Chlorpyrifos

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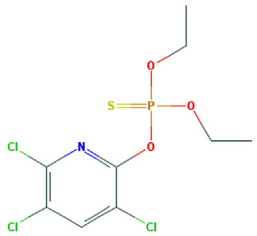
Chemical Profile

- Chemical Abstracts Service Registry Number: CAS 2921-88-2
- Chemical Name: *O*,*O*-Diethyl *O*-3,5,6-trichloropyridin-2-yl phosphorothioate
- Synonyms: Brodan, Detmol UA, Dowco 179, Dursban, Empire, Eradex, Lorsban, Paqeant, Piridane, Scout, Stipend
- Chemical Class: Organophosphate, Insecticide, Acaricide, Nematocide
- Chemical Structure: (from Pubchem) http://pubchem.ncbi.nlm.nih.gov/image/structurefly.cgi?cid=2730&width=400&height=400
- Molecular Formula: $C_9H_{11}Cl_3NO_3PS$
- Molecular Weight: 350.59 g mol^{-1}
- Density: 1.51 g cm^{-3} at 21 °C
- Vapor Pressure: 0.00002 mm Hg (0.003 Pa) at 25 °C
- Boiling Point: >320 °C
- Melting Point: 41–42 °C
- Flash Point: >200 °F
- Conversion Factor: 1 ppm = 14.31 mg m^{-3} at 25 °C
- Appearance: Colorless to white, crystalline solid
- Odor: Mild mercaptan



Background

Chlorpyrifos is a chlorinated organophosphorus (OP) ester manufactured as an insecticide, acaricide, and miticide. Like the other OP insecticides, the most prominent toxicity of chlorpyrifos is associated with binding and inhibition of the enzyme acetylcholinesterase (AChE) in insects and mammals. Chlorpyrifos requires metabolic activation to chlorpyrifos oxon to yield anticholinesterase activity.

First sold in 1965, chlorpyrifos is used globally to control agricultural and structural pests and mosquitos. In the 1990s, chlorpyrifos ranked as one of the top selling pesticides in the world, for the most part, replacing the persistent organochlorine insecticides. Over the last decade, concerns regarding toxicity to the developing nervous system have limited its use. By 2001, residential uses and uses in schools and parks were prohibited, and many agricultural uses were restricted and the US Residential use limitations were also imposed in Canada, Australia, and the European Union (EU). It continues to be used in large quantities to control crop damage worldwide. In the developing countries, excessive agricultural application and lack of protective devices result in hundreds of thousands of deaths yearly.

Uses

Chlorpyrifos is one of the most widely used OPs insecticides worldwide. During 1987–98, over 20 million pounds were used in the United States. Although registered for many fruits, vegetables, and grain crops, over 60% of chlorpyrifos is applied to four crops: corn, tree nuts, tree fruits, and soybeans. Once among the most widely applied pesticides in the US homes to control termites, cockroaches, and fleas, such uses were banned in 2001. Roach bait is the only residential use exempted from cancelation, because it is not expected to result in a significant exposure. Today, nonagricultural uses in the United States are limited to mosquito control for public health purposes and insect control on golf courses. In 2006, the major manufacturers of chlorpyrifos in the United States and the EU began a global phase out of nonagricultural uses of chlorpyrifos. However, other manufactures may continue to support residential uses outside the United States and EU.

Environmental Fate and Behavior

Chlorpyrifos is soluble in organic solvents (e.g., isooctane, methanol), but has low solubility in water (<2 mg l^{-1} solubility at 25 °C). The calculated Henry's law constant of 0.00001 atm m^3 mol^{-1} indicates possibility of volatilization from surface water. The odor threshold of chlorpyrifos is 0.14 mg m^{-3} (10 ppb). The estimated half-life for reacting with photochemically generated hydroxyl radicals in the air is 6.3 h. Photolysis of chlorpyrifos produces dechlorinated products.

Chlorpyrifos undergoes abiotic hydrolysis, photodegradation, and biotic degradation in soil and water. Depending on the soil type and climate, its soil persistence varies from 2 weeks to over 1 year. Microbial degradation is indicated by the shorter half-lives in natural soils than sterile soils. Chemical hydrolysis produces *O*-ethyl-*O*-3,5,6-trichloro-2-pyridyl phosphorothioate or 3,5,6-trichloro-2-pyridinol (TCP) and phosphorthioic acid at alkaline conditions. Half-lives in river and well waters vary from 4.8 to 38 days, with the rate of hydrolysis increasing with temperature and alkalinity. The estimated Log K_{oc} of 3.73 predicts strong adsorption to soil and resist leaching to groundwater. Chlorpyrifos can persist indoors for several months.

