or presence of reduced plasma ChE activity following administration of chlorpyrifos (in capsules) to groups of four healthy male adults for 9 and 21 days, respectively.

The Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.03 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 0.03 \text{ mg/L (rounded to } 30 \text{ } \mu\text{g/L)}$$

where:

- 0.03 mg/kg/day = NOAEL, based on the absence of decreased plasma ChE activity in male human subjects exposed to chlorpyrifos via the oral route for 21 days (Dow Chemical Company, 1972).
- 10 kg = assumed body weight of a child.
- 10 = uncertainty factor, chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from a human study is employed.
- 1 L/day = assumed daily water consumption of a child.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.03 \text{ mg/kg/day}) (70 \text{ kg})}{(10) (2 \text{ L/day})} = 0.105 \text{ mg/L (rounded to } 100 \text{ } \mu\text{g/L)}$$

where:

- 0.03 mg/kg/day = NOAEL, based on the absence of decreased plasma ChE activity in male human subjects exposed to chlorpyrifos via the oral route for 21 days (Dow Chemical Company, 1972).
- 70 kg = assumed body weight of an adult.
- 10 = uncertainty factor, chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from a human study is employed.
- 2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious health effects during a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA in drinking water alone is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed.

If the contaminant is classified as a known, probable, or possible human carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution must be exercised in making a decision on how to deal with possible lifetime exposure to this substance. For human (A) or probable human (B) carcinogens, a Lifetime HA is not recommended. For possible human carcinogens (C), an additional 10-fold safety factor is used to calculate the Lifetime HA. The risk manager must balance this assessment of carcinogenic potential and the quality of the data against the likelihood of occurrence and significance of health effects related to noncarcinogenic endpoints of toxicity. To assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the range of 1 in 10,000 to 1 in 1,000,000 for the 70-kg adult drinking 2 L of water/day are provided in the Evaluation of Carcinogenic Potential section.

The oral-exposure study with humans by Dow Chemical Company (1972) has been selected to serve as the basis for the Lifetime HA because it contains adequate human exposure data that are supported by animal data. A NOAEL of 0.03 mg/kg/day for humans was identified in this study. Three animal studies also were considered for the calculation of the Reference Dose (RfD), Drinking Water Equivalent Level (DWEL), and Lifetime HA. The chronic (2-year) feeding study in rats (McCollister et al., 1974) was judged unacceptable due to insufficient numbers of animals (25/sex/dose with an additional 5 to 7/sex/dose for interim sacrifices). The other animal studies, which included the reproduction study with rats by Dow Chemical Company (1972) and the chronic feeding study with dogs by McCollister et al. (1974), were considered adequate. However, the human oral-exposure study by Dow Chemical Company (1972) was judged most appropriate for the calculation of the Lifetime HA for chlorpyrifos. Although this human study was coreclassified as supplementary because only four males/dose were used, when considered with the

available experimental data in animals, the NOAEL for ChE inhibition in humans (0.03 mg/kg/day) appeared comparable to that in rats (0.1 mg/kg/day) and dogs (0.03 mg/kg/day).

Using the human study (Dow Chemical Company, 1972), the Lifetime HA is derived as follows:

Step 1: Determination of the RfD

$$\text{RfD} = \frac{(0.03 \text{ mg/kg/day})}{(10)} = 0.003 \text{ mg/kg/day}$$

where:

0.03 mg/kg/day = NOAEL, based on the absence of decreased plasma ChE activity in male human subjects exposed to chlorpyrifos via the oral route for 21 days (Dow Chemical Company, 1972).

10 = uncertainty factor, chosen in accordance with EPA or NAS/OW guidelines in which a NOEL from a human study is employed.

Step 2: Determination of the DWEL

$$\text{DWEL} = \frac{(0.003 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.105 \text{ mg/L (rounded to } 100 \text{ } \mu\text{g/L)}$$

where:

0.003 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime HA

$$\text{Lifetime HA} = (0.1 \text{ mg/L}) (20\%) = 0.02 \text{ mg/L (} 20 \text{ } \mu\text{g/L)}$$

where:

0.105 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenicity was found in rats or dogs fed up to 3.0 mg chlorpyrifos/kg/day for 1 to 2 years (McCollister et al., 1974).
- The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenic potential of chlorpyrifos.
- Applying the criteria in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), chlorpyrifos may be classified in Group D: not classifiable. This category is for agents with inadequate animal evidence for carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE, AND STANDARDS

- The American Conference of Governmental Industrial Hygienists recommends a Threshold Limit Value-Time-Weighted Average of 0.2 mg/m³ and a Short-term Exposure Limit of 0.6 mg/m³ for dermal exposures (ACGIH, 1988).
- The Food and Agriculture Organization/World Health Organization (FAO/ WHO, 1984) Acceptable Daily Intake for chlorpyrifos is 0.01 mg/kg/day (Gartrell et al., 1985).

VII. ANALYTICAL METHODS

- Chlorpyrifos is one of the phosphorus-containing pesticides. The relative ease with which this pesticide can be monitored by element-specific detectors has usually led to its inclusion in pesticide monitoring studies. Chlorpyrifos can be analyzed by Methods 622 (U.S. EPA, 1982) and 507 (U.S. EPA, 1988). In both methods a liter of sample is extracted with methylene chloride, the solvent is then exchanged for hexane or methyl tertiary butyl ether. Analysis is by an element-specific thermionic nitrogen-phosphorus detector, which allows even relatively “dirty” samples to be analyzed with no clean-up. The estimated detection limit for this residue is 0.3 µg/L.

VIII. TREATMENT TECHNOLOGIES

- There is presently no information available describing treatment technologies capable of removing chlorpyrifos from contaminated drinking water supplies.
- Chlorpyrifos may be amenable to removal by activated carbon adsorption due to its solubility.
- Chlorpyrifos is probably not amenable to removal by aeration on the basis of its Henry’s Coefficient value.

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III. DRINKING WATER HEALTH ADVISORIES

Substance Name: Chlorpyrifos
 CASRN: 2921-88-2
 Primary Synonyms: Dowco 179; Chlorpyrifos-ethyl; Phosphorothioic acid, 0,0,-diethyl 0-(3,5,6-trichloro-2-pyridyl) ester; Pyrinex

The Office of Water provides Drinking Water Health Advisories (HAs) as technical guidance for the protection of public health. HAs are not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 20%. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in the Health Advisory Background Document.

III.A.1 ONE-DAY HEALTH ADVISORY FOR A CHILD

Appropriate data for calculating the One-day HA are not available. The Ten-day HA of 0.03 mg/L is recommended as a conservative estimate for a One-day HA for a 10-kg child

III.A.2 TEN-DAY HEALTH ADVISORY FOR A CHILD

FA: 3E-2 mg/L
 NOAEL: 0.03 mg/kg/day
 UF: 10 (allows for intrahuman variability when using a NOAEL from a human study)
 Assumptions: 1 L/day water consumption for a 10-kg child
 Principle Study: Dow Chemical Company, 1972
 Discussion: Groups of four healthy adult men received chlorpyrifos in capsule form at doses of 0, 0.014, 0.03, or 0.10 mg/kg/day for 28, 28, 21, or 9 days, respectively. Plasma cholinesterase (ChE) activity was reduced by about 65% compared to the control value at the high dose and one subject experienced a runny nose and blurred vision at this level. No adverse effects were observed at lower levels. A NOAEL of 0.03 mg/kg/day was identified in this study.

