In addition to regulating pesticide use and application, the FIFRA requires that the pesticide manufacturer be registered with the EPA. The EPA, under agreement with the U.S. Food and Drug Administration, establishes pesticide tolerances for raw foods and produce. Pesticides that might be considered food additives are controlled by the EPA under the Food, Drug, and Cosmetic Act. Once a pesticide is discarded, it becomes a hazardous waste and then falls under regulation by the Resource Conservation and Recovery Act rather than by the FIFRA.

The 1978 amendment to the FIFRA allows manufacturers of pesticides to obtain a waiver on submission of data demonstrating efficacy of their product, except when the product has a direct relation to or effect on public health. In addition, the 1978 amendment allows for public disclosure of the safety and health data regarding pesticide regulation. The 1978 amendment also transfers to states the responsibility to enforce pesticide use regulations if they can demonstrate that they possess the means to do so. The EPA reserves the right to revoke any state's responsibility for pesticide regulation if that state is unable or unwilling to enforce the regulations.

REFERENCES

1. Al-Saleh IM. Pesticides: a review article. *J Environ Pathol Toxicol* 1994;13:151–161.
2. Marrs TC. Organophosphate poisoning. *Pharmacol Ther* 1993;58:51–66.
3. Morita H, Yanagisawa N, Nakajima, et al. Sarin poisoning in Matsumoto. *Lancet* 1995;346:290–293.
4. Okumura T, Nobukatsu T, Ishimatsu S, et al. Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med* 1996;28:129–135.
5. Machemer LH, Pickel M. Carbamate insecticides. *Toxicology* 1994;91:29–36.
6. Levine RS, Doull J. Global estimates of acute pesticide morbidity and mortality. *Rev Environ Contam Toxicol* 1992;129:29–50.
7. Litovitz TL, Felberg L, White S, et al. 1995 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 1996;14:487–531.
8. Koelle GB. Pharmacology of organophosphates. *J Appl Toxicol* 1994;14:105–109.
9. Jeyaratnam J, Maroni M. Organophosphorus compounds. *Toxicology* 1994; 91:15–27.
10. Sussman JL, Harel M, Frolow F, et al. Atomic structure of acetylcholinesterase from *Torpedo californie*: a prototypic acetylcholine-binding protein. *Science* 1991;253:872–879.
11. Mason J, Waine E, Stevenson A, et al. Aging and spontaneous reactivation of human plasma cholinesterase activity after inhibition by organophosphorus pesticides. *Hum Exp Toxicol* 1993;12:556–559.
12. Sanderson D, Edson E. Toxicological properties of the organophosphate insecticide dimethioate. *Br J Ind Med* 1964;21:52–64.
13. Chatonnet A, Lockridge O. Comparison of butyrylcholinesterase and acetylcholinesterase. *Biochem J* 1989;260:625–634.
14. Lotti M. Cholinesterase inhibition: complexities in interpretation. *Clin Chem* 1995;41:1814–1818.
15. Nouira S, Abroug F, Elatrous S, et al. Prognostic value of serum cholinesterase in organophosphate poisoning. *Chest* 1994;106:1811–1814.
16. McDonough J, Jaax N, Crowley R, et al. Atropine and/or diazepam therapy protects against soman-induced neural and cardiac pathology. *Fundam Appl Toxicol* 1989;13:256–276.
17. Fisher J. Guillain-Barré syndrome following organophosphate poisoning. *JAMA* 1977;238:1950.
18. Coye M, Barnett P, Midtling J, Velasco A, et al. Clinical confirmation of organophosphate poisoning of agricultural workers. *Am J Ind Med* 1986;10:399–409.
19. Hayes W. *Pesticides studied in man.* Baltimore: Williams & Wilkins, 1982: 2884–435.
20. Zwiener RJ, Ginsburg CM. Organophosphate and carbamate poisoning in infants and children. *Pediatrics* 1988;81:121–126.
21. Midtling JE, Barnett PG, Coye MJ, et al. Clinical management of field worker organophosphate poisoning. *West J Med* 1985;142:514.
22. Ames RG, Brown SK, Mengle DC, Kahn E, Stratton JW, Jackson RJ. Cholinesterase activity depression among California agricultural pesticide applicators. *Am J Ind Med* 1989;15:143–150.
23. Mellar D, Fraser I, Kruger M. Hyperglycemia in anticholinesterase poisoning. *Can Med Assoc J* 1981;124:745–747.
24. Mackey C. Anticholinesterase insecticide poisoning. *Heart Lung* 1982; 11:479–484.
25. Hui K. Metabolic disturbances in organophosphate insecticide poisoning [letter]. *Arch Pathol Lab Med* 1983;104:154.
26. Haubenstock A. More on the triad of pancreatitis, hyperamylasemia and hyperglycemia. *JAMA* 1983;249:1563.
27. Hayes M, Van Der Westhuizen N, Gelfand M. Organophosphate poisoning in Rhodesia. *S Afr Med J* 1978;53:230–234.
28. Robson N, Robertson I, Whittaker M. Plasma cholinesterase changes during the puerperium. *Anesthesia* 1986;41:243–249.
29. Whittaker M, Charlier AR, Ramaswamy S. Changes in plasma cholinesterase isoenzymes due to oral contraceptives. *J Reprod Fertil* 1971;26:373–375.
30. Ludomirsky A, Klein H, Sarelli P, et al. Q-T prolongation and polymorphous ("torsade de pointes") ventricular arrhythmias associated with organophosphorus insecticide poisoning. *Am J Cardiol* 1982;49:1654–1658.
31. Brill D, Maisel A, Prabhu R. Polymorphic ventricular tachycardia and other complex arrhythmias in organophosphate insecticide poisoning. *J Electrocardiol* 1984;17(1):97–102.
32. Dunn MA, Sidell FR. Progress in medical defense against nerve agents. *JAMA* 1989;262:649–652.
33. Mortensen ML. Management of acute childhood poisonings caused by selected insecticides and herbicides. *Pediatr Clin North Am* 1986;33:421–445.
34. Willems J, Bisschop H, Verstraete A. Cholinesterase reactivation in organophosphorus poisoned patients depends on the plasma concentrations of the oxime pralidoxime methylsulfate and of the organophosphate. *Arch Toxicol* 1993;67:79–84.
35. Waser PG, Alioth-Streichenberg CM, Hopff WH, et al. Interaction of obidoxime with sarin in aqueous solution. *Arch Toxicol* 1992;66:211–215.
36. Thompson DF, Thompson GD, Greenwood RB, et al. Therapeutic dosing of pralidoxime chloride. *Drug Intell Clin Pharmacol* 1987;21:590–593.
37. Farrar HC, Wells TG, Kearns GL. Use of continuous infusion of pralidoxime for treatment of organophosphate poisoning in children. *J Pediatr* 1990;116: 658–661.
38. Kassa J. Comparison of efficacy of two oximes (HI-6 and obidoxime) in soman poisoning in rats. *Toxicology* 1995;101:167–174.
39. Das Gupta S, Ghosh AK, Moorthy MV, et al. Comparative studies of pralidoxime, trimedoxime, obidoxime and diethyxime in acute fluostigmine poisoning in rats. *Pharmazie* 1982;37:605.
40. Kusic R, Jovanovic D, Randjelovic S, et al. HI-6 in man: efficacy of the oxime in poisoning by organophosphorus insecticides. *Hum Exp Toxicol* 1991;10:113–118.
41. Burgess J, Bernstein J, Hurlbut K. Aldicarb poisoning. *Arch Intern Med* 1994;154:221–224.
42. Ekins B, Geller R. Methomyl-induced carbamate poisoning treated with pralidoxime chloride. *West J Med* 1994;161(1):68–70.
43. Wu SY, Casida JE. Subacute neurotoxicity induced in mice by potent organophosphorus neuropathy target esterase inhibitors. *Toxicol Appl Pharmacol* 1996;139:195–202.
44. Pope CN, Tanaka D, Padilla S. The role for neurotoxic esterase (NTE) in the prevention and potentiation of organophosphorus-induced delayed neurotoxicity (OPIDN). *Chem-Biol Interact* 1993;87:395–406.
45. Abou-Donia MB. The cytoskeleton as a target for organophosphorus ester–induced delayed neurotoxicity (OPIDN). *Chem Biol Interact* 1993;87:383–393.
46. Lotti M, Becker CE, Aminoff MJ. Organophosphate polyneuropathy: pathogenesis and prevention. *Neurology* 1984;34:658–662.
47. Gordon JJ, Inns RH, Johnson MK, et al. The delayed neuropathic effects of nerve agents and some other organophosphorus compounds. *Arch Toxicol* 1983;52:71–82.
48. Senanayake N, Johnson MK. Acute polyneuropathy after poisoning by a new organophosphate insecticide. *Med Intell* 1982;306:155–159.
49. Cherniack M. Organophosphorus esters and polyneuropathy. *Ann Intern Med* 1986;104:264–266.
50. Savage E, Keefe T, Mounce L, et al. Chronic neurological sequelae of acute organophosphate pesticide poisoning. *Arch Environ Health* 1988;43:38–45.
51. Rosenstock L, Keifer M, Daniel W, et al. Chronic central nervous system effects of acute organophosphate pesticide intoxication. *Lancet* 1991;338: 223–227.
52. Steeland K, Jenkins B, Ames R, et al. Chronic sequelae to organophosphate pesticide poisoning. *Am J Public Health* 1994;84:731–736.
53. Yokoyama K, Shunichi A, Murata K. Chronic neurobehavioral effects of Tokyo subway sarin poisoning in relation to post-traumatic stress disorder. *Arch Environ Health* 1998;53(4):249–256.
54. Dementi B. Ocular effects of organophosphates: a historical perspective of Saku disease. *J Appl Toxicol* 1994;14:119–129.

