

CHLORPYRIFOS

TECHNICAL FACT SHEET

NPIC Technical Fact Sheets provide information that is complex and intended for individuals with a scientific background and/or familiarity with toxicology and risk assessment. This document is intended to promote informed decision-making. Please refer to the General Fact Sheet for less technical information.

Chemical Class and Type:

- Chlorpyrifos is a broad-spectrum, chlorinated organophosphate (OP) insecticide, acaricide and nematicide. Chlorpyrifos is the common name for the chemical 0,0-diethyl 0-(3,5,6-trichloro-2-pyridinyl)-phosphorothioate. The Chemical Abstracts Service (CAS) registry number is 2921-88-2.¹
- Chlorpyrifos was first registered for use in the United States in 1965.¹ The United States Environmental Protection Agency (U.S. EPA) completed the OP cumulative risk assessment in July 2006. At that time, the reregistration eligibility decision for chlorpyrifos was considered complete.¹ See the text box on **Laboratory Testing**.

Laboratory Testing: Before pesticides are registered by the U.S. EPA, they must undergo laboratory testing for short-term (acute) and long-term (chronic) health effects. Laboratory animals are purposely given high enough doses to cause toxic effects. These tests help scientists judge how these chemicals might affect humans, domestic animals, and wildlife in cases of overexposure.

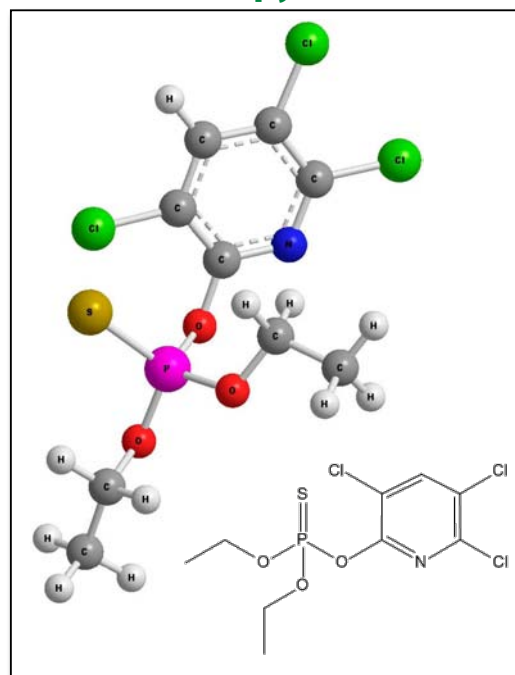
Physical / Chemical Properties:

- Chlorpyrifos is a colorless to white crystalline solid.^{1,2} Chlorpyrifos has a mild mercaptan (thiol) odor, similar to the smell of sulfur compounds found in rotten eggs, onions, garlic and skunks.^{2,3}
- Vapor pressure⁴: 1.87×10^{-5} mmHg at 25 °C
- Octanol-Water Partition Coefficient ($\log K_{ow}$)²: 4.70
- Henry's constant may be determined by estimation or experimentally derived. Reported values include: 4.2×10^{-6} atm·m³/mol at 25 °C and 6.7×10^{-6} atm·m³/mol, depending on the technique used.^{2,4}
- Molecular weight¹: 350.6 g/mol
- Solubility (water)²: 0.0014 g/L at 25 °C
- Soil Sorption Coefficient (K_{oc})⁵: 360 to 31,000 depending on soil type and environmental conditions.

Uses:

- Chlorpyrifos is used on agricultural food and feed crops, cattle ear tags, golf course turf, industrial plants and vehicles, non-structural wood treatments including processed wood products, fence posts and utility poles, and to control public health pests such as mosquitoes and fire ants. Chlorpyrifos is registered for indoor residential use only in the form of containerized baits.¹ Uses for individual products containing chlorpyrifos vary widely. Always read and follow the label when applying pesticide products.
- Chlorpyrifos is a non-systemic insecticide designed to be effective by direct contact, ingestion, and inhalation.²
- Signal words for products containing chlorpyrifos may range from Caution to Danger. The signal word reflects the combined toxicity of the active ingredient and other ingredients in the product. See the pesticide label on the product and refer to the NPIC fact sheets on [Signal Words](#) and [Inert or "Other" Ingredients](#).

Molecular Structure - Chlorpyrifos



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- To find a list of products containing chlorpyrifos which are registered in your state, visit the website http://npic.orst.edu/reg/state_agencies.html and search by "active ingredient."

Mode of Action:

Target Organisms

- Chlorpyrifos is a broad-spectrum insecticide which kills insects upon contact by affecting the normal function of the nervous system.⁴ Chlorpyrifos affects the nervous system by inhibiting the breakdown of acetylcholine (ACh), a neurotransmitter.⁵ When insects are exposed, chlorpyrifos binds to the active site of the cholinesterase (ChE) enzyme, which prevents breakdown of ACh in the synaptic cleft.⁶ The resulting accumulation of ACh in the synaptic cleft causes overstimulation of the neuronal cells, which leads to neurotoxicity and eventually death.^{6,7}
- Chlorpyrifos shares a common mechanism of toxicity with other organophosphate insecticides such as malathion and parathion, thus, chlorpyrifos would not be effective against organophosphate-resistant insect populations.

Non-target Organisms

- The mode of action of chlorpyrifos is similar for target and non-target organisms.⁸
- Acetylcholine is found throughout the mammalian nervous system, including at cholinergic synapses in the central nervous system, the junction of post-ganglionic parasympathetic neurons in exocrine glands and smooth and cardiac muscles, at pre- and post-ganglionic neurons in the autonomic nervous system, at neuromuscular junctions of the somatic nervous system, and on the surface of red blood cells.^{8,9}
- Chlorpyrifos affects ChE levels differently in various systems throughout the body. Scientists have observed plasma and red blood cell ChE inhibition in experimental animals at doses lower than those required to cause ChE inhibition in the brain.⁵
- The physiological functions of the neuropathy target esterase (NTE) enzyme were studied in genetically altered mice, which lacked the NTE enzyme. The results demonstrated that NTE plays an essential role in placental development, blood vessel development and protein synthesis in the central nervous system.¹⁰ Chlorpyrifos can inhibit NTE by binding to the active site of the enzyme. Inhibition of the NTE enzyme results in loss of myelin and degeneration of axon fibers of the peripheral and central nerves.^{8,9}
- Chlorpyrifos can cause permanent inhibition of the ChE or NTE enzymes, a process known as aging. Cleavage of an alkyl group from the chlorpyrifos residue produces a negative charge at the active site of the enzyme. This causes an unbreakable bond to form between the phosphorous atom on chlorpyrifos and the active site of the ChE or NTE enzyme.^{9,10}
- Chlorpyrifos also interacts with other enzymes, such as carboxylesterases and A-esterases. The functional role of these enzymes is not well understood, although they occur in many mammalian systems.⁶