III.A.3 LONGER-TERM HEALTH ADVISORY FOR A CHILD

HA: 3E-2 mg/L
 NOAEL: 0.03 mg/kg/day
 UF: 10 (allows for intrahuman variability when using a NOAEL from a human study)
 Assumptions: 1 L/day water consumption for a 10-kg child
 Principle Study: Dow Chemical Company, 1972 (Study described in section III.A.2.)
 Discussion: Although several adequate subchronic animal studies are available, the data indicate that humans are more sensitive than other species to orally administered chlorpyrifos. In addition, human data have identified a NOAEL and LOAEL for inhibition of plasma cholinesterase activity.

III.A.4 LONGER-TERM HEALTH ADVISORY FOR AN ADULT

HA: 1E-1 mg/L
 NOAEL 0.03 mg/kg/day
 UF: 10 (allows for intrahuman variability when using a NOAEL from a human study)

Assumptions: 2 L/day water consumption for a 70-kg adult

Principle Study: Dow Chemical Company, 1972 (Study described in section III.A.2.)

III.A.5 DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL: 1E-1 mg/L
 Basis: Oral RfD = 3E-3 mg/kg/day (verified 3/11/86)
 Lifetime HA: 2E-2 mg/L (20% exposure by drinking water)
 UF: 10 (allows for intrahuman variability when using a NOAEL from a human study)

Assumptions: 2 L/day water consumption for a 70-kg adult

Principal Study: Dow Chemical Company, 1972 (Study described in section III.A.2.)

III.A.6 ORGANOLEPTIC PROPERTIES

No taste or odor thresholds have been identified for chlorpyrifos

III.A.7 ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Available analytical methods are EPA Methods 622 (U.S. EPA, 1982) and 507 (U.S. EPA, 1988). In these methods, the sample is extracted with methylene chloride, the solvent is exchanged for hexane or methyl tertiary butyl ether, and the sample is analyzed using an element-specific thermionic nitrogen-phosphorus detector.

III.A.8 WATER TREATMENT

No information is available regarding treatment technologies capable of removing chlorpyrifos from contaminated water. However, based on the solubility and volatility of chlorpyrifos, granular activated carbon (GAC) adsorption would probably be more suitable than other technologies, such as aeration.

III.A.9 EPA DOCUMENTATION AND REVIEW OF HAS

Source Document: U.S. EPA. 1992. Drinking Water Health Advisory for Chlorpyrifos. Office of Water, Washington, D.C.

III.A.10 EPA CONTACT

Amal Mahfouz/OST (202) 260-9568

III.A.11 BIBLIOGRAPHY

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nitrogen- and phosphorus-containing pesticides in water by gas chromatography with a nitrogen-phosphorus detector. Cincinnati, OH: Environmental Monitoring and Support Laboratory. December.

REVISION HISTORY

April 1992

CHLORPYRIFOS

Drinking Water Health Advisory
Office of Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water (OW), provides information on the health effects, analytical methodology, and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

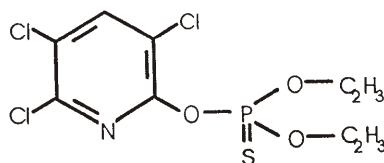
Health Advisories serve as informal technical guidance to assist Federal, State, and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime), and Lifetime exposures based on data describing noncarcinogenic endpoints of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifelong exposure and the ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit, or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 2921-88-2

Structural Formula



Chlorpyrifos

Synonyms

- Brodan; Chlorpyrifos; Chlorpyrifos-ethyl; Detmol U.A.; Dowco 179; Dursban; Dursban F; Ent 27311; Eradex; Ethion, dry; Lorsban; NA 2783 (Dot); OMS-0971; Phosphorothioic acid, O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) ester; Pyrinex.

Uses

- Chlorpyrifos is a broad-spectrum insecticide with many uses. An estimated 7 to 11 million pounds of chlorpyrifos are produced each year in the United States for domestic use. Of the total domestic chlorpyrifos usage, 57% is applied to corn and 5 to 6% to cotton. Commercial pest control and lawn and garden services consume 20 to 22% of the annual chlorpyrifos usage, followed by domestic household and lawn and garden application (9 to 13%).

Properties (Kenaga, 1980; Windholz et al., 1983; Worthing, 1987)

Chemical Formula	C ₉ H ₁₁ Cl ₃ NO ₃ PS
Molecular Weight	350.57
Physical State (25° C)	White, granular crystals
Boiling Point	--
Melting Point	41 to 43.5° C
Density	--
Vapor Pressure (25° C)	1.87 x 10 ⁻⁵ mm Hg
Water Solubility (25° C)	2 ppm
Specific Gravity	--
Log Octanol/Water Partition	4.99
Coefficient (log K _{ow})	--
Taste Threshold (water)	--
Odor Threshold (water)	--
Conversion Factor	--
(ppm air as mg/m ³)	--

Occurrence

- Based on a 3-year, 20-city nationwide study conducted by the Food and Drug Administration, Gartrell et al. (1985) estimated that the average daily intake of chlorpyrifos from food and beverages (including water) is approximately 0.001 to 0.005 µg/kg. Contaminated grain and cereal products and garden fruits were the food groups through which exposure occurred.

Environmental Fate

- Chlorpyrifos hydrolyzes readily in water; its rate of hydrolysis increases with temperature (Worthing, 1987). When mixed with distilled water (pH 6.5) or pasture water (pH 7 to 9), chlorpyrifos levels dropped an average of 25% at 24° C and 48% at 38° C within 8 hours (Schaefer and Dupras, Jr., 1969).

- Chlorpyrifos administered at a rate of 3.4 kg chlorpyrifos/hectare (ha) dissipated fairly rapidly in sand and organic muck soils with respective half-lives of 2 and 8 weeks in the top 15 cm of soil (Chapman and Harris, 1980). Low levels of chlorpyrifos (2 to 3% of the amount applied) remained in both soils for up to 2 years. 3,5,6-Trichloro-2-pyridinol was the primary degradation product, reaching maximum concentrations of 13 and 39% of the chlorpyrifos applied to the sand and muck soils, respectively. The

concentrations of the oxygen analog of chlorpyrifos were ≤ 0.004 ppm in all samples. Chlorpyrifos (EC, emulsifiable concentrate), applied at 4 kg chlorpyrifos/ha to turf grass, dissipated rapidly with a half-life of <14 days in the soil and turf cover (Sears and Chapman, 1979). Movement of chlorpyrifos from the turf into the soil was minimal (<18% of the recovered chlorpyrifos at any time during the study).