CHAPTER 99
Organochlorine Pesticides

Mark D. Van Ert and John B. Sullivan, Jr.

Chlorinated hydrocarbon pesticides include DDT, DDE, and DDD; hexachlorocyclohexane (HCH) and isomers, including lindane (γ-HCH); cyclodiene compounds; chlordecone, kelevan, and mirex; toxaphene; and dicofol and methoxychlor (Table 99-1). The general toxicity of chlorinated hydrocarbon insecti-

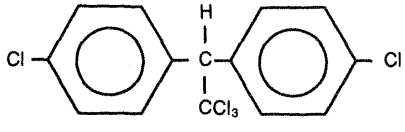
TABLE 99-1. Organochlorine pesticides

DDT
DDE
DDD (Rothane)
Aldrin
Dieldrin
Endrin
Endosulfan
Isobenzan (telodrin)
Chlordane
Heptachlor
Hexachlorocyclohexane (technical-grade)
Lindane (γ-hexachlorocyclohexane)
Chlordecone (Kepone)
Kelevan
Mirex (Dechlorane)
Dicofol (Kelthane)
Methoxychlor (Marlate)
Toxaphene

cides is central nervous system (CNS) stimulation or depression, depending on the compound and dose. Cyclodienes, HCHs, and toxaphene pesticides inhibit chloride influx in the CNS induced by gamma-aminobutyric acid (GABA) and thus interfere with GABA receptor function (1,2). This mechanism of inhibition is consistent with the clinical symptoms of CNS excitation and seizures seen in acute toxicity from organochlorine pesticides. In general, aldrin, dieldrin, lindane, toxaphene, endrin, and chlordane exposures via the oral, dermal, or inhalational route can cause seizures, muscle tremors, confusion, agitation, and coma as common manifestations.

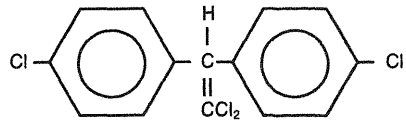
DDT, DDE, AND DDD

DDT [dichlorodiphenyl trichloroethane or 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl) ethane] was widely used for controlling insects, particularly those that carried typhus and malaria. Technical DDT is a mixture of three forms: *p,p'*-DDT, *o,p'*-DDT, and *o,o'*-DDT. These analogs of DDT are odorless, white crystalline solids. DDE [dichlorodiphenyl-dichloroethylene, 1,1-dichloro-2,3-bis(*p*-chlorophenyl) ethylene] and DDD [1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethane] are minor contaminants found in technical DDT (3). DDT is no longer used as a pesticide in the United States. However, it is still used widely in other areas of the world for the control of insect disease vectors.