Oxidation of chlorpyrifos to its more toxic metabolite chlorpyrifos oxon could occur through photolysis, aerobic metabolism, and chlorination. Water chlorination is the major route of chlorpyrifos oxon formation. It is subsequently rapidly

hydrolyzed to TCP. TCP and its glucuronide conjugates have been detected in fish tissues. The measured K_{ow} of 4.8 indicates a potential for bioaccumulation in aquatic and terrestrial food chains.

Exposure and Exposure Monitoring

Exposure to chlorpyrifos may occur through ingestion of residues in the diet, inhalation of vapors, and dermal absorption following skin contact. Prior to 2001, residential exposure to chlorpyrifos was widespread. Today, exposure to the general public occurs principally via the diet. Residential exposure is still possible from the remaining registered uses for mosquito control and on golf course turf. Indoor air and house dust exposures may add to the total in-home exposures in heavily agricultural areas. Dermal and inhalation exposure pathways are likely to dominate workers' exposures from handling chlorpyrifos or reentering treated fields.

Enforceable maximum residue levels of chlorpyrifos (or 'tolerances' in the United States) are established for more than 100 food commodities. These are the highest levels allowable in or on these commodities. At a given exposure concentration, children generally have higher body burden due to their higher intake (inhalation volume, amount of food intake) or contact on a per body weight basis.

Toxicokinetics

The estimated oral absorption of chlorpyrifos is 70–99% in rats and humans. In rats, peak blood level of chlorpyrifos and its metabolites occurs between 3 and 6 h after dosing. The estimated dermal absorption is 3–10% based on the urinary recovery of metabolites. The inhalation absorption is mostly indicated by the inhibition of ChE activities.

In animals and humans, chlorpyrifos is extensively metabolized by the liver cytochrome P-450 enzymes (CYP). Oxidative desulfuration results in the potent ChE inhibitor chlorpyrifos oxon. Dearylation of chlorpyrifos and chlorpyrifos oxon by CYP produces TCP and diethyl thiophosphate (DETP). Hydrolyses of chlorpyrifos oxon by A-esterases (paraoxonases, PON1) forms TCP and diethylphosphate (DEP). Extrahepatic metabolism may occur in tissues such as brain and intestine. In animals, the highest levels of chlorpyrifos are found in the fat. It also binds to plasma proteins, such as albumin. Chlorpyrifos is detected in rat and human milk. In rats, transplacental transfer to the fetus is evidenced by the ChE inhibition in fetal plasma and brain and by the presence of chlorpyrifos in the fetal liver, brain, placenta, umbilical cord, and amniotic fluid.

The urine is the main route of elimination for chlorpyrifos, where 84% of a single oral dose in rats is found within 72 h. About 5% is excreted in the bile/feces. The major urinary metabolites are TCP, DEP, DETP, glucuronide, and sulfate conjugates. In humans, 70% is excreted in urine as conjugated TCP within 5 days of a single oral exposure. Levels of urinary TCP are commonly used in human biomonitoring studies. The elimination half-life for chlorpyrifos in rats and humans is 10–27 h.

Mechanism of Toxicity

The classical mechanism of toxicity of chlorpyrifos is related to the ability of its oxon metabolite to bind and inhibit the serine hydrolase AChE. The nervous system is the primary target because AChE hydrolyzes the neurotransmitter acetylcholine thereby terminating its synaptic action. Inhibition of AChE increases the availability of acetylcholine at the neural synapse leading to excessive stimulation of the cholinergic pathways in the central and peripheral nervous systems. Significant inactivation of AChE causes acute cholinergic effects, morbidity, or death.

Chlorpyrifos oxon interacts with other esterases such as butyrylcholinesterase, neuropathy target esterase (NTE), carboxylesterase, and PON1. Carboxylesterases and PON1 are key enzymes involved in detoxification of chlorpyrifos. Carboxylesterases act as alternative targets to AChE for chlorpyrifos oxon thereby decreasing its concentration in blood. Gender and age differences are observed in the carboxylesterase activity in animals. PON1 is a polymorphic enzyme with allozymes differing in their ability for hydrolytic detoxification of chlorpyrifos oxon. The PON1 status is an important determinant in modulating the acute toxicity of chlorpyrifos. Butyrylcholinesterase may function as a molecular scavenger for chlorpyrifos in the blood or substitute for AChE where it is low. NTE may be involved in the OP-induced delayed neurotoxicity syndrome.