- Breakdown of chlorpyrifos in soil primarily results from microbial metabolism (Miles et al., 1979). Chlorpyrifos (10 ppm) is degraded more rapidly in sandy loam soil (half-life, <1 week) than in organic soil (half-life, 2.5 weeks). In sterilized soils, the half-life for chlorpyrifos is > 17 weeks. Half-lives of 11 to 141 days were reported in another study in soils ranging in texture from loamy sand to clay (Bidlack, 1979). 3,5,6-Trichloro-2-methoxy-pyridine and two unidentified minor metabolites of chlorpyrifos were recovered after a 1-year incubation period; most of the radiocarbon, however, was recovered as $^{14}\text{CO}_2$ with small amounts incorporated into soil organic matter.
- After 30 days of aerobic aging of soil, ^{14}C -chlorpyrifos degraded with half-lives of 15 days in loam and 58 days in clay soils. The half-lives in treated and anaerobically incubated loam and clay were 39 and 51 days, respectively. The major degradation product formed was 3,5,6-trichloro-2-pyridinol. Degradation of this compound was very slow. Evolution of $^{14}\text{CO}_2$ was insignificant, and incorporation of ^{14}C into the soil organic matter was slow. Relatively low levels (<3%) of 3,5,6-trichloro-2-methoxy-pyridine and two unidentified metabolites were present in small amounts of the samples (Bidlack, 1979).
- Chlorpyrifos was immobile in loamy sand and sandy loam soil; only 2 to 13% of the applied radioactivity leached out of the zone of application with 6 to 10 inches of water. Mobility in beach sand was low. After leaching with 10 inches of water, 78.9% of the surface-applied chlorpyrifos remained in the top inch of sand (Dow Chemical Company, 1972).
- Chlorpyrifos was not persistent in pond water treated at 0.05 lb active ingredient per acre (a.i./a) or in a polluted aquatic environment treated at 0.23 to 0.27 lb a.i./a (Schaefer and Dupras, 1970; Madder, 1977). The rates of decline were not determined, and losses to underlying segments were not investigated. Chlorpyrifos applied to pond or rice floodwater as a slow-release formulation (chlorinated polyethylene pellets) exhibited no patterns of decline in 22 weeks (Nelson and Evans, 1973). The concentration of chlorpyrifos was extremely variable in the top 1 inch of pond sediment and rice plot soil; however, there was a clear trend toward the partitioning of chlorpyrifos from water onto soil and sediments.
- ^{14}C -Chlorpyrifos residues found in wheat, soybeans and beets planted 119 days after treatment of loamy sand soil with ^{14}C -chlorpyrifos at 2 lb a.i./acre amounted to 0.31, 0.31 and 0.03 ppm chlorpyrifos equivalents, respectively. Chlorpyrifos was largely degraded in the soil before the crops were planted, however, and the plant residues consisted primarily of unidentified ^{14}C residues. Residues in wheat and soybeans concentrated in the vegetative portions of the plants (Bauriedel et al., 1976).

III. PHARMACOKINETICS

Absorption

- Chlorpyrifos (unlabeled, 99.8% pure) was readily absorbed from the gastrointestinal (GI) tract in six men given a single oral dose at 0.5 mg/kg (Nolan et al., 1984). Absorption was estimated to be approximately 70% over a 5-day period. Blood chlorpyrifos levels remained low (<30 ng/mL) throughout the study. Mean blood concentrations of the principal metabolite of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (3,5,6-TCP), peaked at 0.93 $\mu\text{g/mL}$ 6 hours after ingestion. There was a 1- to 2-hour delay in the absorption of the oral dose.
- Approximately 90% of a single oral dose of 50 mg ^{36}Cl -chlorpyrifos/kg (in corn oil) was absorbed from the GI tract of male Wistar rats within 2 to 3 days after dosing (Smith et al., 1967).

- A single oral dose of ^{14}C -chlorpyrifos (2,6-ring-labeled) (19.1 mg/kg, 23.5 $^{\circ}\text{Ci}/\text{mg}$; or 6.9 mg/kg, 48.4 $^{\circ}\text{Ci}/\text{mg}$) was absorbed rapidly by male Sprague-Dawley rats (Dow Chemical Company, 1972). At least 73% of the ^{14}C -chlorpyrifos was absorbed by the rats within 3 days after administration. Only 1.6 to 2.5% of the administered radioactivity remained in the tissues and carcass at 72 hours postdosing; blood ^{14}C levels peaked 1 to 3 hours after dosing, accounting for 3 to 6% of the ingested ^{14}C -chlorpyrifos. About 68 to 76%, 5 to 15%, and 0.15 to 0.63% of the administered ^{14}C was eliminated in the urine, feces and expired air, respectively, within 72 hours. The authors reported that absorption may have been slightly reduced in some animals as a result of predose starvation and frequent bleeding at 2-hour intervals.
- Less than 3% of single doses of analytical grade (unlabeled, 99.8% pure) chlorpyrifos (5.0 mg/kg, dissolved in dipropylene glycol methyl ether or methylene chloride) was absorbed 7 days after dermal application to six men (Nolan et al., 1984). Blood levels of 3,5,6-TCP, which were used to determine absorption and clearance rates of chlorpyrifos, peaked at 0.063 $\mu\text{g}/\text{mL}$ 24 hours post-dosing. The average half-life for the appearance of 3,5,6-TCP in the blood was 22.5 hours.

Distribution

- Because of the rapid elimination of chlorpyrifos and its metabolites following administration of a single oral dose of 0.5 mg/kg to six men (Nolan et al., 1984), they are not expected to accumulate to any appreciable extent in humans.
- The highest levels of radioactivity in male Wistar rats given a single oral dosage of ^{36}Cl -chlorpyrifos (50 mg/kg) were recovered at 4 hours post-dosing in the kidneys, liver, lung and fat (0.0924, 0.0690, 0.406 and 0.317 mmol radioactive equivalents/kg tissue, respectively) (Smith et al., 1967). Radioactivity was eliminated rapidly from the liver ($t_{1/2}$, 10 hours), kidney ($t_{1/2}$, 12 hours) and muscle ($t_{1/2}$, 16 hours) but was retained for a longer period of time by fat tissue ($t_{1/2}$, 62 hours).
- Tissue ^{14}C residue levels were low (< 1 ppm) 72 hours after male Sprague-Dawley rats were given a single oral dosage of [2,6- ^{14}C pyridyl]chlorpyrifos (19.1 mg/kg; 23.5 $^{\circ}\text{Ci}/\text{mg}$) (Dow Chemical Company, 1972). Fat and intestines contained the highest levels of radioactivity (approximately 0.757 and 0.363 ppm, respectively); brain ^{14}C residue concentrations were <0.010 ppm.

Metabolism

- Very low levels (<30 mg/mL) of unchanged chlorpyrifos were found in the blood and no parent compound was recovered in the urine during the 5 days after six men were given a single oral dose (0.5 mg/kg) of the pesticide (Nolan et al., 1984). Most of the chlorpyrifos was converted to 3,5,6-TCP; however, other metabolites were not identified.
- In studies of workers exposed occupationally to chlorpyrifos, several urinary metabolites of the insecticide were identified by gas chromatography. O,O- Diethyl phosphate was found in 96% of the urine specimens, and O,O-diethyl phosphorothionate was recovered from 28% of the samples (Hayes et al., 1980; Loes and Bradway, 1977). Hayes et al. (1980) reported that 8-hour exposure levels were <27.6 $\mu\text{g}/\text{m}^3$ for workers exposed to spray emulsions of Dursban E-2 containing 23.5% chlorpyrifos.
- Two major metabolites, ^{36}Cl -3,5,6-trichloro-2-pyridyl phosphate and ^{36}Cl -3,5,6-TCP were recovered from the urine and feces of male Wistar rats administered a single oral dose of 50 mg ^{36}Cl -chlorpyrifos/kg (in corn oil) (Smith et al., 1967).
- Male Sprague-Dawley rats given a single oral dose of ^{14}C -chlorpyrifos (19.1 mg/kg, 23.5 $^{\circ}\text{Ci}/\text{mg}$) excreted 3,5,6-TCP as the major metabolite and another unidentified compound in the urine (Dow Chemical Company, 1972). A total of 1% of the ^{14}C recovered in expired air, almost all of which was ^{14}C -CO₂, suggesting that some cleavage of the pyridyl ring had occurred.