Acute Toxicity:

Oral

- Chlorpyrifos is moderately toxic to mice and rats.¹ The oral LD₅₀ for mice is 60 mg/kg; for rats it ranges from 95 to 270 mg/kg.^{1,2,11} See the text boxes on **Toxicity Classification** and **LD₅₀/LC₅₀**.
- Chlorpyrifos is slightly toxic to rabbits. The acute oral LD₅₀ in rabbits ranges from 1000 to 2000 mg/kg.²
- Chlorpyrifos is moderately toxic to guinea pigs and sheep. The acute oral LD₅₀ in guinea pigs ranges from 500 to 504 mg/kg and 800 mg/kg in sheep.^{2,11}
- Chlorpyrifos is highly toxic to chickens. The acute oral LD₅₀ in chickens ranges from 32 mg/kg to 102 mg/kg.^{2,11}

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- Data from two human studies indicate that humans may be more sensitive to chlorpyrifos compared to rats or dogs, following acute oral and dermal exposure, based on plasma ChE inhibition and blurred vision. Rats have relatively more acetylcholinesterase while humans and dogs have a higher concentration of butyrylcholinesterase (BuChE). Butyrylcholinesterase appears to be more sensitive to ChE inhibitors than AChE. This sensitivity may contribute to the different effects observed in rats, compared to humans and dogs.⁵
- Research has shown that neonates and the young are more susceptible than adults to adverse effects from exposure to chlorpyrifos at levels below those causing ChE inhibition.⁵ Researchers reported adverse neurobehavioral effects in rats,^{12,13} effects on rat neuronal cell development,¹⁴ DNA synthesis in rats,¹⁵ gene transcription and cell differentiation in *in vitro* models,¹⁶ synaptogenesis in rats,¹⁷ and behavioral and social effects in rat neonates and adolescent mice.^{6,18} Rat neonates showed up to a 9-fold greater sensitivity to chlorpyrifos compared with adult rats at the highest doses tested.¹⁹
- Based on lethality and measurements of ChE inhibition in several studies, female rats appear to have a slightly elevated sensitivity to oral chlorpyrifos exposure compared to males.^{5,20}
- In cattle, bulls are more sensitive to chlorpyrifos exposure compared to cows.²¹

LD₅₀/LC₅₀: A common measure of acute toxicity is the lethal dose (LD₅₀) or lethal concentration (LC₅₀) that causes death (resulting from a single or limited exposure) in 50 percent of the treated animals. LD₅₀ is generally expressed as the dose in milligrams (mg) of chemical per kilogram (kg) of body weight. LC₅₀ is often expressed as mg of chemical per volume (e.g., liter (L)) of medium (i.e., air or water) the organism is exposed to. Chemicals are considered highly toxic when the LD₅₀/LC₅₀ is small and practically non-toxic when the value is large. However, the LD₅₀/LC₅₀ does not reflect any effects from long-term exposure (i.e., cancer, birth defects or reproductive toxicity) that may occur at levels below those that cause death.

Dermal

- Chlorpyrifos absorbs more easily through rat skin than human skin. Chlorpyrifos is not readily absorbed through human skin.^{22,23}
- Skin-applied chlorpyrifos has low toxicity based on animal studies. The acute dermal LD₅₀ for rabbits is >5,000 mg/kg and >2,000 mg/kg for rats,² although an acute dermal LD₅₀ of 202 mg/kg has also been reported for rats.¹

TOXICITY CLASSIFICATION - CHLORPYRIFOS

	High Toxicity	Moderate Toxicity	Low Toxicity	Very Low Toxicity
Acute Oral LD ₅₀	Up to and including 50 mg/kg (≤ 50 mg/kg)	Greater than 50 through 500 mg/kg (> 50 – 500 mg/kg)	Greater than 500 through 5000 mg/kg (> 500 – 5000 mg/kg)	Greater than 5000 mg/kg (> 5000 mg/kg)
Inhalation LC ₅₀	Up to and including 0.05 mg/L (≤ 0.05 mg/L) (aerosol)	Greater than 0.05 through 0.5 mg/L (>0.05 – 0.5 mg/L)	Greater than 0.5 through 2.0 mg/L (> 0.05 – 2.0 mg/L)	Greater than 2.0 mg/L (> 2.0 mg/L) (dust)
Dermal LD ₅₀	Up to and including 200 mg/kg (≤ 200 mg/kg)	Greater than 200 through 2000 mg/kg (> 200 - 2000 mg/kg)	Greater than 2000 through 5000 mg/kg (>2000 – 5000 mg/kg)	Greater than 5000 mg/kg (> 5000 mg/kg)
Primary Eye Irritation	Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than 21 days	Corneal involvement or other eye irritation clearing in 8 – 21 days	Corneal involvement or other eye irritation clearing in 7 days or less	Minimal effects clearing in less than 24 hours
Primary Skin Irritation	Corrosive (tissue destruction into the dermis and/or scarring)	Severe irritation at 72 hours (severe erythema or edema)	Moderate irritation at 72 hours (moderate erythema)	Mild or slight irritation at 72 hours (no irritation or erythema)

The highlighted boxes reflect the values in the “Acute Toxicity” section of this fact sheet. Modeled after the U.S. Environmental Protection Agency, Office of Pesticide Programs, Label Review Manual, Chapter 7: Precautionary Labeling. <http://www.epa.gov/oppfead1/labeling/lrm/chap-07.pdf>

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- Chlorpyrifos is a mild skin and moderate eye irritant based on rabbit studies. Chlorpyrifos is not a skin sensitizer according to results of tests on guinea pigs.²
- The acute dermal NOAEL for chlorpyrifos is 5 mg/kg/day. The NOAEL is based on a 21-day dermal study where rats were exposed to 10 mg/kg/day. In this study, researchers observed 45% plasma ChE inhibition and 16% red blood cell ChE inhibition after four days of exposure to the LOAEL (10 mg/kg/day).⁵ See the text box on **NOAEL, NOEL, LOAEL, and LOEL**.