Chlorpyrifos itself is a week ChE inhibitor. In risk assessment, the co-occurrence of chlorpyrifos and chlorpyrifos oxon is addressed by applying a toxicity equivalence factor or relative potency factor of 10 to chlorpyrifos oxon.

Concerns were raised regarding regulatory standards of chlorpyrifos established based on its inhibitory effects on ChE activity that may overlook potentially more sensitive noncholinergic mechanisms. Besides AChE, potential targets include neurogenesis, nervous system development, cytotoxicity, macromolecule synthesis, neurotransmitter receptors, oxidative stress, cell signaling, nuclear transcription factors, and neuronal-glial cell interactions.

Acute and Short-Term Toxicity

Animal

Chlorpyrifos is classified by US Environmental Protection Agency (USEPA) as a moderate oral toxicant (Category II). The acute oral LD_{50} is 32 mg kg^{-1} for hens and 82–504 mg kg^{-1} for rats, mice, and guinea pigs. The oral LD_{50} for chlorpyrifos oxon is >100 mg kg^{-1} in male rats and 300 mg kg^{-1} in female rats. The oral toxicity of chlorpyrifos oxon may be attenuated by extensive hepatic metabolism before entering systemic circulation. Chlorpyrifos dermal LD_{50} in rats is 202 mg kg^{-1} day^{-1}. The 4-h inhalation LC_{50} in rats is >2 mg l^{-1}. Chlorpyrifos is a Category IV skin and eye irritant (slight conjunctival and dermal irritation).

The main targets of chlorpyrifos toxicity after short-term oral exposure are the nervous system and the developing offspring. Cholinergic syndromes from overstimulation of the muscarinic and nicotinic-type acetylcholine receptors include hypersalivation, respiratory distress, miosis, muscular twitches, tremors, ataxia, diarrhea, and vomiting. Other nonlethal effects are hematological and liver enzyme changes,

chromodacryorrhea, tachycardia, renal effects, hypothermia, and body weight decreases. No delayed neuropathy was observed in hens receiving a single or 20 repeated oral doses of chlorpyrifos.

Young animals are three- to fourfold more sensitive to ChE inhibition than adults. Applying the Benchmark Dose (BMD) analysis, USEPA established a lower bound of BMD (BMDL) at 0.36 mg kg^{-1} day^{-1} based on 10% red blood cell (RBC) ChE inhibition in postnatal day (PND) 11 pups after a single oral exposure. For acute chlorpyrifos oxon exposure, the similarly determined BMDL is 0.08 mg kg^{-1} day^{-1}.

Pregnant animals are 2- to12-fold more sensitive than nonpregnant adults to ChE inhibition, which may reflect the capacity of key detoxification enzymes such as paraoxonase and P450 isozymes.

Human

Human deaths are reported due to accidental exposure or intentional ingestion of chlorpyrifos. The exposure level or duration is generally unknown. Death is caused by respiratory and cardiovascular failure.

Nonlethal acute poisoning affects the central nervous system and cardiovascular and respiratory systems. Common clinical signs of cholinergic toxicity in humans are numbness, dizziness, tremor, abdominal cramps, sweating, lacrimation, salivation, and blurred vision. High doses (>300 mg kg^{-1}) lead to unconsciousness, convulsions, cyanosis, and uncontrolled urination. In some acute poisoning cases, sequelae (intermediate syndrome) characterized by muscle paralysis were reported 1–4 weeks after exposure. In clinical studies of male adults, the lowest observed effect level (LOEL) for inhibition of plasma ChE is 0.5 mg kg^{-1}.

Chronic Toxicity

Animal

Mortality occurred in pregnant rats at 5 mg kg^{-1} day^{-1} and pregnant mice at 25 mg kg^{-1} day^{-1}. Nonlethal LOELs for nonpregnant adults included 2–15 mg kg^{-1} day^{-1} for increased adrenal gland, brain, and heart weight in rats, 3–45 mg kg^{-1} day^{-1} for increased liver weight and hepatocyte vacuolation in dogs and mice, 15 mg kg^{-1} day^{-1} for changes in hematologic parameters in rats, 1.2–25 mg kg^{-1} day^{-1} for decreases in body weight, bodyweight gains, and food consumption in mice and rats, and 45 mg kg^{-1} $day^{-1}$for ocular opacity and hair loss in mice. USEPA established a BMDL of 0.09 mg kg^{-1} day^{-1} based on 10% RBC ChE inhibition in PND 11 male rats after 11 days of oral exposures.

