

Solid Organochlorine Insecticides

EPA has sharply curtailed the availability of many organochlorines, particularly DDT, aldrin, dieldrin, heptachlor, mirex, chlordecone, and chlordane. Others, however, remain the active ingredients of various home and garden products and some agricultural, structural, and environmental pest control products. Hexachlorobenzene is a fungicide used as a seed protectant and is discussed further in Chapter 15, Fungicides.

Technical hexachlorocyclohexane (misnamed benzene hexachloride, BHC) includes multiple stereoisomers; only the gamma isomer (lindane) is insecticidal. Lindane is the active ingredient of some pest control products used in the home and garden, on the farm, and in forestry and animal husbandry. It is also the active agent in the medicine Kwell[®], used for human ectoparasitic disease. Lindane has been reported on numerous occasions to be associated with acute neurological toxicity either from ingestion or in persons treated for scabies or lice.¹⁻⁶

Toxicology

In varying degrees, organochlorines are absorbed from the gut and also by the lung and across the skin. The efficiency of dermal absorption is variable. Hexachlorocyclohexane, including lindane, the cyclodienes (aldrin, dieldrin, endrin, chlordane, heptachlor), and endosulfan are efficiently absorbed across the skin, while dermal absorption efficiencies of DDT, dicofol, marlate, toxaphene, and mirex are substantially less.⁷ Lindane has a documented 9.3% dermal absorption rate,⁸ and is absorbed even more efficiently across abraded skin.^{1,9} This becomes especially important when taking into account its use on children with severe dermatitis associated with scabies. Fat and fat solvents enhance gastrointestinal, and probably dermal, absorption of organochlorines. While most of the solid organochlorines are not highly volatile, pesticide-laden aerosol or dust particles trapped in respiratory mucous and subsequently swallowed may lead to significant gastrointestinal absorption.

Following exposure to some organochlorines (notably DDT), a significant part of the absorbed dose is stored in fat tissue as the unchanged parent compound. Most organochlorines are in some degree dechlorinated, oxidized, then conjugated. The chief route of excretion is biliary, although nearly all organochlorines yield measurable urinary metabolites. Unfortunately, many of the unmetabolized pesticides are efficiently reabsorbed by the intestine (enterohepatic circulation), substantially retarding fecal excretion.

HIGHLIGHTS

Signs and Symptoms:

- Absorbed dose is stored in fat tissue
- Sensory disturbances: hyperesthesia and paresthesia, headache, dizziness, nausea, hyperexcitable state
- Convulsions

Treatment:

- Anticonvulsants (benzodiazepines)
- Administer oxygen
- Cardiopulmonary monitoring

Contraindicated:

- Epinephrine, other adrenergic amines, atropine
- Animal or vegetable oils or fats taken orally

Commercial Products

aldrin*
benzene hexachloride (BHC)*
HCH
hexachlor
hexachloran
chlordane*
(multiple trade names)
chlordecone*
Kepone
chlorobenzilate
DDT*
(multiple trade names)
dicofol
Kelthane
(multiple trade names)
dieldrin*
Dieldrite
dienochlor
Pentac
endosulfan
(multiple trade names)
endrin*
Hexadrin
heptachlor**
(multiple trade names)
hexachlorobenzene*
lindane
gamma BHC or HCH
Kwell
(multiple trade names)
methoxychlor
Marlate
mirex*
terpene polychlorinates*
Strobane
toxaphene*

* All U.S. registrations have been cancelled.

** Registered in the United States only for underground use in power lines for fire ants.

Metabolic dispositions of DDT and DDE (a DDT degradation product), the beta isomer of hexachlorocyclohexane, dieldrin, heptachlor epoxide, and mirex tend to be slow, leading to storage in body fat. Storable lipophilic compounds are likely to be excreted in maternal milk.^{6,10,11} On the other hand, rapid metabolic dispositions of lindane, methoxychlor, dienochlor, endrin, chlorobenzilate, dicofol, toxaphene, perthane, and endosulfan reduce the likelihood that these organochlorines will be detected as residues in body fat, blood, or milk.