- In an *in vitro* study using rat hepatic microsomes, ^{14}C -chlorpyrifos (10 mg/mL, 10.6 mCi/mmol) was readily metabolized to 3,5,6-TCP (Dow Chemical Company, 1972). No other metabolites were found. The reaction was NADPH-dependent, and binding of chlorpyrifos to microsomes occurred prior to catabolism. These findings were also noted in studies by Sultatos et al. (1981, 1982, 1985) and Sultatos and Murphy (1983). They indicated that chlorpyrifos may be metabolized by a glutathione-mediated process. Male Charles River Swiss mice injected with chlorpyrifos (70 mg/kg) displayed a “moderate but transient” depletion of hepatic glutathione (Sultatos et al., 1982).
- Mostafa et al. (1983) reported that the *in vivo* alkylating activities of 1- ^{14}C -ethyl- labeled chlorpyrifos were high following intraperitoneal injection of 5- or 15- mg/kg doses in male mice (strain not given). Labeled 7-ethylguanine found in hepatic RNA hydrolysates measured approximately $5.5 \times 10^{-3}\%$ of the administered radioactivity. The two major unidentified radioactive peaks associated with hepatic DNA hydrolysates corresponded to $3 \times 10^{-2}\%$ and $2.3 \times 10^{-3}\%$ of the applied ^{14}C dose. The authors reported that the total incorporation of ^{14}C into mouse liver nucleic acids was greater for RNA than for DNA. In addition, the degree of ^{14}C -incorporation appeared to be dose related.

Excretion

- Within 5 days after ingesting single oral dose of chlorpyrifos (0.5 mg/kg), six men eliminated an average of 70% of the administered insecticide via the urine, with a urinary elimination half-life of 27 hours (Nolan et al., 1984). Fecal elimination of chlorpyrifos and/or its metabolites was not measured.
- Smith et al. (1967) reported that approximately 90% of a radioactive dose of ^{36}Cl - chlorpyrifos (50 mg/kg) administered orally to male Wistar rats was excreted in the urine within 2 to 3 days. The remaining 10% was eliminated in the feces.
- Approximately 68 to 70%, 14 to 15%, and 0.15 to 0.39% of a single oral dose of ^{14}C -chlorpyrifos (19.1 mg/kg, 23.5 $^{\circ}\text{Ci}/\text{mg}$) administered to two male Sprague- Dawley rats were eliminated in the urine, feces and exhaled air, respectively, within 72 hours after dosing (Dow Chemical Company, 1972). Thus, the urine provided the primary route of elimination for the insecticide and/or its metabolites.
- Essentially all of the 3% of a dermal dose (5.0 mg/kg) of chlorpyrifos absorbed by male volunteers was eliminated in the urine within 7 days post-administration (Nolan et al., 1984). An elimination half-life of 27 hours was reported.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- Plasma cholinesterase (ChE) activity was depressed to about 15% of predose levels following administration of a single oral dose of 0.5 mg chlorpyrifos/kg to six men (Nolan et al., 1984). Enzyme activity returned to near-normal (i.e., 80 to 90% of predose levels) within 4 weeks. No other signs or symptoms of toxicity were observed during the 30-day post- treatment period.
- In a study by Dow Chemical Company (1972), 16 human male volunteers (four/dose) received 0, 0.014, 0.03 or 0.10 mg chlorpyrifos/kg/day (in capsule form) for 28, 28, 21 or 9 days, respectively. The high-dose treatment (0.10 mg/kg/day) was discontinued after 9 days due to a runny nose and blurred vision in one individual. The authors did not state why administration of the 0.03 mg/kg dose was terminated on day 21. Mean plasma ChE activity in the high-dose (0.10 mg/kg) group was inhibited by about 30% when compared to the mean control value ($p < 0.05$) and by about 65% when compared to baseline (i.e.,

pretreatment) levels. In the group receiving 0.03 mg/kg/day doses, plasma ChE activity averaged about 70% of pretreatment levels and 87% of concurrent control values; however, these differences were not statistically significant. Plasma ChE activity was comparable for low-dose and control individuals. Plasma ChE activities of all affected persons returned to pretreatment levels within 4 weeks after administration of test material was terminated. No effect on erythrocyte ChE activity was observed at any dose. This study identified a No-Observed-Adverse-Effect Level (NOAEL) of 0.03 mg/kg/day and a Lowest-Observed-Adverse-Effect Level (LOAEL) of 0.1 mg/kg/day based on the absence or presence of decreased plasma ChE activity.

- Five office workers exposed to chlorpyrifos in the air (levels not reported) for 5 to 21 hours over a 3-day period had significantly ($p < 0.01$) reduced erythrocyte ChE levels 1 month after exposure, when compared to values obtained 4 months post-exposure (Hodgson et al., 1986). Erythrocyte ChE activity measured on the first day after exposure was estimated to be approximately 33% of the 4-month value. Physical examinations, nerve conduction studies, and routine blood and urine tests were normal for all but one worker, who developed numbness and tingling in the fingertips of both hands 3 weeks after exposure. Most of the individuals complained of fatigue, weakness and anxiety and experienced diarrhea, abdominal pain and nausea within hours and also during the first 3 weeks after exposure to chlorpyrifos. Symptoms were resolved by 4 weeks, and no chlorpyrifos was detected in the office air 2 weeks after the initial exposure period.
- A 42-year-old man who ingested approximately 300 mg chlorpyrifos/kg was comatose and showed acute signs of cholinergic toxicity through day 17. Longer term neurological effects (leg weakness, reduced or abolished tendon reflex, reduced or lost vibration sense, and muscle denervation) were present from day 40 and became progressively worse with time (Lotti et al., 1986). Blood concentration of chlorpyrifos dropped in an exponential manner from 680 nmol/L on day 3 to 49 nmol/L on day 10; none was detected 13 days after ingestion. Blood ChE, plasma butylcholinesterase and lymphocyte neuropathy target esterase (NTE) activity levels were markedly depressed on day 30 but began to increase thereafter, through day 90. Inhibition of NTE preceded the development of polyneuropathy.
- An 11-day-old boy, exposed to chlorpyrifos in the home, became lethargic and cyanotic prior to respiratory arrest (Dunphy et al., 1980). The infant was resuscitated but remained limp and relatively unresponsive to stimuli. His red blood cell ChE activity level was about 50% below normal. After 8 days, the infant appeared well but ChE activity was not measured. Exposure was probably via both the oral and cutaneous routes, since chlorpyrifos residues were found on dish towels, food preparation surfaces and the infant's clothing. Direct inhalation exposure may also have occurred since the house reportedly smelled strongly of insecticides when the baby was taken to the hospital.
- Insecticide-related signs or symptoms of toxicity were not observed in any of six men who received a single dermal application of 5.0 mg chlorpyrifos/kg (Nolan et al., 1984). Mean plasma ChE activity was depressed slightly (to about 13% of predose levels) but did not exhibit a consistent pattern among the individual volunteers.
- Seven human adults (sex not reported) were exposed dermally, by patch tests, to 1.0, 1.5, 3.0, 5.0 or 7.5 mg chlorpyrifos/kg; the total exposure areas ranged from 2.25 to 1350 in², and the length of exposure was 12 hours (Dow Chemical Company, 1972). No skin irritation was observed in any of the subjects, and both erythrocyte and plasma ChE levels remained unchanged throughout the experimental period. In addition, no morphological alterations were observed in lymphocytes obtained from exposed sites. The data indicate that low levels of chlorpyrifos do not present a significant toxicity hazard from acute skin exposure.
- Plasma ChE activities in a group of seven adult humans (sex not reported) decreased by about 30% following multiple 12-hour dermal exposures to chlorpyrifos (Dow Chemical Company, 1972). During the first test period, individuals received three applications of 25 mg chlorpyrifos/kg, and in the second

experiment, each subject received applications of 5 mg chlorpyrifos/kg. No other effects, including dermal irritation, were observed. ChE activity levels returned to normal within 7 to 9 days after the final exposure.