Human

Effects reported in workers chronically exposed to chlorpyrifos included impaired memory, disorientation, speech difficulties, nausea, and weakness. In clinical studies, the LOEL for inhibition of plasma ChE for repeated 28-day oral exposures is 0.01 mg kg^{-1} day^{-1}, 50-fold lower than for a single oral exposure.

Both population-based multiyear biomonitoring (e.g., National Health and Nutrition Examination Survey (NHANES)) and longitudinal farming-related monitoring provide data that facilitate recent efforts to relate the exposure to OP toxicity in human population. Epidemiological studies using chlorpyrifos specific markers are discussed under Developmental Neurotoxicity.

Immunotoxicity

Studies in rodents, cats, and dogs conducted over the past four decades indicate that at doses causing significant ChE inhibition, chlorpyrifos does not alter the immune system function.

Reproductive and Developmental Toxicity

Animal

In prenatal developmental studies, pregnant rats and mice received chlorpyrifos up to 15–25 mg kg^{-1} day^{-1} orally on gestation days (GD) 6–15 or pregnant rabbits received 140 mg kg^{-1} day^{-1} on GD 7–19. Fetal growth retardation and malformations were observed in the presence of maternal toxicity.

In two- and three-generation studies, rats fed 0.3–5 mg kg^{-1} day^{-1} chlorpyrifos mated normally and exhibited normal pregnancy, offspring, and lactation, although maternal and fetal body weights were impacted at 5 mg kg^{-1} day^{-1}. Available data suggest that chlorpyrifos is not teratognic and does not adversely affect reproduction. Inhibition of RBC ChE activity had the lowest LOEL of 0.1–0.3 mg kg^{-1} day^{-1}.

Human

Collective results from three major prospective cohort studies indicated association of indoor and outdoor exposure to chlorpyrifos during pregnancy to decreased birth size, decreased gestational age at birth, and decreased head circumference, especially at low maternal PON1 levels. These studies evaluated pre- and postnatal pesticide exposure in mother–infant pairs and birth and developmental outcomes in neonates, infants, and young children. The Columbia University in New York City study focused on chlorpyrifos levels in the umbilical cord and maternal plasma as a direct biomarker for chlorpyrifos *in utero* fetal exposure. The other two studies from Mount Sinai Hospital in New York City and from the University of California at Berkeley measured TCP (a metabolite of chlorpyrifos and chlorpyrifos methyl) and nonspecific OP metabolites in maternal urine.

Studies in men using urinary TCP as an indicator for chlorpyrifos exposure revealed an association with decreased testosterone or alterations in the homeostasis of thyroid and sex steroid hormones. Their TCP levels fall within the range of the NHANES data for the general US population.

Developmental Neurotoxicity

Chlorpyrifos causes developmental neurotoxicity at doses not altering pregnancy and general health of the offspring, and in the absence of fetal brain ChE inhibition. At a subtoxic dose (i.e., 1 mg kg^{-1} day^{-1}), gestational and early postnatal

exposure in rats and mice produced long-lasting impairment of locomotor activity (exploration and rearing), deficit in the cognitive function (spatial learning and memory), and social interaction (aggression and maternal behavior in adulthood). A number of noncholinergic mechanisms have been suggested for the neurodevelopmental perturbations; however, evidence for alternative targets is not conclusive.

The developmental neurotoxicity reported in rats and mice provides implications for humans with documented developmental exposure, such as the participants in the epidemiologic studies previously described who had measured chlorpyrifos levels in maternal and umbilical cord blood. At 3 years of age, children from higher chlorpyrifos levels in the umbilical cord plasma showed delays in cognitive and motor functions and problems with attention.

Genotoxicity

Several limited assays showed that chlorpyrifos is negative for gene mutation (*Salmonella*, *Escherichia coli*, Chinese hamster ovary cell hypoxanthine-guanine phosphoribosyl transferase forward mutation) and chromosomal aberration (rat lymphocytes, mouse bone marrow micronucleus). DNA damage assays were negative in mammalian cells (unscheduled DNA synthesis in WI-38 human embryonic lung fibroblast cell line and rat hepatocytes) but positive in yeast, *E. coli*, and *Bacillus subtilis*.

Carcinogenicity

No evidence of carcinogenicity through dietary exposures was found in F344 rats and CD-1 mice.