The chief acute toxic action of organochlorine pesticides is on the nervous system, where these compounds induce a hyperexcitable state in the brain.¹² This effect is manifest mainly as convulsions, sometimes limited to myoclonic jerking, but often expressed as violent seizures. Convulsions caused by cyclodienes may recur over periods of several days. Other less severe signs of neurologic toxicity such as paresthesias, tremor, ataxia, and hyperreflexia are also characteristic of acute organochlorine poisoning. Agents such as DDT and methoxychlor tend to cause the less severe effects, while the cyclodienes, mirex, and lindane are associated with the more severe seizures and fatalities.⁷ Convulsions may cause death by interfering with pulmonary gas exchange and by generating severe metabolic acidosis.

High tissue concentrations of organochlorines increase myocardial irritability, predisposing to cardiac arrhythmia. When tissue organochlorine concentrations drop below threshold levels, recovery from the poisoning occurs. Organochlorines are not cholinesterase inhibitors.

High tissue levels of some organochlorines (notably DDT, DDE, and cyclodienes) have been shown to induce hepatic microsomal drug-metabolizing enzymes.¹³ This tends to accelerate excretion of the pesticides themselves, but may also stimulate biotransformation of critical natural substances, such as steroid hormones and therapeutic drugs, occasionally necessitating re-evaluation of required dosages in persons intensively exposed to organochlorines. Human absorption of organochlorine sufficient to cause enzyme induction is likely to occur only as a result of prolonged intensive exposure.

Ingestion of hexachlorobenzene-treated wheat has been associated with human dermal toxicity diagnosed as porphyria cutanea tarda. The skin blisters, becomes very sensitive to sunlight, and heals poorly, resulting in scarring and contracture formation.¹⁴ Unlike other organochlorine compounds, there have been no reported cases of convulsions caused by the fungicide hexachlorobenzene. Lindane and chlordane have rarely been associated anecdotally with certain hematological disorders, including aplastic anemia and megaloblastic anemia.^{15,16}

There has been considerable interest recently in the interaction of organochlorines with endocrine receptors, particularly estrogen and androgen receptors. *In vitro* studies and animal experimentation have supported the view that the function of the endocrine system may be altered by these interactions.^{17,18} This in turn may alter the reproductive development and success of animals and humans. In addition, some organochlorines may inhibit lactation and may also be developmental toxicants.¹⁰ Due to evidence of carcinogenic

potential, some organochlorines have lost registration for use in the United States or had their uses restricted. Although these effects are important, they are beyond the scope of this manual.

Signs and Symptoms of Poisoning

Early manifestations of poisoning by some organochlorine pesticides, particularly DDT, are often sensory disturbances: hyperesthesia and paresthesia of the face and extremities. Headache, dizziness, nausea, vomiting, incoordination, tremor, and mental confusion are also reported. More severe poisoning causes myoclonic jerking movements, then generalized tonic-clonic convulsions. Coma and respiratory depression may follow the seizures.

Poisoning by the cyclodienes and toxaphene is more likely to begin with the sudden onset of convulsions, and is often not preceded by the premonitory manifestations mentioned above. Seizures caused by cyclodienes may appear as long as 48 hours after exposure, and then may recur periodically over several days following the initial episode. Because lindane and toxaphene are more rapidly biotransformed in the body and excreted, they are less likely than dieldrin, aldrin, and chlordane to cause delayed or recurrent seizures.

Confirmation of Poisoning

Organochlorine pesticides and/or their metabolites can sometimes be identified in blood by gas-liquid chromatographic examination of samples taken within a few days of significant pesticide absorption. Such tests are performed by a limited number of government, university, and private laboratories, which can usually be contacted through poison control centers or health departments. Some organochlorine pesticides or their products (notably DDT, dieldrin, mirex, heptachlor, epoxide, chlordecone) persist in tissues and blood for weeks or months after absorption, but others are likely to be excreted in a few days, limiting the likelihood of detection. Blood levels tend to correlate more with acute toxicity, while levels found in adipose tissue and breast milk usually reflect more long-term and historic exposure.¹⁹