- Spray workers exposed to 0.5% chlorpyrifos emulsion in field trials for malaria control showed decreased plasma and erythrocyte ChE activity levels (Eliason et al., 1969). In this study, five of seven sprayers showed more than a 50% reduction in ChE within 2 weeks after spraying began.
- In a study by Ludwig et al. (1970), groups of two to three human volunteers were exposed to one of several thermal aerosols containing chlorpyrifos. Exposures of 3 to 8 minutes at concentrations of about $0.8 \mu\text{m}/\text{m}^3$ produced no significant changes in ChE levels. This concentration is similar to the application rate recommended in thermal fogging.

Long-term Exposure

- Plasma ChE was significantly ($p < 0.001$) inhibited in a group of 17 workers exposed occupationally to a Time-Weighted Average (TWA) of 7.54 mg chlorpyrifos/ m^3 for 8 hours/day, 5 days/week, for 2 years, when compared to age- and sex-matched controls (Hayes et al., 1980). Most workers experienced headaches and complained of aggravated nasal or respiratory problems. General physical examinations were normal, however as were erythrocyte ChE activity levels.
- Two groups of machine-operating farm workers (numbers not reported) exposed daily to a granular insecticide containing 5% chlorpyrifos were examined over a 2-year period (Majczakowa et al., 1985). These tractor drivers and feeder operators were in contact with insecticide concentrations not exceeding 0.015 and 0.040 mg/m^3 , respectively, based on samples periodically analyzed from breathing areas of workers. The authors reported that up to 2 mg chlorpyrifos were recovered from the workers' hands at various sampling intervals. Average potential exposure at work to chlorpyrifos was estimated to be 0.373 mg/hour for the first year of the study and 0.034 mg/hour for the second year. No signs of toxicity or changes in blood ChE activity were observed.

Animals

Short-term Exposure

- An oral LD_{50} of 152 mg/kg was reported for female mice and 169 mg/kg for female rats given chlorpyrifos by intubation in soy bean oil (details of the chlorpyrifos formulation were not provided) (Berteau and Deen, 1978). Oral LD_{50} values for male and female rats ranged from 118 to 245 mg/kg; no significant sex-related differences were observed (Gaines, 1969; McCollister et al., 1974). The acute oral LD_{50} for male guinea pigs was 504 mg/kg, and no deaths were noted in male and female rabbits dosed with 1,000 mg/kg (McCollister et al., 1974).
- In a study conducted by Dow Chemical Company (1972), each of three rhesus monkeys (sex not specified) was given a single oral dose of 3.5 mg chlorpyrifos/kg. Erythrocyte ChE levels were 60% below pretreatment levels at 4 hours post-dosing but increased to 66, 80 and 82% of baseline values at 8, 24 and 48 hours, respectively. Plasma ChE levels were more severely affected and were only 6, 8, 14 and 30% of baseline values at the respective sampling times tested above.
- Two rhesus monkeys (sex not reported) given a single oral dose of 2 mg/kg/day chlorpyrifos for 3 consecutive days showed no clinical signs of toxicity (Dow Chemical Company, 1972). 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 (to 60 to 65% of control levels) were observed on the second and third days of the study.

- In a range-finding study conducted by Dow Chemical Company (1972), pairs of beagle dogs consuming a diet containing 0.6 ppm (0.015 mg/kg/day, based on Lehman, 1959) chlorpyrifos for 12 days showed no changes in either plasma or erythrocyte 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% within 7 days after the study began. In another study, dogs fed 6, 20 or 60 ppm (0.15, 0.5 and 1.5 mg/kg/day) chlorpyrifos for 35 days showed reduced plasma ChE activity 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 NOAEL was 0.015 mg/kg/day for dogs exposed orally to chlorpyrifos.
- Symptoms of severe ChE inhibition developed in beagle dogs (two/sex/ group) fed 2,000 (50 mg/kg/day) or 600 (15 mg/kg/day) ppm chlorpyrifos in the diet for 5 and 16 days, respectively (Dow Chemical Company, 1972; conversions based on Lehman, 1959). These dogs were taken off their respective diets and placed on a 200-ppm diet. Additional groups of dogs consumed a 200-ppm (5-mg/kg/day) diet for up to 45 days or a 20- or 60- ppm (0.5 or 1.5 mg/kg/day) diet for up to 88 days. Slowed growth was observed in all males and in females consuming 200 ppm chlorpyrifos. Plasma and erythrocyte ChEs were depressed in all groups of animals. Brain ChE activity was decreased in both sexes receiving 200 ppm but only in females consuming the 60-ppm diet. Gross and histological examination of tissues was normal in all dogs. This study identified a brain ChE-depression NOAEL of 0.5 mg/kg/day and a LOAEL of 1.5 mg/kg/day for beagles of both sexes.
- Acute dermal and inhalation exposures to chlorpyrifos (in 65% xylene) were as toxic to mice and rats as were oral exposures. A dermal LD₅₀ value of 202 mg/kg for rats was reported by Gaines (1969), and inhalation LC₅₀ values of 152 and 169 mg/kg were reported for female mice and rats, respectively, by Berteau and Deen (1978).
- In a study by Berteau and Dean (1978), groups of 16 mature female NAMRU mice (30 to 35 g) inhaled a 65% xylene aerosol cloud containing the equivalent of 0.1 to 50 mg chlorpyrifos/kg for 27 to 50 minutes. Dose-related decreases in plasma acetylcholinesterase were observed; enzyme activity was 55% of predosing activity following exposure to 0.2 mg/kg and less than 10% after exposure to 50 mg/kg.
- 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 lachrymation, slight nasal discharge and gasping during exposure (Dow Chemical Company, 1972). Animals appeared normal during the 14-day post-inhalation period, and postmortem examination of tissues revealed no gross pathological changes.

Dermal/Ocular Effects

- Chlorpyrifos (0.5 mL of a 24% solution) was applied to the intact and abraded skin of six New Zealand albino rabbits (sex and age not reported) (Dow Chemical Company, 1972). Animals were exposed to the test material for 24 hours. Moderate to severe erythema developed on all exposed areas; slight necrosis was observed on four of the intact areas and five of the abraded areas. All exposed skin areas had some degree of edema. Reactions of intact and abraded skin of three additional rabbits exposed to chlorpyrifos (24% in solution) for 6 hours included slight erythema, slight edema and slight necrosis within 10, 30 to 60, and 90 to 210 minutes, respectively.
- Instillation of chlorpyrifos (0.1 mL of a 24% solution) into the conjunctival sac of the right eye of six New Zealand albino rabbits (sex and age not reported) produced conjunctival redness, iritis and corneal injury in all treated eyes (Dow Chemical Company, 1972).
- No skin or eye irritation developed in any of the 40 adult male and female mongrel dogs (number/sex not reported) or 85 puppies dipped repeatedly in 0.0125, 0.025, 0.05 or 0.10% chlorpyrifos solutions (Dow Chemical Company, 1972). Adults were dipped three to six times at 15- or 30-day intervals;

puppies (6 to 8 weeks old) were dipped up to three times in the 0.025% solution but only once in the 0.05% solution.

- Percutaneous injections of 1.0, 2.0 or 3.98 g chlorpyrifos (as a 25% solution) into groups of four albino rabbits (sex not reported) induced slight to moderate erythema, swelling, and necrosis (Dow Chemical Company, 1972). On mid-dose rabbit died 3 days after exposure, and three high-dose animals died within 6 to 9 days post-dosing.

