

*Section III*

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**HERBICIDES**

## HIGHLIGHTS

## Signs and Symptoms:

- Irritating to skin and mucous membranes
- Vomiting, diarrhea, headache, confusion, bizarre or aggressive behavior, peculiar odor on breath
- Metabolic acidosis, renal failure, tachycardia

## Treatment:

- Washing, GI decontamination
- Administer IV
- Forced alkaline diuresis

# Chlorophenoxy Herbicides

Chlorophenoxy compounds are sometimes mixed into commercial fertilizers to control growth of broadleaf weeds. Several hundred commercial products contain chlorophenoxy herbicides in various forms, concentrations, and combinations. In some cases, the same name is used for products with different ingredients. The exact composition must therefore be determined from the product label. Sodium, potassium, and alkylamine salts are commonly formulated as aqueous solutions, while the less water-soluble esters are applied as emulsions. Low molecular weight esters are more volatile than the acids, salts, or long-chain esters.

## Toxicology

Some of the chlorophenoxy acids, salts, and esters are moderately irritating to skin, eyes, and respiratory and gastrointestinal linings. In a few individuals, local depigmentation has apparently resulted from protracted dermal contact with chlorophenoxy compounds.

Chlorophenoxy compounds are well absorbed from the gastrointestinal tract.<sup>1</sup> They are less well absorbed from the lung. Cutaneous absorption appears to be minimal.<sup>2</sup> The compounds are not significantly stored in fat. Excretion occurs almost entirely by way of urine. Apart from some conjugation of the acids, there is limited biotransformation in the body.<sup>1,2</sup> The compounds are highly protein bound.<sup>2</sup> The average residence half-life of 2,4-D in humans is between 13 and 39 hours,<sup>1,3,4,5</sup> while that of 2,4,5-T is about 24 hours. Excretion is greatly enhanced in alkaline urine,<sup>4,5,6</sup> and with a half-life as prolonged as 70-90 hours with acidic urine.<sup>6</sup> Half-life is also longer with large doses and prolonged exposure.

Given in large doses to experimental animals, 2,4-D causes vomiting, diarrhea, anorexia, weight loss, ulcers of the mouth and pharynx, and toxic injury to the liver, kidneys, and central nervous system. Myotonia (stiffness and incoordination of hind extremities) develops in some species and is apparently due to CNS damage: demyelination has been observed in the dorsal columns of the cord, and EEG changes have indicated functional disturbances in the brains of heavily-dosed experimental animals.

Ingestion of large amounts of chlorophenoxy acids has resulted in severe metabolic acidosis in humans. Such cases have been associated with electrocar-

diographic changes, myotonia, muscle weakness, myoglobinuria, and elevated serum creatine phosphokinase, all reflecting injury to striated muscle. Chlorophenoxy acids are weak uncouplers of oxidative phosphorylation; therefore, extraordinary doses may produce hyperthermia from increased production of body heat.<sup>5</sup>

In the manufacture of some of these herbicides, other more toxic substances can be formed at excessive temperatures. These include chlorinated dibenzo dioxin (CDD) and chlorinated dibenzo furan (CDF). The 2,3,7,8-tetra CDD form is extraordinarily toxic to multiple mammalian tissues; it is formed only in the synthesis of 2,4,5-T. Hexa-, hepta-, and octa-compounds exhibit less systemic toxicity, but are the likely cause of chloracne (a chronic, disfiguring skin condition) seen in workers engaged in the manufacture of 2,4,5-T and certain other chlorinated organic compounds.<sup>7</sup> Although toxic effects, notably chloracne, have been observed in manufacturing plant workers, these effects have not been observed in formulators or applicators regularly exposed to 2,4,5-T or other chlorophenoxy compounds. All uses of 2,4,5-T in the U.S. have been cancelled.

The medical literature contains reports of peripheral neuropathy following what seemed to be minor dermal exposures to 2,4-D.<sup>8</sup> It is not certain that exposures to other neurotoxicants were entirely excluded in these cases. Single doses of 5 mg/kg body weight of 2,4-D and 2,4,5-T have been administered to human subjects without any adverse effects. One subject consumed 500 mg of 2,4-D per day for 3 weeks without experiencing symptoms or signs of illness.

## Signs and Symptoms of Poisoning

Chlorophenoxy compounds are moderately irritating to skin and mucous membranes. Inhalation of sprays may cause burning sensations in the nasopharynx and chest, and coughing may result. Prolonged inhalation sometimes causes dizziness. Adjuvant chemicals added to enhance foliage penetration might account for the irritant effects of some formulations.

Manifestations of systemic toxicity of chlorophenoxy compounds are known mainly from clinical experience with cases of deliberate suicidal ingestion of large quantities. Most reports of fatal outcomes involve renal failure, acidosis, electrolyte imbalance, and a resultant multiple organ failure.<sup>3,6,9</sup> The agents most often involved in these incidents have been 2,4-D and mecoprop. The toxic effects of other chlorophenoxy compounds are probably similar but not identical.

