

## CHAPTER 7

# Organochlorines

The U.S. Environmental Protection Agency has sharply curtailed the availability of most organochlorines. While use continues in many other regions of the world, in the United States only dicofol and endosulfan are still registered as pesticides. Lindane is still marketed as a second-line agent for treatment of lice and scabies under the trade names Kwell and Thionex, although it is no longer recommended by the American Academy of Pediatrics and has been banned in California. This is the result of multiple cases of acute neurological toxicity either from ingestion or in persons treated for scabies or lice.<sup>1,2,3,4,5,6,7</sup> In recent years, the most frequently reported serious or fatal events were from endosulfan.<sup>8,9,10,11,12,13,14</sup>

### Toxicology

**Organochlorines** are absorbed from the gut, by the lungs and across the skin in varying degrees. **Hexachlorocyclohexane, lindane, the cyclodienes (aldrin, dieldrin, endrin, chlordane, heptachlor)** and **endosulfan** are efficiently absorbed across the skin, while dermal absorption efficiencies of **DDT, dicofol, methoxychlor, toxaphene** and **mirex** are substantially less.<sup>15</sup> Lindane has an estimated 9.3% dermal absorption rate<sup>16</sup> and is absorbed even more efficiently across abraded skin.<sup>4,17</sup> 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. Many formulations of organochlorines are in hydrocarbon solvents that probably promote absorption. While most of the solid organochlorines are not highly volatile, pesticide-laden aerosols or dust particles trapped in respiratory mucous and subsequently swallowed may be vehicles leading 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 parent compound. Most organochlorines are in some degree dechlorinated, oxidized and 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. 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.<sup>6,18,19</sup> In contrast, rapid metabolic disposition 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 the organochlorine pesticides is on the central nervous system, where these compounds induce a hyperexcitable state in the brain leading to convulsions or other less severe signs of neurologic toxicity such as myoclonic jerking, paresthesias, tremor, ataxia and hyperreflexia.<sup>20</sup> Convulsions caused by cyclodienes may recur over periods of several days and are also characteristic of acute organochlorine poisoning. Agents such as DDT and methoxychlor tend

### HIGHLIGHTS

Only dicofol, endosulfan, lindane still registered for use in U.S.

Absorbed from the gut, by the lungs and across skin

Fat and fat solvents enhance absorption

Most are dechlorinated, oxidized, then conjugated

Chief toxic action is on CNS

### SIGNS & SYMPTOMS

Sensory disturbances: hyperesthesia & paresthesias of face & extremities

Possible headache, dizziness, nausea, vomiting, tremor, confusion

Cyclodienes & toxaphene poisoning may result in seizures (including delayed ones) without other symptoms

Severe poisonings: convulsions, respiratory depression, coma

### TREATMENT

Manage convulsions

Administer oxygen

Decontaminate skin

Consider GI decontamination

Monitor cardiac, pulmonary status

### CONTRAINDICATED

Epinephrine, other adrenergic amines, atropine in most cases

Animal or vegetable oils by mouth

## COMMERCIAL PRODUCTS

aldrin\*  
BHC\* (HCH, hexachlor, hexachloran)  
chlordane\* (multiple trade names)  
chlorobenzilate\*  
DDT\* (multiple trade names)  
dicofol (multiple trade names)  
dieldrin\*  
dienochlor (Pentac)\*  
endosulfan (Thionex)  
endrin\*  
heptachlor\*  
hexachlorobenzene\*  
lindane (gamma BHC or HCH)\*  
methoxychlor (Marlate)\*  
mirex\*  
toxaphene\*

\*All U.S. registrations are suspended.

to cause the less severe effects, while the cyclodienes, mirex and lindane are associated with the more severe seizures and fatalities.<sup>15</sup> 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.<sup>21</sup> This tends to accelerate excretion of the pesticides themselves but may also stimulate biotransformation of endogenous steroid hormones and exogenous therapeutic drugs, occasionally necessitating reevaluation of required dosages of therapeutic drugs 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 forms blisters and becomes very sensitive to sunlight. Subsequent poor healing results in scarring and contracture formation.<sup>22</sup> Unlike other organochlorine compounds, no cases of convulsions caused by the fungicide hexachlorobenzene have been reported in the medical literature. Lindane and chlordane have been infrequently associated with hematological disorders, including aplastic anemia and megaloblastic anemia.<sup>23,24,25</sup>