Long-term Exposure

- Groups of 20 albino rats (10/sex/dose) were maintained on diets containing 10, 30, 100 or 300 ppm chlorpyrifos (approximately 0.5, 1.5, 5 or 15 mg/kg, respectively, based on Lehman, 1959) for 90 days (Dow Chemical Company, 1972). Another group of rats that received 1,000 ppm (50 mg/kg) chlorpyrifos in the feed was included in this study, but due to high mortality, this group was terminated after 28 days. Plasma and erythrocyte ChE activity levels were depressed in a dose-related manner, at 1,000 ppm the average plasma ChE activity for both sexes was less than 1% of the control value. Brain ChE activity also was reduced to about 30%, 20% and 10% of control values in animals consuming 100, 300 and 1,000 ppm chlorpyrifos, respectively. Exposure to 0.5 mg/kg/day for 90 days caused a 3 to 7% reduction in brain ChE activity, and 1.5- mg/kg/day doses reduced brain ChE activity by 19 to 22% after 90 days (neither was significantly different from control values at $p = 0.05$). The animals dosed at 1,000 ppm exhibited signs of severe ChE depression (e.g., tremors, bloody noses, circling and backing, ulceration of the cornea and nostrils), decreased food consumption, significant weight loss and increased mortality. Rats consuming the 300-ppm feed experienced tremors, slight diuresis and slight growth retardation. Consumption of the three lowest doses produced no signs of toxicity. The NOAEL based on reduced brain ChE activity was 0.5 mg/kg/day.
- In a 91-day study conducted by Dow Chemical Company (1972), groups of 20 albino rats (10/sex/dose) fed 3.0 or 10.0 mg chlorpyrifos/kg/day exhibited reduced plasma and erythrocyte ChE activities (35 to 58% and 14 to 26% of control values, respectively) and showed slight to severe signs of ChE inhibition and toxicity (e.g., hunched appearance, tremors, weight loss). Rats consuming a 0.3- or 1.0- mg/kg/day diet had depressed plasma and erythrocyte ChE levels. Male rats given 0.3 mg chlorpyrifos/kg/day had reduced body weight gains. No adverse effects were observed at the 0.03- or 0.1- mg/kg/day dose levels. Survival was not affected at any exposure level, and ChE activities returned to normal within 1 to 2 weeks after withdrawal of the test compound from the diet. This study identified a NOAEL of 0.1 mg/kg/day and a LOAEL of 0.3 mg/kg/day (for male rats).
- Albino rats (20/sex/group) consuming dietary levels of 0.03, 0.15 or 0.75 mg chlorpyrifos/kg/day for 6 months showed no significant clinical or histological signs or symptoms of organophosphate poisoning (Dow Chemical Company, 1972). Animals ingesting the high-dose feed exhibited reduced plasma and erythrocyte ChE activities (i.e., 35 to 60% and 50% of control values, respectively). Brain ChE activity was not affected at any treatment level. This study identified a NOAEL of 0.15 mg chlorpyrifos/kg/day.
- A group of 20 Sprague-Dawley rats (4 weeks old, sexes combined) were fed diets containing 100 ppm chlorpyrifos (5 mg/kg/day) for 1 year. Seventeen animals also consumed a diet supplemented with both chlorpyrifos (100 ppm) and corn oil (final concentration, 20%) (Buchet et al., 1977; conversions based on Lehman, 1959). Control animals consumed nonsupplemented or corn oil-only supplemented diets (19 and 18, respectively). All rats grew normally and had normal levels of hormone sensitive lipase, lipoprotein lipase, serum fatty acids (free and total), serum glycerol and serum cholesterol (total). Total glycerol and cholesterol content of the aorta in test animals were also comparable to controls, but total aortic fatty acids were increased in animals consuming both chlorpyrifos and 20% oil in the diet. Total blood ChE activity was reduced by 40% in the chlorpyrifos-exposed group on the normal feed and by 60% in those animals on

the fat-enriched regimen. A LOAEL of 5 mg/kg/day, based on reduced ChE activity and increased total aortic fatty acids, was identified in this study.

- In a study conducted by McCollister et al. (1974), groups of 7-week-old Sherman rats (25/sex/dose) fed a diet containing 1.0 or 3.0 mg chlorpyrifos/kg/day for 2 years exhibited significantly ($p < 0.05$) depressed plasma ChE activity levels. Erythrocyte ChE activities were depressed ($p < 0.05$) by approximately 67% and 85% of control values in rats fed the 1.0- and 3.0-mg/kg/day diets, respectively; brain ChE activity was significantly ($p < 0.05$) reduced (to about 57% of controls) in the high-dose animals only. Effects on ChE activity were reversible when consumption of a chlorpyrifos-free diet was resumed. ChE activity in animals fed 0.1 mg/kg/day was comparable to control values. No clinical signs of toxicity were observed at any dose. A NOAEL of 0.1 mg chlorpyrifos/kg/day based on plasma ChE activity, and a NOAEL of 3.0 mg/kg/day based on systemic effects were established in this study.
- Groups of three or four rhesus monkeys (males and females combined) that received chlorpyrifos by gavage at doses of 0.08, 0.4 or 2.0 mg/kg/day for 6 months showed no significant compound-related clinical effects compared to control animals (Dow Chemical Company, 1972). The only evidence of exposure to chlorpyrifos was reduced plasma and erythrocyte ChE activities in the mid- and high-dose monkeys (significance levels not reported). Midbrain and cerebrum ChE values were not affected in any group. Histological examination revealed that the liver and kidney showed no abnormalities in any of the animals. A NOAEL of 0.08 mg/kg/day was identified, based on the absence of inhibition of ChE at this dose.
- Plasma ChE activity was depressed by 40 to 75% of pretest or control values in groups of three or four male and female beagle dogs (aged 10 to 11 months) given 0.1, 1.0 or 3.0 mg chlorpyrifos/kg/day in the diet for 1 to 2 years (McCollister et al., 1974). Brain ChE activity was slightly depressed (by 8 to 21% of the control value) at the highest dose level; however, these decreases were not statistically significant ($p < 0.05$). Both plasma and brain ChE activities returned to normal when dosed animals were placed on the control diet. No significant health effects were observed at any dose. (0.01 and 0.03 mg/kg/day) using the following criteria: mortality, body weight, food intake, hematological and clinical chemistry parameters, organ weight, tumor incidence, and gross and histopathological examination of tissues. The only notable difference was a statistically significant ($p < 0.05$) increase in the mean liver-to-body weight ratio of high-dose males administered chlorpyrifos for 2 years. The NOAEL for dogs identified in this study was 0.03 mg chlorpyrifos/kg/day based on plasma ChE activity levels and was 3.0 mg/kg/day based on systemic effects.

Reproductive Effects

- In a three-generation reproduction study, groups of 15 male and 15 female Sprague-Dawley albino rats that received up to 1.0 mg chlorpyrifos/kg/day in the feed showed no adverse reproductive or postnatal effects, as judged by fertility, gestation, viability and lactation indices (Dow Chemical Company, 1972). Litter size, pup weight and sex ratios of offspring from treated rats also were unaffected by exposure to the test compound. In addition, ingestion of chlorpyrifos (0.03, 0.1 or 0.3 mg/kg/day by the first-generation rats and 0.1, 0.3 or 1.0 mg/kg/day by the 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 rats (both sexes) consuming the 1.0-mg/kg/day diet had depressed plasma and erythrocyte ChE activities, as did females given feed containing 0.3 mg chlorpyrifos/kg/day. It was concluded that the reproductive NOAEL from this study is 0.1 mg/kg/day.
- Dow Chemical Company (1972) reported 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. 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, 63 ± 7 days).

- Everett (1982) studied the effects of dermal applications of a test material consisting of 43.2% chlorpyrifos on 185 Holstein bulls. No other dosing information was provided. In the 172 bulls that did not exhibit severe toxic effects, semen production initially was depressed but returned to normal within 6 months post-treatment. Normal semen production was measured for at least 12 months post-treatment. Six bulls became very sick following exposure to chlorpyrifos, and their semen production did not return to normal within 12 months. The remaining seven bulls died after being treated with the insecticide.