NOAEL: No Observable Adverse Effect Level

NOEL: No Observed Effect Level

LOAEL: Lowest Observable Adverse Effect Level

LOEL: Lowest Observed Effect Level

Inhalation

- Chlorpyrifos is considered moderately toxic by inhalation. The 4- to 6-hour LC₅₀ is >0.2 mg/L in rats.^{2,11}
- The NOAEL for short- and intermediate-term inhalation is 0.1 mg/kg/day. The NOAEL is based on two separate 90-day studies of rats where researchers observed no effect at the highest vapor concentration tested.⁵

Signs of Toxicity - Animals

- Acute signs of toxicity can appear within minutes of exposure to chlorpyrifos. The signs typically appear at muscarinic receptor sites first, followed by nicotinic receptor sites and finally at central nervous system receptor sites.⁹
- Muscarinic signs from acute exposure to chlorpyrifos include abdominal pain, bronchospasm, constricted pupils, coughing, decreased heart rate, defecation, difficulty breathing, diminished appetite, distress, vomiting and increased tear production, salivation, and urination. Nicotinic signs include muscle tremors that are noted first in the head and then the body, generalized sustained muscle contractions, stiffness, weakness with paresis, and paralysis. Reported signs from extremely high oral doses include an increase in heart rate and constriction of the pupils. Central nervous system signs include diminished appetite, anxiety, restlessness, hyperactivity, depression, clonic-tonic seizures, depressed respiration, and coma.⁹
- Cats have experienced lethal effects from chlorpyrifos at doses of 10 to 40 mg/kg.⁹
- An exposure to chlorpyrifos may result in an intermediate syndrome, in which signs appear more than 24 hours after exposure, and can last several days or even weeks. Signs have been reported to develop within 24 to 72 hours in dogs and cats. It appears that intermediate syndrome involves tolerance to the overstimulation of ACh in muscarinic receptors. This tolerance does not develop at nicotinic receptors, and therefore the syndrome is characterized primarily by nicotinic effects. Signs from intermediate syndrome include: weakness of the neck, front limbs and respiratory muscles, diminished appetite, depression, diarrhea, muscle tremors, unusual posturing and behavior (including cervical ventroflexion), and death. Additional signs may include cranial nerve defects and clonic-tonic convulsions.^{9,24}
- When chlorpyrifos was registered for residential use, dermal exposure of cats to chlorpyrifos residues in the home environment was the most commonly reported cause of intermediate syndrome in domestic animals. In such cases, symptoms appeared 3-10 days after exposure to chlorpyrifos.⁹ See the **NPIC fact sheet** on [Pets and Pesticide Use](#).
- Another phenomenon, Organophosphate Induced Delayed Neuropathy (OPIDN) differs from intermediate syndrome in that the onset of signs may occur weeks after an acute, high-dose exposure to OPs.²⁵ Cats and chickens exposed to supra-lethal doses of chlorpyrifos showed signs consistent with delayed neuropathy. In both cases, the animals were treated with atropine to resolve acute cholinergic symptoms. Ataxia, altered movements, and impairment of spatial perception were reported signs of delayed neuropathy.^{26,27} OPIDN signs are primarily evident in the hind or pelvic limbs of exposed animals.²⁴

Signs of Toxicity - Humans

- Signs and symptoms typically develop within minutes to hours after an acute exposure to chlorpyrifos. Initial signs and symptoms include tearing of the eyes, runny nose, increased saliva and sweat production, nausea, dizziness and headache. Signs of progression include muscle twitching, weakness or tremors, lack of coordination, vomiting, abdominal cramps, diarrhea, and pupil constriction with blurred or darkened vision.^{8,28,29} Signs of severe toxicity include increased heart rate, unconsciousness, loss of control of the urine or bowels, convulsions, respiratory depression, and paralysis.^{8,28}
- Psychiatric symptoms associated with acute exposure include anxiety, depression, memory loss, confusion, stupor, bizarre behavior, and restlessness.^{8,28,29}
- Children may experience different signs and symptoms from exposure to chlorpyrifos than adults, and diagnosis of poisoning in general may be more difficult.^{8,29} Commonly reported signs and symptoms in poisonings with children include seizures, flaccid muscle weakness, pupil constriction, excess salivation, and mental status changes including lethargy and coma. Some of the typical symptoms seen in adults, such as decreased heart rate, muscle twitching, increased tear production, and sweating, are less common in children.⁸
- Single, high-dose exposures to organophosphates in humans can also result in intermediate syndrome. Signs and symptoms typically occur 24-96 hours after exposure. As in animals, the syndrome is characterized by the absence of muscarinic signs. Signs of toxicity result from the inhibition of nicotinic receptors. Signs observed in humans include reduced tendon reflexes, cranial nerve palsies, weakness in the facial, neck, proximal limb muscles, and partial respiratory paralysis.⁸
- Delayed neurological symptoms, beginning 1-4 weeks after exposure, may also result from an acute, high-dose exposure to OPs.¹¹ As in animals, this prolonged delay in neurological symptoms is referred to as OPIDN and onset depends on the dose and route of exposure. Reports of OPIDN from exposure to chlorpyrifos are limited to acute, high-dose exposures where treatment with therapeutic agents was used to resolve acute cholinergic toxicity.³⁰ In one case, a 42-year old man intentionally ingested chlorpyrifos in a suicide attempt, and in a second case, a 3-year-old boy accidentally ingested chlorpyrifos.^{31,32} It has been suggested that supralethal doses followed with antidotal therapy, rather than low-level, chronic exposures, would be necessary for chlorpyrifos to cause OPIDN in humans.³⁰
- OPIDN typically affects the lower extremities and can cause cramping, muscle pain, weakness and paresthesia, which is described as numbness and tingling sensations. In more severe cases, musculoskeletal effects including depression of tendon reflexes in the arms, symmetrical wasting, flaccid weakness, and paralysis of distal muscles (most commonly the legs) have been reported. Signs and symptoms from OPIDN may persist from weeks to years.^{8,10,25}
- Always follow label instructions and take steps to avoid exposure. If any exposures occur, be sure to follow the First Aid instructions on the product label carefully. For additional treatment advice, contact the Poison Control Center at 1-800-222-1222. If you wish to report an incident, please call 1-800-858-7378.