Chemical formula	$C_{14}H_9Cl_5$
Chemical name	*p,p'*-DDT
Synonyms	1,1,1-trichloro-2,2-bis(*p*-chlorphenyl) ethane; dichlorodiphenyl trichloroethane,4,4' DDT
Trade names	Genitox, Anofex, Detoxen, Pentachlorin, Dicophane, Chlorophenothane

Figure 99-1. DDT. (From ref. 3, with permission.)



Chemical formula	$C_{14}H_8Cl_4$
Chemical name	*p,p'*-DDE
Synonyms	DDT dihydrochloride; dichlorodiphenyldichloroethylene; 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene

Figure 99-2. DDE. (From ref. 3, with permission.)

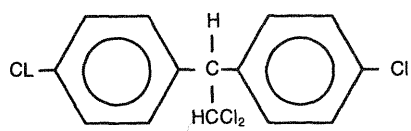
Chemical and Physical Properties

Chemical structures of DDT, DDE, and DDD are shown in Figures 99-1 through 99-3. Technical DDT is formed by condensing chloral hydrate with chlorobenzene in the presence of sulfuric acid (3). DDT was first synthesized in 1874, and its insecticide properties were discovered in 1939 (3). In 1972, the U.S. Environmental Protection Agency (EPA) banned the use of DDT except in cases of public health emergencies. Peak usage of DDT in the United States occurred in 1963, when 80 million kg of DDT was applied to agricultural areas (3).

Human Exposure to DDT, DDE, and DDD

Despite being banned in the United States in 1972, DDT still is used heavily in other areas of the world for control of disease-transmitting insects. Questions regarding DDT use remain unanswered: (i) Does DDT or its metabolites cause human cancer? (ii) Does the bioaccumulation of DDT, DDE, and DDD pose some unknown health effect to future generations? (iii) Does the persistence of DDT and its metabolites in the environment pose environmental health risks to animals and humans? DDT persists for long periods after soil application and is converted to DDE, which persists even longer. DDT, DDE, and DDD may leach into water supplies from soil and crops. DDT and DDE bioaccumulate up the food chain (3,4).

DDT and its primary metabolites, DDE and DDD, have been found at hazardous-waste sites on the National Priority List in the United States. DDT and its metabolites are ubiquitous in the environment and are constantly being transformed and redistributed. Volatilization of DDT and DDE account for losses from soil and water (3,4). DDD is less volatile than either DDT or DDE. DDT, DDE, and DDD are highly lipid soluble and thus concentrate in human and animal adipose tissue. The long envi-



Chemical formula	$C_{14}H_{10}Cl_4$
Chemical name	*p,p'*-DDD
Synonyms	1,1-bis(4-chlorophenyl)-2,2-dichloroethane; 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethane
Trade names	DDD; Rothane; Dilene

Figure 99-3. DDD. (From ref. 3, with permission.)

TABLE 99-2. Regulations applicable to DDT, DDE, or DDD

Agency	Description	Value
Federal and international agencies, regulations		
WHO	Conditional acceptable daily intake in food	0.005 mg/kg
WHO	Evidence of human carcinogenicity	ND
OSHA	TWA	1 mg/m^3
EPA	Maximum contaminant level in drinking water	NA
EPA	Reportable quantity	1 lb (proposed)
EPA	Listing as a hazardous-waste substance	ND
EPA	Listing as toxic pollutant	ND
	Listed in RCRA Appendix IX for groundwater monitoring	ND
EPA	TSCA chemical substance inventory	ND
EPA	Recommended action levels for sum of residues	
	Range	0.05 (grapes, tomatoes) to 3.0 (carrots) ppm
	Most fruits and vegetables	0.1–0.5 ppm
	Eggs	0.5 ppm
	Grains	0.5 ppm
	Milk	0.05 ppm
	Meat	5 ppm
EPA	Reference dose (oral)	5.0×10^{-4} mg/kg/day
	Potency factor (oral, inhalation)	3.4×10^{-1} mg/kg/day (DDT, DDE)
		2.4×10^{-1} mg/kg/day (DDD)
FIFRA	Most uses canceled in 1972	
Federal agencies, guidelines		
NIOSH	IDLH	ND
	TWA (air and skin)	1 mg/m^3
ACGIH	TWA	1 mg/m^3
NAS	Suggested no-adverse-response level (SNARL)	ND
	7-day	ND
	24-hour	ND
EPA	Ambient water quality criteria to protect human health	2.85 µg/L (DDT)
		ND (DDD and DDE)
EPA	Carcinogenic classification	B2[a]
	Water and fish and shellfish ingestion	0.0024 ng/L (DDT) (risk level corresponding to 10^{-7})
		2.6×10^{-6} µg/L for concentrations $<1 \times 10^3$ µg/L (DDD)
	Fish and shellfish consumption only	0.0024 ng/L (DDT) (risk level corresponding to 10^{-7})
State environmental agencies, regulations and guidelines		
	Drinking water quality standards for DDT in several states	
Alabama		No special or state rule
Alaska		No special or state rule
Arizona		No special or state rule
California		No special or state rule
Colorado		No special or state rule
Delaware		No special or state rule
Connecticut		No special or state rule
Florida		No special or state rule
Georgia		No special or state rule
Hawaii		No special or state rule
Idaho		No special or state rule
Illinois		50 µg/L
Indiana		No special or state rule
Iowa		No special or state rule
Kansas		0.42 µg/L (DDT)
		2.4×10^{-5} µg/L (DDE)
		2.4×10^{-5} µg/L (DDD)
Kentucky		No special or state rule
Maine		0.83 µg/L
Maryland		No special or state rule
Massachusetts		No special or state rule
Minnesota		1.0 µg/L
Mississippi		No special or state rule
Missouri		No special or state rule
Montana		No special or state rule
Nebraska		No special or state rule
Nevada		No special or state rule
New Hampshire		No special or state rule

(continued)