Developmental Effects

- In a developmental study conducted by Deacon et al. (1980), 40 to 47 pregnant CF-1 mice were dosed, by gavage, with 1, 10 or 25 mg chlorpyrifos/kg/day on gestation days 6 through 15. Fifty-one animals were used in the control group. Severe maternal toxicity, including mortality, clinical signs of ChE inhibition, and significant ($p < 0.05$) decreases in maternal body weight gains and food and water consumption were reported at 25 mg/kg/day. Plasma and erythrocyte ChE levels were significantly ($p < 0.05$) reduced at all dose levels tested when compared with controls. Developmental toxic effects were reported at 25 mg/kg/day. The findings included significant reductions in fetal body weight and crown-rump lengths. Exencephaly was noted in four fetuses from three litters of mice dosed with 25 mg/kg/day (nonsignificant) and in five fetuses from five litters in the 1-mg/kg/day dose group (significant at $p < 0.05$). Significant increases ($p < 0.05$) in the incidences of delayed ossification of the skull and sternbrae were also reported at the highest dose level. The incidence of sternbrae abnormalities was high ($p < 0.05$) among fetuses born to dams in the lowest dose group (1 mg/kg/day). These results were not repeatable, however, when additional groups of 35 to 41 CF-1 mice were given 0, 0.1, 1 or 10 mg chlorpyrifos/kg by gavage on gestation days 6 through 15 (Deacon et al., 1980). Thus, although the first study suggests a fetal LOAEL of 1 mg/kg/day based on reduced ChE activity and adverse developmental effects, the data are equivocal due to the lack of any significant response in the second group of test animals. From both studies combined, the NOAEL appears to be 0.1 mg/kg/day.

- 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 insecticide by gavage at 1.0 mg/kg/day on gestation days 6 through 15 (Dow Chemical Company, 1972). Parental females received chlorpyrifos in the diet at levels of 0.1, 0.3 or 1.0 mg/kg/day for the rest of their lives. Maternal weight gains and food consumption, corpora lutea, resorptions, fetus viability, pup weights and sex ratios also appeared to be unaffected.

- In the dog reproduction study by Dow Chemical Company (1972), 58 of 85 (68%) pups born to mongrel dogs that had been dipped repeatedly in chlorpyrifos (0.025, 0.05 or 0.10% solutions) died before 8 weeks of age. Only one puppy death was attributed to chlorpyrifos (due to symptoms suggestive of organophosphate toxicity). No other details were given.

Mutagenicity

- Chlorpyrifos was not mutagenic in *Salmonella typhimurium* or *Escherichia coli* either in the absence or presence of both mammalian and plant microsomes (Gentile et al., 1982; Moriya et al., 1983; Shirasu et al., 1976, Waters et al., 1982). Similarly, chlorpyrifos did not induce reverse mutations in *Zea mays* (Gentile et al., 1982; Seehy et al., 1984) or cause sex-linked recessive lethal mutations in *Drosophila melanogaster* (Waters et al., 1982).
- Evidence of *in vivo* induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells following intraperitoneal or oral administration of chlorpyrifos have been reported (Amer and Fahmy, 1982). Chlorpyrifos induced mitotic suppression and increased the frequency of chromosome aberrations in *Vicia faba* (Abdou and Abdei-Wahab, 1985). It produced clastogenic effects in barley (Kaur and Grover, 1985).

- Chlorpyrifos, without exogenous metabolic activation, was genotoxic in DNA polymerase I-deficient *E. coli* and recombination-deficient *S. typhimurium* (Waters et al., 1982). However, inconsistent results have been seen in the *Bacillus subtilis* rec-assay. Waters et al. (1982) reported a positive response, but Shirasu et al. (1976) and Kada et al. (1980) found no genotoxic activity. Chlorpyrifos was not recombinogenic in *Saccharomyces cerevisiae* D₃ either with or without rat liver microsomes (Waters et al., 1982) or in *S. cerevisiae* D₄ with or without mammalian and plant microsomes (Gentile et al., 1982). Unscheduled DNA synthesis was not increased in chlorpyrifos-treated human lung fibroblast (Waters et al., 1982). Chlorpyrifos was judged negative for the induction of sister chromatid exchanges in Chinese hamster ovary cells, chick embryos (Muscarella et al., 1984), and the LAZ-007 human lymphoid cell line (Sobti et al., 1982).

Carcinogenicity

- Chlorpyrifos was not tumorigenic in a chronic feeding study in which 7-week-old Sherman rats were administered up to 3.0 mg chlorpyrifos/kg/ day for 2 years (McCollister et al., 1974). Thirty rats/sex/dose were used; an additional five to seven rats/sex/group killed for interim gross and microscopic pathological examinations were normal throughout the experimental period. In this study too few animals were included to fully assess the carcinogenicity of chlorpyrifos in rats. Since there was no evidence of toxicity at tested doses, a minimal toxic dose (MID) may not have been used.
- No excess tumors developed in groups of 10- to 11-month-old beagle dogs (three or four/sex/group) fed 0.01, 0.03, 0.1, 1.0 or 3.0 mg chlorpyrifos/kg in the diet for 1 to 2 years (McCollister et al., 1974). In addition, gross and microscopic examination of tissues was normal for all dose levels throughout the experimental period. However, this study is considered of limited usefulness in providing data to assess the carcinogenic potential of chlorpyrifos: the study was relatively short (i.e., less-than-lifetime for dogs), and the animals may not have been tested at MID.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term, and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) (BW)}{(UF) (\text{___} \text{ L/day})} = \text{___} \text{ mg/L } (\text{___} \text{ } \mu\text{g/L})$$

where:

- NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.
- BW = assumed body weight of a child (10 kg) or an adult (70 kg).
- UF = uncertainty factors (10, 100, 1,000, or 10,000), in accordance with EPA or NAS/OW guidelines.
- ___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 U day).

One-day Health Advisory

No suitable information was found in the available literature for determining the One-day Health Advisory (HA) for chlorpyrifos. The Ten-day HA for a child, 30 $\mu\text{g/L}$, calculated below, is recommended for use as a conservative estimate for a 1-day exposure to chlorpyrifos.

Ten-day Health Advisory

The human oral-exposure study by Dow Chemical Company (1972) has been selected to serve as the basis for the Ten-day HA because it contains adequate human data of appropriate length. In this study, groups of four healthy adult men were administered chlorpyrifos in capsule form at doses of 0, 0.014, 0.03 or 0.10 mg/kg for 28, 28, 21 or 9 days, respectively. Adverse health effects were observed only in the high-dose (0.10 mg/kg) group; at this exposure level, plasma ChE activity was reduced by approximately 65% when compared to control values. One individual in this group also experienced a runny nose and blurred vision. A NOAEL of 0.03 mg/kg/day was identified from this study.

Another study by Dow Chemical Company (1972), in which a NOAEL of 0.015 mg/kg was reported for beagle dogs consuming chlorpyrifos in the feed for 12 days, was also considered for the calculation of the Ten-day HA. However, this value was not used because the available human data were within one order of magnitude of the animal data. Therefore, the results of this dog study support the human data used to calculate the Ten-day HA but are not the most appropriate for the derivation of this HA.