Chronic Toxicity:

Animals

- The most sensitive endpoint in rats, mice and dogs chronically exposed to chlorpyrifos is inhibition of ChE in the plasma, red blood cells and brain. Dogs showed increased liver weights at doses of 3 mg/kg/day. Rats exposed to 7-10 mg/kg/day displayed fluctuations in body weight as well as adverse effects on the eyes, adrenal glands and liver chemistry. Mice appear to be less sensitive to chronic oral exposures of chlorpyrifos, with decreases in body weights and increases in tissue abnormalities occurring at doses of 45-48 mg/kg/day.⁵
- In rats, age-related differences in sensitivity to chronic chlorpyrifos exposure do not appear to be as significant as the age-related sensitivity differences observed in rats exposed to acute doses of chlorpyrifos.¹⁹
- The chronic dermal NOAEL and the long-term inhalation NOAEL are 0.03 mg/kg/day based on five chronic toxicity studies reported in dogs and rats. These studies demonstrated adverse effects including plasma and red blood cell ChE inhibition at 0.22 to 0.30 mg/kg/day.⁵

- Both sexes of Fischer 344 rats exposed orally to 1 mg/kg/day of technical grade chlorpyrifos for 2 years had significantly reduced plasma and red blood cell cholinesterase levels.³³
- Chronic, low level exposures to organophosphates may lead to the development of a tolerance to the effects of ChE inhibition in exposed animals. Though the exact mechanism of tolerance development has not been identified, it is possible that changes in postsynaptic receptors may mitigate some of the anticholinesterase effects.³⁴ When a tolerance to anticholinesterase compounds has developed, animals may appear more resistant to the effects of ChE inhibition, and signs of toxicity may be decreased or disappear entirely. Some experimental animals have also shown the ability to handle higher doses of organophosphates than unexposed animals.^{34,35}

Humans

- A panel of scientists reviewed the available research on chlorpyrifos and its potential to affect human health. The researchers concluded that the current literature does not show that chronic chlorpyrifos exposure causes adverse effects on human health beyond cholinesterase inhibition. The group suggested that further research be conducted on workers in chlorpyrifos manufacturing, as they are likely to be exposed with more frequency and possibly at higher levels than the general population. The group suggested that further research should focus on the potential for chlorpyrifos to cause peripheral neuropathy and cognitive and affective disorders.³⁶
- An occupational study was conducted to evaluate the potential for chronic, low-level exposure to chlorpyrifos to affect the central nervous system. Investigators used a prospective cohort study design involving one group of chlorpyrifos-manufacturing workers and a control group. The chlorpyrifos-exposed workers had significantly higher levels of a chlorpyrifos urinary metabolite, 3,5,6-trichloro-2-pyridinol (TCP), and had lower average BuChE levels. There was no significant difference in neurological symptoms or signs between the two groups, nor was there clinical evidence of adverse effects on the central nervous system at baseline or at the 1-year follow-up evaluation.³⁷ See the text box on **Exposure**.

Exposure: Effects of chlorpyrifos on human health and the environment depend on how much chlorpyrifos is present and the length and frequency of exposure. Effects also depend on the health of a person and/or certain environmental factors.

- Male volunteers consumed doses up to 0.1 mg/kg/day for up to seven weeks. Significant plasma cholinesterase inhibition was observed, which ranged from 36-82% at the highest dose after nine days of treatment. On the final day of the study, one of the four men in the highest dose group had a runny nose, blurred vision, and felt faint. Exposure in the highest dose group was discontinued due to plasma cholinesterase inhibition greater than 20-30%, the study guideline. Plasma cholinesterase levels resolved to baseline levels after 25 days of recovery.³⁸
- Acute, high-dose exposures to chlorpyrifos described in case reports have shown evidence of delayed neuropathy.^{30,31,32} Supralethal exposures occurred in two of the cases, and interventions were required to reverse acute toxic effects. Delayed effects were noted, but due to the nature of clinical reports, limited information regarding signs, symptoms and/or laboratory results are available for these cases.³⁰

Endocrine Disruption:

- Chlorpyrifos is included in the 2007 draft list of initial chemicals for screening under the U.S. EPA Endocrine Disruptor Screening Program (EDSP). The list of chemicals was generated based on exposure potential, not based on whether the pesticide is a known or likely potential cause of endocrine effects.³⁹
- No data were found regarding possible effects of chlorpyrifos on endocrine systems.

Carcinogenicity:

Animals

- Chlorpyrifos did not induce treatment-related tumors or carcinogenicity in two chronic rat and two chronic mouse studies.⁵
- Rats exposed to chlorpyrifos for two years at 0.05, 0.10, 1.0 and 10.0 mg/kg/day did not show any carcinogenic effects.³³
- Scientists observed no genotoxic effects from chlorpyrifos in a range of *in vitro* and *in vivo* studies.²
- According to the Agency for Toxic Substances and Disease Registry (ATSDR), animal studies do not indicate that chlorpyrifos causes cancer.⁷

Humans

- In 1993, chlorpyrifos was classified in Group E, evidence of non-carcinogenicity for humans, by the U.S. EPA.⁴⁰ See the text box on **Cancer**.
- No human data were found regarding carcinogenic effects of chlorpyrifos.

Cancer: Government agencies in the United States and abroad have developed programs to evaluate the potential for a chemical to cause cancer. Testing guidelines and classification systems vary. To learn more about the meaning of various cancer classification descriptors listed in this fact sheet, please visit the appropriate reference, or call NPIC.