TABLE 99-2. *(continued)*

Agency	Description	Value
New Mexico		No special or state rule
New York		No special or state rule
North Carolina		No special or state rule
Ohio		No special or state rule
Oklahoma		No special or state rule
Oregon		No special or state rule
Rhode Island		No special or state rule
South Carolina		No special or state rule
South Dakota		No special or state rule
Tennessee		No special or state rule
Texas		No special or state rule
Utah		No special or state rule
Vermont		No special or state rule
Virginia		No special or state rule
West Virginia		No special or state rule
Wisconsin		No special or state rule
	Acceptable ambient air concentrations of DDT in several states	
Connecticut		5 $\mu g/m^3$ (8 h)
Kansas		2.381 $\mu g/m^3$ (DDT) (annual) 2.4×10^{-5} µg/kg (DDE) (guideline) 2.4×10^{-5} µg/L (DDD) (guideline)
Nevada		0.04 $\mu g/m^3$ (8 h)
Pennsylvania (Philadelphia)		1.8 $\mu g/m^3$ (DDT) (1 yr) 1.8 $\mu g/m^3$ (DDE)
Virginia		16 $\mu g/m^3$ (24 h)

ACGIH, American Conference of Governmental Industrial Hygienists; EPA, U.S. Environmental Protection Agency; FIFRA, Federal Insecticide, Fungicide, and Rodenticide Act; IDLH, immediately dangerous to life and health; NAS, National Academy of Sciences; NA, not applicable; ND, no data; NIOSH, National Institute for Occupational Safety and Health; OSHA, U.S. Occupational Safety and Health Administration; TSCA, U. S. Toxic Substances Control Act; TWA, time-weighted average; WHO, World Health Organization.
[a]EPA weight-of-evidence classification scheme for carcinogens: A, human carcinogen—sufficient evidence from human epidemiologic studies; B1, probable human carcinogen—limited evidence from epidemiological studies and adequate evidence from animal studies; B2, probable human carcinogen—inadequate evidence from epidemiologic studies and adequate evidence from animal studies; C, possible human carcinogen—limited evidence in animals in the absence of human data; D, not classified as to human carcinogenicity; and E, evidence of noncarcinogenicity.
Adapted from ref. 3, with permission.

ronmental half-life of these compounds, coupled with their lipophilic properties, results in bioaccumulation.

Photooxidation and biodegradation of DDT can occur in air, soil, and water. DDT and DDE are slowly degraded to CO_2 and hydrochloric acid by solar radiation (3,4). Environmental concentrations of DDT, DDE, and DDD worldwide have tended to remain relatively constant despite continued widespread application, owing to their continuous biological oxidation by ultraviolet light (4).

The loss of DDT from soils is primarily through volatilization, water runoff, and chemical transformation. Some biodegradation occurs by aerobic and anaerobic microorganisms. Aerobic metabolism results in a conversion of DDT to DDE. Anaerobic conditions result in conversion of DDT to DDD. DDT conversion to DDE is slower than its conversion to DDD. The DDE and DDD metabolites of DDT are resistant to further transformation, and the half-life estimates for biodegradation of DDT in soil range from 2 to 15 years (3,4). Human exposures occur mainly through diet via bioaccumulation up the food chain and from breastfeeding.

Low levels of DDT and its metabolites will continue to be present in the environment because other countries are still applying it. Because of the partitioning of DDT and DDE into human breast milk, breast-fed infants will receive DDT and DDE from the mother. Exposure to DDT and its metabolites by inhalation is negligible.

Distribution of DDT in the Environment

DDT and its analogs are detected by gas chromatography–mass spectrometry in both environmental samples and human tissues. DDE, the primary metabolite of DDT, commonly is found in samples of human adipose tissue.

Regulations relating to DDT and its analogs are presented in Table 99-2. DDT, DDE, and DDD are also listed in the Toxic Chemicals Substance Section 313 of the Emergency Planning and Community Right to Know Act of 1986 Superfund Amendment Reauthorization Act (SARA Title III).

Airborne concentrations of DDT have been found to range from 1.4 to 1,560 ng per cubic meter and DDE from 1.9 to 131 ng per cubic meter (3). Since the ban on DDT use was enacted, air concentrations have been declining. Over the period 1974 to 1975, the arithmetic mean DDT air concentration decreased from 11.9 to 7.5 ng per cubic meter (3). Air samples collected in the Gulf of Mexico in 1977 showed a DDT range of 0.010 to 0.078 ng per cubic meter (3).

The U.S. National Soils Monitoring Program has followed the soil pattern concentration of DDT since its banning. DDT and DDE residues in soils have been steadily declining since 1972. In 1970, soil DDT concentrations averaged 0.18 parts per million (ppm), decreasing to 0.02 ppm by 1972 (3).

The concentrations of DDT and DDE also declined in foods between 1965 to 1975.

The median concentration of DDT and DDE in water samples in the United States is approximately 1 part per trillion (ppt) (3). Industrial effluents have shown concentrations of 10 ppt of DDT, DDE, and DDD. Overall, the concentrations of DDT and its residues appear to be decreasing in the environment since 1972.

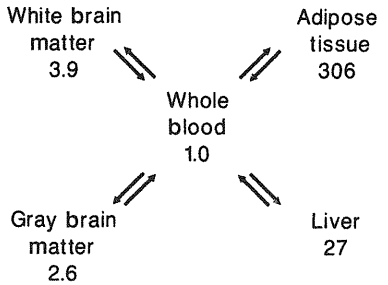


Figure 99-4. Relationship of the distribution of DDT and related chemicals among blood and certain tissues in humans. (From ref. 21, with permission.)

Absorption, Metabolism, and Excretion

DDT and its metabolites, DDE and DDD, are found in samples of human blood, adipose tissue, human breast milk, umbilical cord blood, and placental tissue (5–13). However, there is no correlation between the concentrations in human tissues and environmental concentrations. Higher ratios of DDD or DDT to DDE may indicate recent exposure, as DDT and DDD have shorter half-lives (3). Concentrations of DDT in fatty tissue are 300 times higher than those in blood (3). The partitioning of DDT among tissues as compared to blood demonstrates the high lipid solubility of the compound (Fig. 99-4). Due to the fact that DDT and DDE are stored in fatty tissues and are released slowly from these sites, making a correlation between concentrations in tissues and the time of exposure is difficult.