Ecotoxicology

The acute LC_{50} for estuarine algae is 140–300 ppb. The 96-h LC_{50} for aquatic invertebrates varies with species, e.g., 0.04 ppb for mysid shrimp, 0.38 ppb for stonefly, and 6.0 for crayfish. The 48-h LC_{50} for *Daphnia magna* is 0.6 ppb. The acute LC_{50} for fish also showed wide species variations, e.g., 0.6 ppb for striped bass and 130–163 ppb for fathead minnow. The toxicity increases with increasing temperature, e.g., for rainbow trout, LC_{50} is 51, 15, and 7.0 ppb at 1.6, 7.2, and 12.7 °C, respectively. The chronic no observed adverse effect concentration (NOAEC) for reproduction is <0.0046 ppb for mysid shrimp, 0.04 ppb for *D. magna*, 0.28 ppb for Atlantic silverside, and 0.57 ppb for fathead minnow.

The acute avian species LD_{50} is 10 mg kg^{-1} for house sparrow and 136 ppm in the diet for mallard duck. The chronic dietary no observed adverse effect level for reproduction is 25 ppm for mallard duck. Toxicities to mammals are presented in the acute and chronic toxicity sections.

Based on estimates of risk quotients in 2006, USEPA concluded high risk of chlorpyrifos to aquatic invertebrate species, fish, birds, and small mammals from a single outdoor application and prolonged risk from multiple applications. Aquatic birds and mammals are additionally at risk from chlorpyrifos bioconcentrating in water bodies.

Other Hazards

Simultaneous exposure to other OPs that are detoxified by carboxylesterase (e.g., malathion, diazinon, azinphos methyl, parathion) results in more extensive toxicity in terms of lethality, clinical signs, and ChE inhibition than with chlorpyrifos alone. Inhibition of carboxylesterase activity may be the cause of these toxicological interactions.

Chlorpyrifos is a potent inhibitor of the human metabolism of environmental chemicals (carbaryl, fipronil, N,N-diethyl-3-methylbenzamide, and the jet fuel components nonane and naphthalene) that are substrates of common CYPs (CYP3A4, CYP2B6) and share biotransformation pathways. Metabolic interactions are reported with endogenous substrates (testosterone and estradiol) and with the antidepressant drug imipramine possibly through competition for CYP3A4 and CYP1A2. All of the CYP inhibitions, also known as 'suicidal or mechanism-based inhibition,' are irreversible and result from the formation of reactive sulfur during chlorpyrifos desulfuration. In rats, chlorpyrifos alters the serotonin systems during neurodevelopment.

Exposure Standards and Guidelines

American Conference of Governmental Industrial Hygienists Threshold Limit Value: 0.1 mg m^{-3} Time-weighted average (TWA); Inhalable fraction and vapor (skin) (A4 – Not Classifiable as a Human Carcinogen)

National Institute for Occupational Safety and Health Recommended Exposure Limit: 0.2 mg m^{-3} TWA; 0.6 mg m^{-3} Short-term exposure limit; (Skin)

USEPA population-adjusted dose (oral): 0.0036 mg kg^{-1} day^{-1} (acute); 0.0003 mg kg^{-1} day^{-1} (chronic)

See also: Behavioral Toxicology; Developmental Toxicology; Toxicity Testing, Developmental; A-esterase; Fermentation (Industrial): Media for Industrial Fermentations; Carboxylesterases; Cholinesterase Inhibition; Common Mechanism of Toxicity in Pesticides; Neurotoxicity; Organophosphorus Compounds; Pesticides; Cytochrome P450; National Institute for Occupational Safety and Health; Carcinogen Classification Schemes; Federal Insecticide, Fungicide, and Rodenticide Act, US; Genetic Toxicology; International Agency for Research on Cancer; Regulation, Toxicology and; Toxicity Testing, Reproductive; Risk Assessment, Human Health; Ecotoxicology; ACGIH® (American Conference of Governmental Industrial Hygienists); Food Quality Protection Act; Children's Environmental Health; Epidemiology; Environmental Fate and Behavior.

Further Reading

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Relevant Websites

http://www.atsdr.cdc.gov – Agency for Toxic Substances and Disease Registry.
http://toxnet.nlm.nih.gov – Hazardous Substance Data Bank.
http://npic.orst.edu – National Pesticide Information Center.
http://www.epa.gov – United States Environmental Protection Agency.
http://www.osha.gov – United States Occupational Safety and Health Administration.