Reproductive or Teratogenic Effects:

Animals

- Researchers have reported behavioral effects from chlorpyrifos in studies with rats, including developmental delays in coordination, reflexes, and locomotor activity.^{41,42} Researchers have also noted altered expressions of social behavior¹⁸ and impaired spatial learning in exposed animals.⁴³ Gender differences in behavioral effects appear to be dependent on the age of the rat at the time of chlorpyrifos exposure.¹⁸
- Several studies have shown an increased sensitivity and susceptibility to adverse biochemical and behavioral effects in developing rats exposed either pre- or post-natally to chlorpyrifos when compared to adults.^{19,20}
- Researchers observed structural changes in brain development of female offspring of rats exposed to chlorpyrifos at 1 mg/kg/day, the lowest dose administered. In the dams, researchers observed inhibition of ChE in plasma and red blood cells at the same dose. The male and female pups of the exposed dams were exposed to 5 mg/kg/day and exhibited decreased body weight, decreased body weight gain, decreased food consumption, reductions in the number of viable offspring, developmental delays, decreased brain weight and morphological changes in the brain.⁵
- Reproductive and developmental effects from chlorpyrifos exposure have been observed at varying developmental stages in rats, mice and rabbits.⁵
- Age-related differences in neurotoxic effects independent of ChE inhibition have been observed in numerous developmental studies with rats, rabbits and mice exposed to chlorpyrifos. Neurotoxic effects observed include: programmed cell death, altered neuronal development, altered gene transcription and cell differentiation, impaired synthesis of DNA, RNA, and proteins, adverse effects on cell reproduction, and changes in brain development.^{18,41,44}

- Some studies have observed neurodevelopmental effects at exposure levels below those causing AChE inhibition, but the mechanism for these effects is uncertain. Researchers have proposed that chlorpyrifos, rather than the oxon or other metabolites, may play a role in developmental neurotoxicity. Due to the relationship between low-level exposures to chlorpyrifos and some observed neurodevelopmental effects, as well as the environmental relevance of low-level exposures, researchers have concluded that further studies are needed to characterize the mechanisms of this potential effect.⁴⁵
- In subacute reproductive studies with mallard ducks (*Anas platyrhynchos*), scientists observed reduced egg production, thinning of eggshells, reduced number of young, and death when hens were fed chlorpyrifos in their diets at concentrations of 60, 100, and 125 ppm. At the highest dose tested, researchers observed an 84% reduction in the number of eggs and 89% reduction in the number of young.⁴

Humans

- A prospective cohort study evaluated the relationship between chlorpyrifos levels in both umbilical cord plasma and mother's plasma at the time of birth, and impacts on neurological and behavioral development of children exposed prenatally. The study included 254 children and assessed cognitive and motor development at 12, 24, and 36 months. Researchers found that children and mothers with detected chlorpyrifos levels at or above 6.17 pg/g plasma were significantly more likely to experience adverse effects, including developmental delays and disorders, attention problems, and attention-deficit/hyperactivity disorder at three years of age compared to children and/or mothers with levels lower than 6.17 pg/g.⁴⁶

Fate in the Body:

Absorption

- Chlorpyrifos is absorbed by all routes of exposure. Urinalysis of exposed human volunteers indicates that approximately 70% is absorbed by the oral route, while less than 3% is absorbed through the skin.²³ Exposure to chlorpyrifos by inhalation results in the fastest appearance of symptoms, followed by oral and then dermal routes of exposure.⁸
- Researchers evaluated the absorption of chlorpyrifos by oral and dermal exposure in five human volunteers. Absorption of chlorpyrifos was based on levels of the dialkylphosphate metabolites of chlorpyrifos, diethylphosphate and diethylthiophosphate. Peak urinary metabolite levels were observed at seven hours following oral exposure. For dermal exposure, peak metabolite concentrations were observed at 17 to 24 hours post-exposure.⁴⁷
- In a similar study, maximum absorption levels for oral and dermal chlorpyrifos exposure were determined with six human volunteers. In this study, oral and dermal absorption rates were based on urinary concentrations of TCP, a primary chlorpyrifos metabolite. For oral exposure, peak levels were measured 6 hours after exposure. Maximum urinary TCP levels occurred 24 hours after dermal exposure.²³
- The chlorine group on chlorpyrifos increases the compound's lipid solubility and half-life in the body, resulting in a more gradual, but persistent, lowering of ChE levels compared to other organophosphorus pesticides.⁹

Distribution

- Chlorpyrifos is distributed throughout the body following exposure.⁹
- Although some chlorpyrifos may be stored in fat tissue, bioaccumulation is not expected to be significant due to an elimination half-life in humans of less than three days.¹¹

Metabolism

- Metabolic bioactivation is necessary for chlorpyrifos to exert cholinesterase inhibition.^{6,48} Bioactivation occurs primarily in the liver by cytochrome P450 enzymes (CYP). The CYP2B6 enzyme metabolizes chlorpyrifos to chlorpyrifos-oxon by replacing the sulfur group with oxygen.⁴⁸

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- Oxidase enzymes in the liver detoxify chlorpyrifos-oxon through inactivation. B-esterases such as carboxylesterase and BuChE become structurally inhibited after the process of inactivation, whereas the A-esterases such as paraoxonase 1 (PON1) can hydrolyze chlorpyrifos-oxon to TCP and remain functional.⁴⁸
- The activity of PON1 in humans is genetically determined and varies among individuals. A higher level of PON1 appears to be protective against cholinergic effects, as evidenced by research in some animals exposed to organophosphates. Thus, certain individuals may have an increased sensitivity to chlorpyrifos toxicity based on a reduced capacity to detoxify chlorpyrifos-oxon.⁵ Rabbits have greater PON1 activity and resistance to toxicity than rats, and birds are more sensitive than mammals in general. Birds have nearly undetectable levels of PON1.⁵
- Chlorpyrifos-oxon is metabolized primarily to TCP in addition to diethylphosphate and diethylthiophosphate.²²
- Glucuronide and sulfate conjugates of TCP have also been observed in the urine of humans and rodents.^{5,49} Chlorpyrifos-oxon is the only metabolite of chlorpyrifos that induces ChE inhibition; therefore all other metabolites are considered less toxic.^{1,22}
- Subchronic or chronic exposure to TCP at 30 mg/kg/day resulted in altered liver enzyme profiles. At exposures of 100 mg/kg/day, researchers noted increases in liver and kidney weights.¹