Environmental exposure concentrations are lower than any dose that will have identifiable health effects. A decline in human tissue concentrations of DDT has occurred since 1972 (4). The estimated daily dietary intake of DDT declined from 0.24 mg per person per day in 1970 to 0.008 mg per person per day in 1973 (4). The World Health Organization (WHO) established an acceptable dietary intake of DDT as 0.005 mg per kg per day and, from 1965 to 1970, the dietary intake of DDT declined to 0.0007 mg per kg per day (4).

The metabolism of DDT, DDE, and DDD has been studied in humans and other animal species (Fig. 99-5). Chronic oral ingestion of DDT induces the hepatic microsomal mixed-function oxidase system (3,4). Humans excrete DDT more slowly than do animals. Also, it is estimated that if all human DDT exposure were terminated, 10 to 20 years would pass before all DDT was removed from human tissue (4). However, DDE, with its longer half-life, will persist for many years beyond this (4).

Clinical Toxicology of DDT

Volunteers given DDT orally have developed symptoms of gait disturbance, malaise, fatigue, headache, nausea, tremors, and vomiting, depending on the dose. Test doses were 750 mg, 1,000 mg, or 1,500 mg of DDT (3). All subjects recovered from their symptoms within 24 hours. Ingestion of DDT, either accidentally or intentionally, can result in similar symptoms. Exposure to large oral doses of DDT can result in excitability, tremors, and convulsions. This neurologic effect probably is a result of interference with sodium and potassium conductance across cell membranes. Other health effects at high exposure concentrations of DDT are irritation of the mucous membranes, nose, throat, and mouth, nausea, and headache.

Carcinogenesis and Immunotoxicity

No information exists on the immunotoxic effects of DDT or its metabolites in humans. Although immunologic effects in animals have been documented, extrapolating these findings to the human condition has been difficult. Even though DDT has produced liver nodules in mice, several other studies in animals have not demonstrated carcinogenesis. No evidence reveals that DDT or its metabolites are human carcinogens. Further, no information establishes a causal relationship between DDT, DDE, and DDD concentrations in blood and fat or other tissues in relation to specific health effects.

The International Agency for Research on Cancer has reviewed the literature on the carcinogenicity of these compounds and has found no convincing evidence of the carcinogenic risk of DDT and DDE in humans, although evidence of DDT carcinogenicity in the mouse model was found. In a large, multicenter prospective study, plasma levels of DDE and poly-

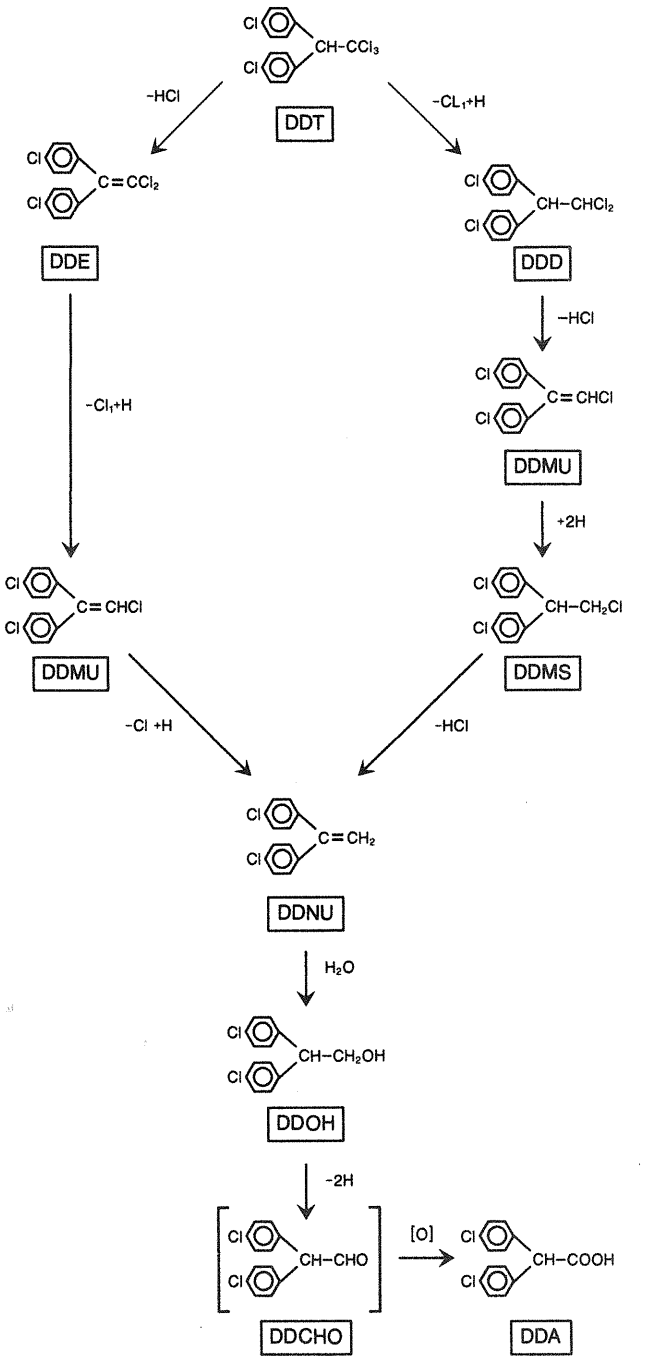


Figure 99-5. Metabolism of DDT. (From ref. 3, with permission.)

chlorinated biphenyls were measured in 240 women who subsequently were given a diagnosis of breast cancer (14). This study was triggered by the observation that breast cancer rates vary by up to fivefold across the globe. In addition, it has been observed that the daughters of women who migrate from a country with a low incidence of breast cancer to a country with a high incidence acquire the breast cancer rate of their new country. Many researchers have interpreted these epidemiologic data as being supportive of the hypothesis that breast cancer rates are strongly linked to environmental and lifestyle factors.