Chromatographic methods make possible detection of most organochlorines at concentrations much lower than those associated with symptoms of toxicity. Therefore, a positive finding in a blood sample does not, of itself, justify a diagnosis of acute poisoning. Lindane appears in the literature more frequently than other compounds. The time of acquisition of the blood level in relation to exposure time must be taken into account when interpreting blood levels. In one study, lindane levels were measured at 10.3 ng/mL in healthy volunteers three days after application to the skin.²⁰

In a study with childhood dermal absorption using children with scabies and a non-affected control group, lindane peaked at 28 ng/mL 6 hours after application in the affected group, and at 24 ng/mL in the control group. At 48

hours, levels were 6 ng/mL and 5 ng/mL respectively. Findings from this study also provide evidence for increased absorption across abraded skin.⁹ A child with severely abraded skin was treated for scabies and developed seizures. Three days after exposure, his lindane level was 54 ng/mL.¹ Most reports of acute toxicity from lindane involve blood levels of 130 ng/mL or greater, with the most severe and fatal cases involving levels exceeding 500 ng/mL.²

DDT, DDE, and a few other organochlorines are still found at very low levels in blood samples from the general U.S. population, presumably due to past and/or current low-level contamination of food by these environmentally persistent pesticides.

In the absence of corresponding elevations of blood levels, the amount of stored pesticides is not likely to be of clinical significance. Measurements of urinary metabolites of some organochlorine pesticides can be useful in monitoring occupational exposures; however, the analytical methods are complex, and are not likely to detect amounts of metabolites generated by minimal exposures.

Treatment

1. Observation. Persons exposed to high levels of organochlorine pesticides by any route should be observed for sensory disturbances, incoordination, speech slurring, mental aberrations, and involuntary motor activity that would warn of imminent convulsions.

2. Convulsions. If convulsions occur, place the victim in the left lateral decubitus position with the head down. Move away furniture or other solid objects that could be a source of injury. If jaw movements are violent, place padded tongue blades between the teeth to protect the tongue. Whenever possible, remove dentures and other removable dental work. Aspirate oral and pharyngeal secretion, and when possible, insert an oropharyngeal airway to maintain an open passage unobstructed by the tongue. Minimize noise and any manipulation of the patient that may trigger seizure activity.

Dosage of Diazepam:

- *Adults:* 5-10 mg IV and repeat every 5-10 minutes to maximum of 30 mg.
- *Children:* 0.2 to 0.5 mg/kg every 5 minutes to maximum of 10 mg in children over 5 years, and maximum of 5 mg in children under 5 years.

Although lorazepam is widely accepted as a treatment of choice for status epilepticus, there are no reports of its use for organochlorine intoxication. Some cases have required aggressive seizure management including the addition of phenobarbital and the induction of pentobarbital coma.

Seizures in patients caused by organochlorine toxicity are likely to be prolonged and difficult to control. Status epilepticus is common. For this reason, patients with seizures that do not respond immediately to anticonvulsants should be transferred as soon as possible to a trauma center and will generally require intensive care admission until seizures are controlled and neurologic status is improved. Initial therapy with benzodiazepines should be instituted.

3. Oxygen. Administer oxygen by mask. Maintain pulmonary gas exchange by mechanically assisted ventilation whenever respiration is depressed.

4. Skin decontamination. Skin decontamination should be done thoroughly, as outlined in Chapter 2.

5. Gastrointestinal decontamination. If organochlorine has been ingested in a quantity sufficient to cause poisoning and the patient presents within an hour, consideration should be given to gastric decontamination procedures, as outlined in Chapter 2. If the patient presents more than an hour after ingestion, activated charcoal may still be beneficial. If the victim is convulsing, it is almost always necessary first to control seizures before attempting gastric decontamination. Activated charcoal administration has been advocated in such poisonings, but there is little human or experimental evidence to support it.