Excretion

- Elimination of chlorpyrifos occurs mainly through the kidneys. Chlorpyrifos is excreted in the urine as TCP, diethylphosphate and diethylthiophosphate.^{11,22}
- In a study with five human volunteers, Griffin and colleagues reported elimination half-lives for oral and dermal exposure of 15.5 hours and 30.0 hours, respectively. Rates were based on levels of diethylphosphate and diethylthiophosphate in the urine. A total of 93% of the oral dose was recovered as urinary metabolites, while 1% of the dermal dose was recovered.⁴⁷
- In a similar study, Nolan *et al* observed an elimination half-life of 27 hours following both dermal and oral exposure, based on urinary TCP levels. Nolan and colleagues recovered 70.0% of the oral dose and 1.3% of the dermal dose in the urine as TCP.²³
- Following oral exposure, rats excreted 90% of ingested chlorpyrifos through the urine and 10% in the feces.¹¹

Medical Tests and Monitoring:

- The most common laboratory tests for organophosphate pesticide exposures are ChE inhibition tests which are used to analyze the blood for lowered levels of plasma or red blood cell AChE. These tests may be conducted by hospital laboratories, local clinical laboratories, or other referred laboratories. Other tests for chlorpyrifos exposure are less common and include detection of the parent compound or metabolites in blood or urine.⁵⁰
- The potential for exposure to chlorpyrifos is present in several occupational fields, including agriculture, manufacturing, animal health technicians, pesticide applicators, and others. A baseline analysis of ChE levels in the blood may be mandatory for people who work closely with organophosphates. Following the establishment of a baseline, ChE testing of workers may be conducted to detect cumulative effects from daily exposure before clinical signs are apparent. Monitoring may also be useful to characterize exposures to the workforce as a whole to identify problem areas in the workplace.^{51,52}
- Humans and animals may be exposed to metabolites of chlorpyrifos through dietary sources and from background levels found in the environment. The metabolites excreted by humans and animals are in the same family of chemicals as degradates that form when chlorpyrifos is broken down in the environment. Therefore, the presence of metabolites in human urine may indicate direct exposure to metabolites themselves, and doesn't necessarily confirm exposure to chlorpyrifos.^{22,53}

- The presence of chlorpyrifos metabolites in the blood or urine does not necessarily indicate that adverse health effects will occur.²²
- The National Health and Nutrition Examination Survey (NHANES) III study found that 82% of the 993 adults measured had detectable levels of TCP in their urine. The Minnesota Children's Exposure Study found that 92% of the 89 children evaluated had detectable concentrations of TCP in their urine. Similarly, a biomonitoring study in North and South Carolina detected urinary metabolites in 100% of the 416 children evaluated.⁵ Amounts of TCP detected in food samples were greater than amounts of the parent chemical, chlorpyrifos, indicating a high background level of TCP in food. High background levels of TCP may contribute to higher detected urinary TCP levels.⁴⁵ See the **NPIC medical case profile** on [Biomarkers of Exposure: Organophosphates](#).

Environmental Fate:

Soil

- Chlorpyrifos is stable in soils with reported half-lives ranging between 7 and 120 days. Studies have found chlorpyrifos in soils for over one year following application. Soil persistence may depend on the formulation, rate of application, soil type, climate and other conditions.^{4,11,54} See the text box on **Half-life**.
- Chlorpyrifos bound to soil may be broken down by UV light, chemical hydrolysis, dechlorination, and soil microbes.^{11,54}
- Chlorpyrifos binds strongly to soils, is relatively immobile, and has low water solubility. In contrast, its degradate TCP adsorbs weakly to soil particles and is moderately mobile and persistent in soils.^{4,11}
- The major degradates of chlorpyrifos found in soils are similar to the metabolites created by plants and animals. The degradates are formed by oxidative dealkylation or hydrolysis to diethyl phosphates and TCP.⁵⁴
- In a study of seven aerobic soils ranging in texture from loamy sand to clay, with soil pH values from 5.4 to 7.4, the soil half-life for radiolabeled chlorpyrifos ranged from 11 to 141 days. After 360 days, researchers detected carbon dioxide (27-88%), TCP (up to 22%), and small amounts of 3,5,6-trichloro-2-methoxy pyridine ($\leq 8\%$) in the soil.^{4,11}
- In medium-textured soils in field conditions in California, Illinois and Michigan, the half-lives reported for chlorpyrifos ranged from 33 to 56 days.⁴
- Chlorpyrifos is less persistent in soils with a higher pH.^{4,11}
- Volatilization of chlorpyrifos from soil is not likely. According to a laboratory volatility study, carbon dioxide appears to be the major volatile degradate of chlorpyrifos. In this study, less than 10% of chlorpyrifos applied to soil volatilized within 30 days after application.⁴

The "half-life" is the time required for half of the compound to break down in the environment.

1 half-life = 50% remaining

2 half-lives = 25% remaining

3 half-lives = 12% remaining

4 half-lives = 6% remaining

5 half-lives = 3% remaining

Half-lives can vary widely based on environmental factors. The amount of chemical remaining after a half-life will always depend on the amount of the chemical originally applied. It should be noted that some chemicals may degrade into compounds of toxicological significance.