Because hormonal activity is associated with the organochlorine chemicals, a working hypothesis was proposed that linked these "environmental estrogens" with breast cancer rates. Hunter et al. (14) did not demonstrate a link between the median level of DDE and breast cancer risk. The median level of DDE was lower in case subjects than among control subjects. Similar data were found with polychlorinated biphenyl levels. These results were consistent with the data published by Krieger et al. in 1994 (15). An editorial in the *New England Journal of Medicine* stated, "The results of Hunter et al., along with those of other studies, should reassure the public that the weakly estrogenic organochlorine compounds such as [polychlorinated biphenyls], DDT, and DDE are not a cause of breast cancer" (16).

HEXACHLOROCYCLOHEXANE AND LINDANE

HCH, sometimes misnamed *benzene hexachloride*, was applied widely through the 1960s and 1970s. Discovered in 1825, HCH was used as a smoke munition in World War I. The insecticide properties of HCH were discovered in 1942. Owing to its chemical structure, various isomeric forms of HCH exist (Fig. 99-6), the best known of these being γ-HCH or lindane. Technical-grade lindane consists of several isomers: α, β, γ, and δ. The toxicity of these isomers, in terms of their effectiveness in controlling insects, is inequitable, γ-HCH being more potent than α-HCH, and α-HCH being more effective than β-HCH (17).

Chemical and Physical Properties

Eight isomers of HCH are known, and all have the empirical formula of $C_6H_6Cl_6$ and a molecular weight of 290.8. The isomeric mixture of HCH is a brown–off-white powder with a musty odor and is soluble in acetone, benzene, and chlorinated hydrocarbon solvents. HCH is almost insoluble in water (18). The γ isomer or lindane is heat-stable and can vaporize without decomposition.

HCH is manufactured by ultraviolet photochlorination of benzene (17). Technical-grade HCH consists of an isomeric mixture of α (70%), β (7%), γ (5%), δ (5%), and others (5%). Fractional crystallization of the γ-HCH isomer yields a 99.8% product of γ-HCH called *lindane* (17). Production of lindane was terminated in 1976 in the United States. Lindane has been available as an emulsifiable concentrate, liquids, powders, gas, pressurized liquids, aerosol sprays, and granules. Besides its past use as an insecticide, lindane still is used as a scabicide for humans and animals. It has also been used on fruit and vegetable crops, for seed treatment, and for animal treatment.

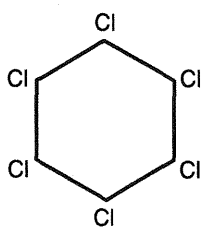


Figure 99-6. Hexachlorocyclohexane (α, β, γ, δ isomers).

Environmental Regulations

Lindane is on the list of chemicals that appears in the Toxic Chemicals Substances Section 313 of the Emergency Planning and Community Right to Know Act of 1986 (SARA Title III). The environmental regulations pertaining to lindane are summarized in Table 99-3.

Human Exposure

Exposure to lindane and other HCH isomers occurs from occupational and environmental sources via dermal contact, inhalation, or ingestion. Lindane and the other HCH isomers can reach the environment through their use as pesticides and during production of the product. HCH can be detected in air, soil, aquatic organisms, and water. Most human exposures occur through the ingestion of plants, animals, and dairy products. α-, β-, γ-, and δ-HCH isomers have been detected at a number of hazardous-waste sites. Lindane has been detected at waste sites in surface water at a mean concentration of 0.5 parts per billion (ppb) and in the soil around these sites at a concentration of 11 ppb (2). The β isomer of HCH has been found in surface water around hazardous-waste sites at a mean concentration of 2.89 ppb and in soil at these sites at a mean concentration of 150 ppb. The δ isomer has been detected at hazardous-waste sites at a mean concentration of 31 ppb and in the soil around these sites at a concentration of 6.6 ppb (18).

Release of lindane into the air has occurred through its application as a pesticide. Release of lindane into surface water occurs from surface runoff or from deposition of the chemical through rain and other forms of precipitation. Low concentrations of lindane have been detected in samples of water runoff in a variety of cities around the United States. Lindane movement in the environment occurs via leaching from soil into groundwater, adsorption to particles in the soil, and volatilization into the atmosphere. An important consideration pertaining to the release of lindane from soil into surface water is the relative content of the organic matter versus clay in the soil. Soil with a higher organic content will adsorb lindane and reduce leaching. Lindane in the soil is degraded primarily by microorganisms. Depending on the isomer, either anaerobic or aerobic conditions will be most conducive to biodegradation (18).

Lindane released into surface water can bioconcentrate in aquatic organisms. The other isomers of HCH, as well as lindane, bioconcentrate up through the food chain. Owing to its lipophilic nature, lindane concentrates in adipose tissue. Very little biodegradation of the HCH isomers occurs.

Monitoring of lindane and other HCH isomers in ambient air in the United States during the period 1970 to 1972 has shown a mean concentration of 0.9 ng per cubic meter in a ten-state area (18). A maximum lindane concentration of 11.7 ng per cubic meter was reported in the same study. Other monitoring that has been performed at a variety of locations in the United States has shown γ-HCH to be present at concentrations of 0.1 to 7.0 ng per cubic meter (18). However, there were no detectable concentrations in rural areas. During a heavy period of pesticide usage in 1972 to 1974, atmospheric concentrations of lindane were as high as 9.3 ng per cubic meter (18).