Evidence has emerged that the organochlorines interact with endocrine receptors, particularly estrogen and androgen receptors. *In vitro* studies and animal experimentation suggest that organochlorines may alter the function of the endocrine system by these interactions.<sup>26,27</sup> In addition, the potential for carcinogenicity has resulted in regulatory action to limit use or remove registration for multiple organochlorines. An extensive literature has accumulated relevant to neurodevelopmental and neurologic effects of chronic low-level exposure to organochlorines.<sup>28,29,30,31,32,33,34</sup> These chronic health implications on the endocrine system and nervous system, and carcinogenic potential are discussed in **Chapter 21, Chronic Effects**.

## Signs and Symptoms of Poisoning

Early manifestations of poisoning by some organochlorine pesticides, particularly DDT, are often sensory disturbances: hyperesthesia and paresthesias of the face and extremities. Headache, dizziness, nausea, vomiting, incoordination, tremor and mental confusion are also reported. More severe poisoning results in myoclonic jerking movements, often followed by 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, 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. Since 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.

There have been reports of mixed poisonings, where anticholinesterase agents such as organophosphates and anticholinesterase carbamates have been mixed with organochlorines. In such cases the cholinergic symptoms may be prominent on presentation, but aggressive treatment of the cholinergic findings leave the subject with the symptoms of the organochlorine poisoning, which need additional treatment.<sup>35,36</sup>

Medical providers should be alert to the possibility of such mixed poisonings in the diagnosis and management of pesticide poisonings.

### 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 metabolic products (notably DDT, dieldrin, mirex, heptachlor epoxide and 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.<sup>37</sup>

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. Current general population tissue concentration levels for many of the organochlorines are available from the Centers for Disease Control and Prevention's Biomonitoring Program and may be helpful in interpreting findings.<sup>38</sup>

Lindane tissue concentration reports appear in the literature more frequently than other compounds. The time of the blood sampling 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 3 days after application to the skin.<sup>39</sup> In a study with childhood dermal absorption in 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.<sup>17</sup> A child with severely abraded skin was treated for scabies and developed seizures. Three days after exposure, his lindane level was 54 ng/mL.<sup>4</sup> 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.<sup>2</sup>

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.

Overall, blood organochlorine levels have the most readily available information for understanding the acute clinical implications of exposures. 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 of Organochlorine Toxicosis

1. Observe persons with suspected very high exposure to organochlorine pesticides by any route for sensory disturbances, incoordination, speech slurring, mental aberrations and involuntary motor activity that would warn of imminent convulsions.

2. If convulsions occur, place the victim in the left lateral decubitus position with the head down. Move away furniture or other solid objects that may 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.
3. Administer oxygen by mask. Maintain pulmonary gas exchange by mechanically assisted ventilation whenever respiration is depressed.
4. Control convulsions. 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.

#### 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 a 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.

5. Decontaminate skin thoroughly, as outlined in **Chapter 3, General Principles**.
6. Consider gastric decontamination procedures as outlined in **Chapter 3** if organochlorine has been ingested in a quantity sufficient to cause poisoning and the patient presents within an hour. 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 this modality.
7. 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 and will usually require intensive care management.

8. Monitor cardiac status of severely poisoned patients by continuous ECG recording to detect arrhythmia.
9. Do not give epinephrine, other adrenergic amines or atropine unless absolutely necessary. The enhanced myocardial irritability induced by chlorinated hydrocarbons predisposes to ventricular fibrillation.
10. Do not give animal or vegetable oils or fats by mouth. They enhance gastrointestinal absorption of the lipophilic organochlorines.
11. Control seizures and myoclonic movements that sometimes persist for several days following acute poisoning by the more slowly excreted organochlorines. Phenobarbital orally is likely to be effective. Dosage should be based on manifestations in the individual case and on information contained in the package insert.
12. Use cholestyramine resin to accelerate the biliary-fecal excretion of the more slowly eliminated organochlorine compounds.<sup>40</sup>

#### **Dosage of Cholestyramine Resin**

- **Adults: 4-gram doses, 4 times a day, before meals and at bedtime.**
- **Children: 240 mg/kg/24 hours, divided, every 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.

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

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