Water

- Chlorpyrifos does not partition easily from soil to water. Therefore, chlorpyrifos found in runoff water is likely a result of soil-bound chlorpyrifos from eroding soil, rather than from dissolved chlorpyrifos.⁴
- Volatilization of chlorpyrifos from water is the most likely route of loss for chlorpyrifos, with volatilization half-lives of 3.5 and 20 days estimated for pond water.¹¹
- During midsummer, the photolysis half-life of chlorpyrifos in water is between three and four weeks.¹¹

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- The rate of hydrolysis for chlorpyrifos increases with temperature and alkalinity. Half-lives ranging from 35 to 78 days have been reported in water with a pH of 7 and a temperature of 25 °C.¹¹
- The U.S. EPA conducted an analysis of well-monitoring data from the United States Geological Survey's (USGS) National Water Quality Assessment (NAWQA) Program database and the EPA's Pesticide Ground Water Database. Chlorpyrifos was detected in less than 1% of the more than 3000 wells sampled. The majority of the water concentrations reported were less than 0.01 ppb, with a maximum concentration of 0.65 ppb. Groundwater contamination could be significantly higher in areas treated with a termiticide containing chlorpyrifos, especially if contamination of a well occurs.⁵
- The U.S. EPA also analyzed NAWQA data for surface water contamination. A total of 1530 agricultural streams and 604 urban streams were tested. Of the streams tested, 15% of the agricultural streams and 26% of the urban streams contained chlorpyrifos at concentrations ranging from 0.026 ppb to 0.400 ppb. However, monitoring data were not collected for the watersheds where chlorpyrifos use is pervasive.⁵ See the **NPIC fact sheet** on [Pesticides in Drinking Water](#).

Air

- Researchers monitored concentrations of chlorpyrifos in outdoor air following ground application of chlorpyrifos in an agricultural setting. Air was sampled for chlorpyrifos and chlorpyrifos-oxon over a four week period during late spring, 24 hours a day, five days per week. Monitoring stations were located within three miles of average daily chlorpyrifos applications of 7.7 pounds per square mile per day. Median air concentrations of chlorpyrifos and chlorpyrifos-oxon were measured at 33 ng/m³ and 22 ng/m³, respectively.⁵⁵
- Chlorpyrifos reacts with photochemically-produced hydroxyl radicals in the atmosphere and degrades to chlorpyrifos-oxon. An atmospheric vapor half-life of 4.2 hours has been estimated for this reaction.⁵⁶ In one study, researchers estimated an outdoor air residence time of 4 and 11 hours for chlorpyrifos and chlorpyrifos oxon, respectively. However, these calculations are based on approximate hydroxyl radical concentrations in a specific geographical area.⁵⁷

Plants

- Chlorpyrifos is not expected to be taken up from soil through the roots of plants.²
- Chlorpyrifos was applied to the leaves and fruit of orange and grapefruit trees, and residues and dissipation on the rinds were measured using gas chromatography. Chlorpyrifos residues on fruit rinds were found to dissipate quickly, with initial mean half-lives of 2.8 days in oranges and 3.7 to 6.7 days in grapefruit, at which point residues were at or below 2 ppm. Chlorpyrifos residues were not found above levels of detection (0.03 ppm) in the edible portion (pulp) of citrus fruit tested.⁵⁸
- Though some chlorpyrifos may be taken up by plants through leaf surfaces, much of the applied chlorpyrifos is usually lost from volatilization, and very little is translocated throughout the plant.⁵⁴ Chlorpyrifos taken up by plant tissues is primarily metabolized to TCP, which is then stored as glycoside conjugates.^{2,54}
- Foliar applied chlorpyrifos on leaf surfaces is lost primarily by volatilization.⁵⁴
- Studies report chlorpyrifos residues remain on plant surfaces for 10 to 14 days after application.¹¹
- Although most of the chlorpyrifos applied to plants is lost through volatilization or converted to TCP and sequestered, desulfuration to the chlorpyrifos oxon on plant surfaces has been reported.⁵⁴

Indoor

- Several studies have reported detections of chlorpyrifos in dust, air, carpets, and on surfaces within indoor environments.^{59,60,61}

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- Research was conducted as part of the Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) study to evaluate the potential exposures of preschool children to chlorpyrifos and TCP in their homes and at day care centers in North Carolina. Monitoring of residues was performed at 129 homes and 13 day care centers, and included indoor and outdoor air, indoor floor dust, duplicate meals, transferable residues and surface wipe samples from floors, food preparation surfaces and children's hands. Urine was also collected from children by caretakers. Chlorpyrifos was detected in the indoor floor dust and indoor air at all locations. Median amounts of TCP were 12 and 29 times higher than those of chlorpyrifos in solid food at homes and daycare centers, respectively. Mean chlorpyrifos levels in homes were 19 ng/m³ in indoor air, 413 ng/g in indoor floor dust and 0.6 ng/g in solid food. Mean chlorpyrifos levels in day care centers were 8.2 ng/m³ in indoor air, 237.0 ng/g in indoor floor dust, and 0.2 ng/g in solid food.⁶¹
- Researchers detected chlorpyrifos in all seven homes tested in a New Jersey study. Concentrations in dust ranged from 0.053 ppm to 15.00 ppm. The highest indoor air concentrations detected were between 151.2 ng/m³ and 154.2 ng/m³.⁵⁹ The air samples with detectable levels of chlorpyrifos were correlated with dust samples that contained the highest levels of chlorpyrifos.⁵⁹
- In another study, researchers tested the indoor air and surfaces of ten urban residences in New Jersey. Chlorpyrifos residues were measured in samples of air and from non-target surfaces including plush toys, smooth surfaces, furniture, windowsills and flooring after the homes were treated with a water emulsion crack and crevice formulation containing 0.25 to 0.50% chlorpyrifos. Chlorpyrifos was detected in all homes within the treated areas throughout the two week post-application period. The highest concentrations of chlorpyrifos detected were 816 ng/m³ in air, 24.6 ng/m³ on non-target surfaces, and 1949 ng per toy on plush toys.⁶⁰ See the **NPIC fact sheet** on [Pesticides in Indoor Air of Homes - Technical](#).