Patients will present within a few hours of ingestion with vomiting, diarrhea, headache, confusion, and bizarre or aggressive behavior. Mental status changes occur with progression to coma in severe cases.<sup>4,5,6</sup> A peculiar odor is often noticed on the breath. Body temperature may be moderately elevated, but this is rarely a life-threatening feature of the poisoning. The respiratory drive is not depressed. Conversely, hyperventilation is sometimes evident, prob-

## Commercial Products

2,4-dichlorophenoxyacetic acid (2,4-D)  
2,4-dichlorophenoxypropionic acid (2,4-DP) dichlorprop  
2,4-dichlorophenoxybutyric acid (2,4-DB)  
2,4,5-trichlorophenoxy acetic acid (2,4,5-T)  
MCPA  
MCPB  
mecoprop (MCPP)  
2-methyl-3, 6 dichlorobenzoic acid  
Banvel  
Dicamba

ably secondary to the metabolic acidosis that occurs. Muscle weakness and peripheral neuropathy have been reported after occupational exposure.<sup>6</sup> Convulsions occur very rarely. With effective urinary excretion of the toxicant, consciousness usually returns in 48-96 hours.<sup>4,5,6</sup>

As mentioned above, chlorophenoxy compounds cause significant metabolic changes. Metabolic acidosis is manifest as a low arterial pH and bicarbonate content. The urine is usually acidic. Skeletal muscle injury, if it occurs, is reflected in elevated creatine phosphokinase, and sometimes myoglobinuria. Moderate elevations of blood urea nitrogen and serum creatinine are commonly found as the toxicant is excreted. Cases of renal failure are reported, often with an accompanying hyperkalemia or hypocalcemia that was thought to result in the cardiovascular instability that led to death.<sup>3,9</sup> Tachycardia is commonly observed, and hypotension has also been reported.<sup>3,4,6</sup> T-wave flattening has also been observed.<sup>5</sup> Mild leukocytosis and biochemical changes indicative of liver cell injury have been reported.

Myotonia and muscle weakness may persist for months after acute poisoning.<sup>5</sup> Electromyographic and nerve conduction studies in some recovering patients have demonstrated a mild proximal neuropathy and myopathy.

## Confirmation of Poisoning

Gas-liquid chromatographic methods are available for detecting chlorophenoxy compounds in blood and urine. These analyses are useful in confirming and assessing the magnitude of chlorophenoxy absorption. Poisoning characterized by unconsciousness has shown initial blood chlorophenoxy concentrations ranging from 80 to more than 1000 mg per liter.<sup>4</sup> Urine samples should be collected as soon as possible after exposure because the herbicides may be almost completely excreted in 24-72 hours under normal conditions. Urine samples can also confirm overexposure. In a study of asymptomatic herbicide applicators, their urinary excretion of chlorophenoxy compounds rarely exceeded 1-2 mg/L.<sup>10</sup> The half-life may be much longer in cases of intoxication depending on the extent of absorption and urine pH.

Analyses can be performed at special laboratories usually known to local poison control centers. If the clinical scenario indicates that excessive exposure to chlorophenoxy compounds has occurred, initiate appropriate treatment measures immediately. Do not wait for chemical confirmation of toxicant absorption.

## Treatment

**1. Precautions.** Individuals with chronic skin disease or known sensitivity to these herbicides should either avoid using them or take strict precautions to avoid contact (respirator, gloves, etc.).

**2. Respiratory protection.** If any symptoms of illness occur during or following inhalation of spray, remove victim from contact with the material for at least 2-3 days. Allow subsequent contact with chlorophenoxy compounds only if effective respiratory protection is practiced.

**3. Skin decontamination.** Flush contaminating chemicals from eyes with copious amounts of clean water for 10-15 minutes. If irritation persists, an ophthalmologic examination should be performed.

**4. Gastrointestinal decontamination.** If substantial amounts of chlorophenoxy compounds have been ingested, spontaneous emesis may occur. Gastric decontamination procedures may be considered, as outlined in Chapter 2.

**5. Intravenous fluids.** Administer intravenous fluids to accelerate excretion of the chlorophenoxy compound, and to limit concentration of the toxicant in the kidney. A urine flow of 4-6 mL/minute is desirable. Intravenous saline/dextrose has sufficed to rescue comatose patients who drank 2,4-D and mecoprop several hours before hospital admission.

**Caution:** Monitor urine protein and cells, BUN, serum creatinine, serum electrolytes, and fluid intake/output carefully to insure that renal function remains unimpaired and that fluid overload does not occur.

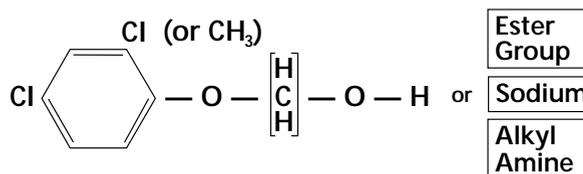
**6. Diuresis.** Forced alkaline diuresis has been used successfully in management of suicidal ingestions of chlorophenoxy compounds, especially when initiated early.<sup>4,5,6</sup> Alkalinizing the urine by including sodium bicarbonate (44-88 mEq per liter) in the intravenous solution accelerates excretion of 2,4-D dramatically and mecoprop excretion substantially. Urine pH should be maintained between 7.6 and 8.8. Include potassium chloride as needed to offset increased potassium losses: add 20-40 mEq of potassium chloride to each liter of intravenous solution. It is crucial to monitor serum electrolytes carefully, especially potassium and calcium.

There may possibly be some hazard to the kidneys when urine concentrations of toxicant are very high, so the integrity of renal function and fluid balance should be monitored carefully as the chlorophenoxy compound is excreted. Renal failure has occurred in patients with severe intoxication during alkaline diuresis. In one case, the diuresis was begun 26 hours after ingestion,<sup>6</sup> and the other two were initiated a couple days after poisoning.<sup>3,9</sup>

**7. Hemodialysis** is not likely to be of significant benefit in poisonings by chlorophenoxy compounds. It has been used in four patients who survived intoxication.<sup>11</sup> However, given the highly protein-bound nature of these herbicides and lack of any other evidence, hemodialysis is not recommended.<sup>2</sup>

**8. Follow-up clinical examination** should include electromyographic and nerve conduction studies to detect any neuropathic changes and neuromuscular junction defects.

## General Chemical Structure



## References

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