The Ten-day HA for the 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.03 \text{ mg/kg/day}) (10 \text{ kg})}{(1 \text{ L/day}) (100)} = 0.03 \text{ mg/L (rounded to } 30 \text{ } \mu\text{g/L)}$$

where:

- 0.03 mg/kg/day = NOAEL, based on the absence of decreased plasma ChE activity in male human subjects exposed to chlorpyrifos via the oral route for 21 days (Dow Chemical Company, 1972).
- 10 kg = assumed weight of child.
- 10 = uncertainty factor, chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from a human study is employed.
- 1 L/day = assumed water consumption of 10-kg child.

Longer-term Health Advisory

The study by Dow Chemical Company (1972) in which humans received daily oral doses of chlorpyrifos for up to 28 consecutive days has been selected to serve as the basis for the Longer-term HA because it contains human data that identify a NOAEL and a LOAEL. Although several adequate subchronic animal studies were available, data from these studies indicate that humans are more sensitive to chlorpyrifos following oral administration than other species. Using human data would, therefore, allow for a more conservative estimate of a Longer-term HA for a 10 kg child. The following studies used plasma and erythrocyte ChE activity levels as the basis for NOAEL and LOAEL values. Two 3-month feeding studies with rats identified NOAELs of 0.1 and 1.5 mg/kg/day; respective LOAELs were 0.3 and 5 mg/kg/day (Dow Chemical Company, 1972). A 6-month study in which rats received chlorpyrifos in the diet identified a NOAEL of 0.15 mg/kg/day and a LOAEL of 0.75 mg/kg/day (Dow Chemical Company, 1972). Finally, monkeys exposed via oral gavage to chlorpyrifos for 6 months showed no adverse effects at 0.08 mg/kg/day doses but had reduced ChE activities at 0.4 mg/kg/day (Dow Chemical Company, 1972). The human study, also conducted by Dow Chemical Company (1972), identified a NOAEL of 0.03 mg/kg/day and a LOAEL of 0.1 mg/kg/day based on the absence or presence of reduced plasma ChE activity following administration of chlorpyrifos (in capsules) to groups of four healthy male adults for 9 and 21 days, respectively.

The Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.03 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 0.03 \text{ mg/L (rounded to } 30 \text{ } \mu\text{g/L)}$$

where:

- 0.03 mg/kg/day = NOAEL, based on the absence of decreased plasma ChE activity in male human subjects exposed to chlorpyrifos via the oral route for 21 days (Dow Chemical Company, 1972).
- 10 kg = assumed body weight of a child.
- 10 = uncertainty factor, chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from a human study is employed.
- 1 L/day = assumed daily water consumption of a child.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.03 \text{ mg/kg/day}) (70 \text{ kg})}{(10) (2 \text{ L/day})} = 0.105 \text{ mg/L (rounded to } 100 \text{ } \mu\text{g/L)}$$

where:

- 0.03 mg/kg/day = NOAEL, based on the absence of decreased plasma ChE activity in male human subjects exposed to chlorpyrifos via the oral route for 21 days (Dow Chemical Company, 1972).
- 70 kg = assumed body weight of an adult.
- 10 = uncertainty factor, chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from a human study is employed.
- 2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious health effects during a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA in drinking water alone is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed.

If the contaminant is classified as a known, probable, or possible human carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution must be exercised in making a decision on how to deal with possible lifetime exposure to this substance. For human (A) or probable human (B) carcinogens, a Lifetime HA is not recommended. For possible human carcinogens (C), an additional 10-fold safety factor is used to calculate the Lifetime HA. The risk manager must balance this assessment of carcinogenic potential and the quality of the data against the likelihood of occurrence and significance of health effects related to noncarcinogenic endpoints of toxicity. To assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the range of 1 in 10,000 to 1 in 1,000,000 for the 70-kg adult drinking 2 L of water/day are provided in the Evaluation of Carcinogenic Potential section.

The oral-exposure study with humans by Dow Chemical Company (1972) has been selected to serve as the basis for the Lifetime HA because it contains adequate human exposure data that are supported by animal data. A NOAEL of 0.03 mg/kg/day for humans was identified in this study. Three animal studies also were considered for the calculation of the Reference Dose (RfD), Drinking Water Equivalent Level (DWEL), and Lifetime HA. The chronic (2-year) feeding study in rats (McCollister et al., 1974) was judged unacceptable due to insufficient numbers of animals (25/sex/dose with an additional 5 to 7/sex/dose for interim sacrifices). The other animal studies, which included the reproduction study with rats by Dow Chemical Company (1972) and the chronic feeding study with dogs by McCollister et al. (1974), were considered adequate. However, the human oral-exposure study by Dow Chemical Company (1972) was judged most appropriate for the calculation of the Lifetime HA for chlorpyrifos. Although this human study was coreclassified as supplementary because only four males/dose were used, when considered with the available experimental data in animals, the NOAEL for ChE inhibition in humans (0.03 mg/kg/day) appeared comparable to that in rats (0.1 mg/kg/day) and dogs (0.03 mg/kg/day).

Using the human study (Dow Chemical Company, 1972), the Lifetime HA is derived as follows:

Step 1: Determination of the RfD

$$\text{RfD} = \frac{(0.03 \text{ mg/kg/day})}{(10)} = 0.003 \text{ mg/kg/day}$$

where:

0.03 mg/kg/day = NOAEL, based on the absence of decreased plasma ChE activity in male human subjects exposed to chlorpyrifos via the oral route for 21 days (Dow Chemical Company, 1972).

10 = uncertainty factor, chosen in accordance with EPA or NAS/OW guidelines in which a NOEL from a human study is employed.

Step 2: Determination of the DWEL

$$\text{DWEL} = \frac{(0.003 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.105 \text{ mg/L (rounded to } 100 \text{ } \mu\text{g/L)}$$

where:

0.003 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime HA

$$\text{Lifetime HA} = (0.1 \text{ mg/L}) (20\%) = 0.02 \text{ mg/L (} 20 \text{ } \mu\text{g/L)}$$

where:

0.105 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenicity was found in rats or dogs fed up to 3.0 mg chlorpyrifos/kg/day for 1 to 2 years (McCollister et al., 1974).
- The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenic potential of chlorpyrifos.
- Applying the criteria in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), chlorpyrifos may be classified in Group D: not classifiable. This category is for agents with inadequate animal evidence for carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE, AND STANDARDS

- The American Conference of Governmental Industrial Hygienists recommends a Threshold Limit Value-Time-Weighted Average of 0.2 mg/m³ and a Short-term Exposure Limit of 0.6 mg/m³ for dermal exposures (ACGIH, 1988).
- The Food and Agriculture Organization/World Health Organization (FAO/WHO, 1984) Acceptable Daily Intake for chlorpyrifos is 0.01 mg/kg/day (Gartrell et al., 1985).

VII. ANALYTICAL METHODS

- Chlorpyrifos is one of the phosphorus-containing pesticides. The relative ease with which this pesticide can be monitored by element-specific detectors has usually led to its inclusion in pesticide monitoring studies. Chlorpyrifos can be analyzed by Methods 622 (U.S. EPA, 1982) and 507 (U.S. EPA, 1988). In both methods a liter of sample is extracted with methylene chloride, the solvent is then exchanged for hexane or methyl tertiary butyl ether. Analysis is by an element-specific thermionic nitrogen-phosphorus detector, which allows even relatively "dirty" samples to be analyzed with no clean-up. The estimated detection limit for this residue is 0.3 µg/L.

VIII. TREATMENT TECHNOLOGIES

- There is presently no information available describing treatment technologies capable of removing chlorpyrifos from contaminated drinking water supplies.
- Chlorpyrifos may be amenable to removal by activated carbon adsorption due to its solubility.
- Chlorpyrifos is probably not amenable to removal by aeration on the basis of its Henry's Coefficient value.

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