In global monitoring of HCH isomers, air samples in the world's remote areas range from 1.1 to 2.0 ng per cubic meter in air and 3.1 to 7.3 ng per L in water (18). Water concentrations of lindane evaluated at numerous areas across the United States have mea-

TABLE 99-3. Regulations and guidelines applicable to hexachlorocyclohexane

Agency	Description	Value
International agencies		
Oral		
WHO	Acceptable daily intake	0.0–0.01 mg/kg
	Allowable tolerances (γ-HCH) range	0.05 mg/kg (potatoes) to 2 mg/kg (lettuce)
	Most fruits and vegetables	0.5 mg/kg
WHO	Guideline for drinking water	0.003 mg/L
Other		
IARC	Carcinogenic classification	Group 3[a]
	α-HCH	
	β-HCH	
	γ-HCH	
National agencies		
Regulations		
Oral		
EPA	Tolerances (γ-HCH) range	0.01 ppm (pecans) to 7 ppm (meat fat)
	Most fruits and vegetables	1 or 3 ppm
EPA	Maximum contaminant level in drinking water (lindane)	0.004 mg/L
FDA	Permissible level in bottled water (lindane)	0.004 mg/L
	Action levels (lindane)	
	Most fruit and vegetables	0.5 ppm
	Cereals	0.1 ppm
	Milk	0.3 ppm
Inhalation		
OSHA	Permissible exposure limit, TWA for lindane (skin)	0.5 mg/m^3
Other		
EPA	Reportable quantity lindane	1 lb
	Extremely hazardous substance	
	Threshold planning quantity for lindane	1,000/10,000 lb
	Listing as toxic waste: discarded commercial products, off-specification species, container residues, and spill residues of lindane. Listing as a hazardous waste constituent. General pretreatment regulations for existing and new sources of pollution.	
	Maximum concentration of contaminants; toxicity (lindane)	0.4 mg/L
	TSCA chemical substance inventory (all isomers)	
	General permits under the National Pollutant Discharge Elimination System	
Guidelines		
Oral		
EPA	Maximum contaminant level goal, proposed, for lindane	0.0002 mg/L
	Health advisories for lindane	
	1-day	1.2 mg/L
	10-day	1.2 mg/L
	Longer-term	
	Adult	0.12 mg/L
	Child	0.033 mg/L
	Lifetime	0.2 μg/L
EPA	Ingestion of water and aquatic organisms	
	α-HCH	0.92–92.0 ng/L
	β-HCH	1.63–163.0 ng/L (risk, 10^{-7}–10^{-5})
	γ-HCH	1.86–186.0 ng/L (risk, 10^{-7}–10^{-5})
	Technical-grade HCH	1.23–23.0 ng/L (risk, 10^{-7}–10^{-5})
	Ingestion of aquatic organisms only	
	α-HCH	1–310.0 ng/L (risk, 10^{-7}–10^{-5})
	β-HCH	5.47–547.0 ng/L (risk, 10^{-7}–10^{-5})
	γ-HCH	6.25–625.0 ng/L (risk, 10^{-7}–10^{-5})
	Technical-grade HCH	4.14–414.0 ng/L (risk, 10^{-7}–10^{-5})
NAS	Suggested no-adverse-effect level for lindane	
	7-day	0.5 mg/L
	24-hour	3.5 mg/L
Inhalation		
ACGIH	Threshold limit value	
	TWA for lindane (skin)	0.5 mg/m^3
NIOSH	IDLH level (all isomers)	1,000 mg/m^3
Other		
EPA	Carcinogenic classification	
	α-HCH	Group B2[b]
	β-HCH	Group C[b]
	γ-HCH	Group B2/C[b,c]
	δ-HCH	Group D[b]

(continued)

TABLE 99-3. Regulations and guidelines applicable to hexachlorocyclohexane

Agency	Description	Value
	Technical-grade HCH	Group B2[b]
	Reference dose, oral (γ-HCH)	3×10^{-4} mg/kg/day
	q_1^*[d] (oral)	
	α-HCH	6.3 $(mg/kg/day)^{-1}$
	β-HCH	1.8 $(mg/kg/day)^{-1}$
	γ-HCH	1.3 $(mg/kg/day)^{-1}$
	Technical-grade HCH	1.8 $(mg/kg/day)^{-1}$
	q_1^*[d] (inhalation)	
	α-HCH	6.3 $(mg/kg/day)^{-1}$
	β-HCH	1.8 $(mg/kg/day)^{-1}$
	Technical-grade HCH	1.8 $(mg/kg/day)^{-1}$

ACGIH, American Conference of Governmental Industrial Hygienists; EPA, U.S. Environmental Protection Agency; FDA, U.S. Food and Drug Administration; HCH, hexachlorocyclohexane; IARC, International Agency for Research on Cancer; IDLH, immediately dangerous to life and health; NAS, National Academy of Sciences; NIOSH, National Institute for Occupational Safety and Health; OSHA, U.S. Occupational Safety and Health Administration; TSCA, U.S. Toxic Substances Control Act; TWA, time-weighted average; WHO, World Health Organization.

[a]IARC weight-of-evidence classification scheme for carcinogens: Group 1, carcinogenic to humans—sufficient evidence from human epidemiologic studies; Group 2A, probably carcinogenic to humans—limited evidence from human epidemiologic studies; Group 2B, probably carcinogenic to humans, inadequate data from human epidemiologic studies and sufficient evidence from animal studies; Group 3, cannot be classified as to its carcinogenicity in humans.

[b]EPA weight-of-evidence classification scheme for carcinogens: A, human carcinogen—sufficient evidence from human epidemiologic studies; B1, probable human carcinogen—limited evidence from epidemiological studies and adequate evidence from animal studies; B2, probable human carcinogen—inadequate evidence from epidemiologic studies and adequate evidence from animal studies; C, possible human carcinogen—limited evidence in animals in the absence of human data; D, not classified as to human carcinogenicity; and E, evidence of noncarcinogenicity.

[c]The EPA Office of Drinking Water and the Office of Pesticide Programs are considering γ-HCH (lindane) as Group C for regulatory purposes pending review.

[d]q_1^* represents the upper-bound estimate of the low dose of the dose-response curve, as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually milligrams per liter of water, milligrams per kilogram of food per day, and grams per cubic meter of air).

Adapted from ref. 3, with permission.

sured between 10 and 319 ppt (18). Lindane is detected in approximately 10% of urban water runoff samples in cities across the United States in concentrations ranging from 0.052 to 0.1 ppt (18).

Given the widespread, but low, environmental concentrations of HCH isomers and their bioconcentration up the food chain, the most important human exposure at the present time is through ingestion of food products, mainly meats and dairy products. HCH isomers have been detected in dairy products, meats, fish, poultry, fruits, oils, fats, leafy vegetables, sugar, and other foods. To a lesser degree, other human exposures occur from the ingestion of drinking water that contains small concentrations of lindane. Previous estimates by the U.S. Department of Health, Education, and Welfare on the average daily intake of lindane have varied from 3 μg per day to a low of 0.22 μg per day (18).