Food Residue

- The United States Department of Agriculture (USDA) Pesticide Data Program collects data on pesticide residues in foods and compiles an annual report of the findings. The 2007 annual summary reported 9734 samples of fruit and vegetable commodities tested for chlorpyrifos residues. Chlorpyrifos was detected in 339 (3.48%) of these samples.⁶²
- Chlorpyrifos residues were found in 18.0% of peaches tested (100 detections), in 15.8% of nectarines tested (89 detections), in 6.8% of broccoli tested (50 detections) and in 5.2% of kale greens (20 detections). Chlorpyrifos residues were also monitored in almonds (46% of samples tested, 166 detections) and corn grain (30% of samples tested, 195 detections).⁶²
- Chlorpyrifos was detected at levels exceeding the U.S. EPA tolerance in one sample each of collard greens (353 samples, 10 with detectable residues) and summer squash (742 samples, 5 with detectable residues). In collard greens, residues were detected in one sample at 6.3 ppm (tolerance of 2.0 ppm). In summer squash, residues were detected in one sample at 0.33 ppm (tolerance 0.10 ppm).⁶²

Ecotoxicity Studies:

Birds

- Chlorpyrifos is very highly toxic to common grackles (*Quiscalus quiscula*) and ring-necked pheasants (*Phasianus colchicus*) with an LD₅₀ of 5.62 mg/kg and 8.41 mg/kg, respectively. Chlorpyrifos is highly toxic to common pigeons (*Columba livia*) and house sparrows (*Passer domesticus*) with an LD₅₀ of 10 mg/kg.⁴
- Chlorpyrifos is highly toxic to chickens with an oral LD₅₀ ranging from 32-102 mg/kg.²
- Chlorpyrifos is moderately toxic to mallard ducks (*Anas platyrhynchos*) with an acute oral LD₅₀ of 490 mg/kg.²
- The American robin (*Turdus migratorius*) is the most frequently reported avian species killed in field incidents with chlorpyrifos.⁴ Currently the acute LD₅₀ for the American robin is unknown.

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Fish and Aquatic Life

- Chlorpyrifos is very highly toxic to aquatic invertebrates, freshwater fish, and other estuarine and marine organisms.¹¹
- The 96-hour LC₅₀ is 0.007-0.051 mg/l for rainbow trout (*Oncorhynchus mykiss*), 0.002-0.010 mg/l for bluegill sunfish (*Lepomis macrochirus*), and 0.12-0.54 mg/l for fathead minnows (*Pimephales promelas*).²
- The 48-hour LC₅₀ for *Daphnia* is 1.7 µg/L. The LC₅₀ for Korean shrimp (*Palaemon macrodactylus*) is 0.05 µg/L.²
- There is potential for chlorpyrifos to bioaccumulate in the tissues of aquatic species.¹ Residues of chlorpyrifos found in fish tissue included the metabolites TCP and two glucuronide conjugates of TCP.⁴ Researchers exposed various fish species to chlorpyrifos continuously during early development, and calculated bioconcentration values ranging from 58 to 5100.⁶³

Terrestrial Invertebrates

- There are data gaps in terrestrial risk assessment due to a lack of quantitative methods available to assess risks posed by dermal and inhalation exposures for wildlife.⁴
- Chlorpyrifos is toxic to bees. The honey bee (*Apis* sp.) oral LD₅₀ is 360 ng/bee.² The contact LD₅₀ for honey bees is 0.059 pounds active ingredient per bee, or 70 ng/bee.^{2,4}
- The 14-day LC₅₀ for worms (*Eisenia foetida*) is 210 mg/kg chlorpyrifos in soil.²
- Foliar residues from spray applications of 0.5 and 1.0 lbs active ingredient/acre demonstrated toxicity to non-target insects for up to 24 hours post-treatment.⁴ See the **NPIC fact sheet** on [Wildlife and Pesticides](#).

Regulatory Guidelines:

- The acute Reference Dose (RfD) for chlorpyrifos is 5×10^{-3} mg/kg/day.¹ See the text box on **Reference Dose (RfD)**.
- The chronic RfD for chlorpyrifos is 3×10^{-4} mg/kg/day.¹ The chronic population adjusted dose (cPAD) is 3×10^{-5} mg/kg/day for sensitive subpopulations.¹
- A Food Quality Protection Act (FQPA) factor of 10 is applied to the acute RfD to derive an acute population adjusted dose (aPAD) which accounts for increased sensitivities in infants, children and females ages 13-50. The aPAD for children and females ages 13-50 is 5×10^{-4} mg/kg/day.¹
- Chlorpyrifos was classified as Group E, evidence of non-carcinogenicity for humans, by the U.S. EPA, in 1993.⁴⁰ See the text box on **Cancer** (page 7).
- The acute drinking water level of concern (DWLOC) for the general U.S. population is 166 ppb, the chronic DWLOC is 10 ppb. The acute DWLOC for all infants less than one year of age is 2.4 ppb; the chronic is 0.2 ppb. The acute DWLOC for children ages 1-6 years is 0.9 ppb; the chronic is 0.15 ppb. The acute DWLOC for females ages 13-50 years is 9 ppb; the chronic is 0.72 ppb.¹
- No drinking water standard exists for chlorpyrifos. However, the U.S. EPA has set a one-day and 10-day health advisory for children at 0.03 mg/L. The drinking water RfD is 3×10^{-4} mg/kg/day. The drinking water equivalent level is 0.01 mg/L and a lifetime health advisory is set at 2×10^{-3} mg/L.⁶⁴

Reference Dose (RfD): The RfD is an estimate of the quantity of chemical that a person could be exposed to every day for the rest of their life with no appreciable risk of adverse health effects. The reference dose is typically measured in milligrams (mg) of chemical per kilogram (kg) of body weight per day.

U.S. Environmental Protection Agency, Technology Transfer Network, Air Toxics Health Effects Glossary, 2009. <http://www.epa.gov/ttnatw01/hlthef/hapglossaryrev.html#RfD>

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- Pesticide exposure reporting laws vary by state. For example, some states may require mandatory medical monitoring with laboratory reporting for workers with blood cholinesterase levels below the normal range.⁶⁵ Reporting rules also vary by state regarding the individual responsible for reporting the results (e.g. the physician ordering the test, the laboratory responsible for sample collection, or the laboratory conducting the test).⁶⁵ See the **NPIC medical case profile** on [Pesticide Incident Reporting](#).
- The National Institute for Occupational Safety and Health (NIOSH) occupational exposure Threshold Limit Value (TLV) for inhalable vapor or aerosol is 0.1 mg/m³.⁵¹
- The NIOSH Recommended Exposure Limit (REL) is 0.2 mg/m³, with a short-term skin exposure limit (15 minutes) of 0.6 mg/m³.⁵¹

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