6. Respiratory failure. Particularly in poisonings by large doses of organochlorine, **monitor pulmonary ventilation** carefully to forestall respiratory failure. Assist pulmonary ventilation mechanically with oxygen whenever respiration is depressed. Since these compounds are often formulated in a hydrocarbon vehicle, hydrocarbon aspiration may occur with ingestion of these agents. The hydrocarbon aspiration should be managed in accordance with accepted medical practice as a case of acute respiratory distress syndrome which will usually require intensive care management.

7. Cardiac monitoring. In severely poisoned patients, monitor cardiac status by continuous ECG recording to detect arrhythmia.

8. Contraindications. Do not give epinephrine, other adrenergic amines, or atropine unless absolutely necessary because of the enhanced myocardial irritability induced by chlorinated hydrocarbons, which predisposes to ventricular fibrillation. Do not give animal or vegetable oils or fats by mouth. They enhance gastrointestinal absorption of the lipophilic organochlorines.

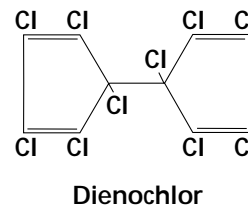
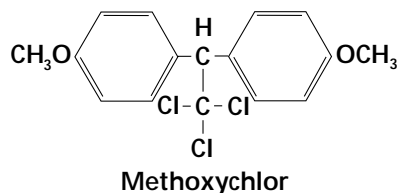
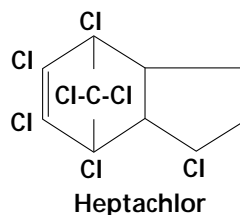
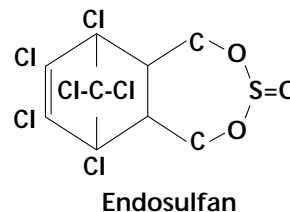
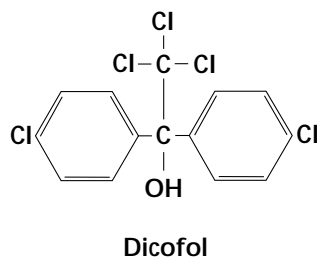
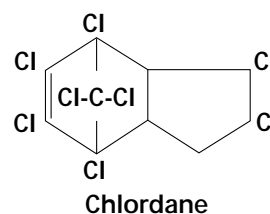
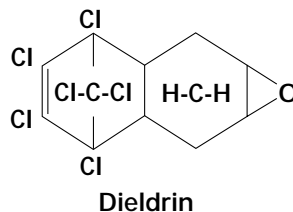
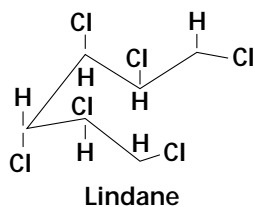
9. Phenobarbital. To control seizures and myoclonic movements that sometimes persist for several days following acute poisoning by the more slowly excreted organochlorines, phenobarbital given orally is likely to be effective.

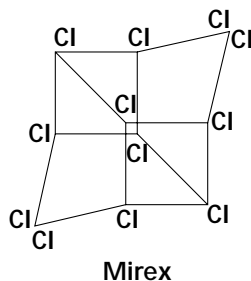
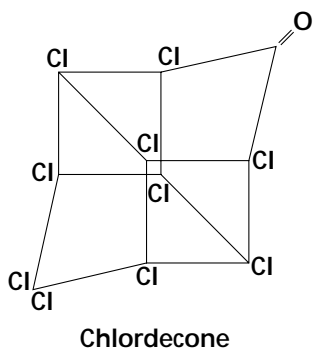
Dosage should be based on manifestations in the individual case and on information contained in the package insert.

10. Cholestyramine resin accelerates the biliary-fecal excretion of the more slowly eliminated organochlorine compounds.²¹ It is usually administered in 4 g doses, 4 times a day, before meals and at bedtime. The usual dose for children is 240 mg/kg/24 hours, divided Q 8 hours. The dose may be mixed with a pulpy fruit or liquid. It should never be given in its dry form and must always be administered with water, other liquids or a pulpy fruit. Prolonged treatment (several weeks or months) may be necessary.

11. Convalescence. During convalescence, enhance carbohydrate, protein, and vitamin intake by diet or parenteral therapy.

General Chemical Structures





References

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