In workers involved in the production of technical HCH and lindane, serum and adipose tissue concentrations of HCH isomers during production increase with exposure time (14,16–18). Human serum concentrations of HCH have been reported in the following ranges: α-HCH, 10 to 273 μg per L; β-HCH, 17 to 760 μg per L; and γ-HCH, 5 to 188 μg per L (17). A significant increase in β-HCH concentrations in the serum of chronically exposed workers was apparent (17). β-HCH adipose concentrations were 300 times greater than serum concentrations (17).

No documented adverse health effects among employees involved in lindane production have been noted as compared to control populations (18,19). Nonetheless, workers who directly handled HCH, as well as exposed nonhandlers, complained of headache, paresthesias, giddiness, malaise, tremors, apprehension, loss of sleep, confusion, vomiting, decreased libido, and impaired memory (20). The total HCH in the serum of those workers ranged from 0.143 to 1.152 μg per L (20). Serum concentrations of HCH are related to the degree and duration of exposure, with β-HCH accumulating more than the other isomers and accounting for nearly 30% of the total HCH serum concentrations (20).

Lindane and other HCH isomers have been detected in the blood and adipose tissue of the general public in a variety of countries (5–13,21–27). Lindane blood concentrations were found to be highest in people in the age group 41 to 60 years (18). The National Human Adipose Tissue Survey conducted in 1982 demonstrated that β-HCH was detected in 87% of samples collected, ranging in concentrations from 19 to 570 ng per gram of tissue (18). In autopsy surveys conducted between 1970 and 1975, β-HCH was present in more than 90% of human adipose tissue samples at a level of 300 ppb (18,21). Reports indicate that the median level of β-HCH in the United States has fallen from a level of 140 ppb to 80 ppb (18). Although the median concentration in human adipose tissue has diminished, the chemical still is detected in virtually 100% of the general population (5–13,21–27).

Factors influencing the body concentration of lindane include age, dietary habits, and location of the country in which the person lives. Higher levels of lindane and other HCH isomers are found in nonvegetarians. Studies of human breast milk have demonstrated HCH isomers in 82% of samples at a mean concentration of 81 ppb and a range of 0 to 480 ppb (18,23,28,29).

Gas chromatography–mass spectrometry methods can detect lindane and HCH isomers at the parts-per-billion level. Although methods are available that can detect and quantify concentrations of HCH isomers, correlating these concentrations with environmental concentrations or toxic effects remains impossible.

Despite the fact that HCH isomers can be detected in blood, serum, urine, and adipose tissue in the general population, the concentration in these tissues does not correlate with adverse health effects. Mean serum concentrations of total HCH in subjects have been reported to be 0.27 ppm for those who did not handle the product and 0.6 ppm for those who directly handled the product (20). Of the total HCH evaluated by assay in the serum of these individuals, 60% to 100% was in the form of the β-HCH isomer. The serum concentrations were reported as follows: 0.07 to 0.72 ppm of β-HCH, 0.004 to 0.18 ppm α-HCH, 0.0 to 0.17 ppm for lindane, and 0.0 to 0.16 ppm for δ-HCH (20). The investigators reported that handlers of HCH, as well as those

TABLE 99-4. Summary of hexachlorocyclohexane (HCH) occupational exposure

Study group	Occupational exposure, serum concentrations (ppm)				
	Total HCH	β-HCH	α-HCH	γ-HCH	δ-HCH
Controls (mean)	0.05 (0–0.37)	0.029 (0–0.1)	0.022 (0–0.26)	0.007 (0–0.01)	0
Handlers (mean)	0.60 (0.20–1.15)	0.41 (0.16–0.72)	0.10 (0.024–0.18)	0.06 (0.01–0.17)	0.04 (0–0.16)
Nonhandlers (mean)	0.266 (0.08–0.66)	0.207 (0.065–0.5)	0.0412 (0.004–0.16)	0.016 (0–0.04)	0.0017 (0–0.022)

	Occupational exposure, adipose tissue concentrations (mg/kg)		
Controls	0.3–2.4	0.01–0.2	0–0.1
Workers	18–103 (45.6 ± 24.4)	1–15 (5.8 ± 5)	0–11 (3.2 ± 3.1)

	Occupational exposure to lindane (γ-HCH)	
	Blood conc. (ppb)	Air conc. (mg/m³)
Nonproduction workers	0.93 (0.3–2.5)	9–49
Production workers with no skin contact, Group I	4.6 (1.9–8.3)	31–1,800
Production workers with no skin contact, Group II	4.1 (1.0–8.9)	11–1,170
Production workers with no skin contact, Group III	30.6 (6.0–93)	11–1,170

Adapted from refs. 17, 20, and 31.

who were not directly exposed, had complained of facial paresthesias, headaches, dizziness, malaise, vomiting, tremors, confusion, and impaired memory (20). Serum levels were measured also in maintenance workers who periodically visited the worksite. Serum concentrations in these workers were much lower than in those workers who were occupationally exposed. Liver functions among the exposed workers were not statistically significantly different from those in controls (30). Table 99-4 summarizes HCH serum and adipose tissue concentrations in various occupational situations (17,23,31).

In one study, exposure levels of α-HCH were 0.002 to 1.99 mg per cubic meter, of β-HCH were 0.001 to 0.38 mg per cubic meter, and of lindane or γ-HCH were 0.004 to 0.15 mg per cubic meter. The mean blood levels of 57 workers measured 0.5 μg of α-HCH, 0.9 μg of β-HCH, and 0.7 μg of γ-HCH per L (17). The accumulation of β-HCH isomer has been demonstrated to increase in a linear fashion with the duration of exposure. Adipose concentrations in samples from autopsies have ranged from 0.03 to 0.47 ppm for total HCH and 0.04 to 0.57 ppm for β-HCH (24).

Animal studies have shown various distribution patterns of HCH isomers, the γ- and β-HCH isomers being stored primarily in the fatty tissues (32). The distribution of lindane also was highest in the fatty tissue, followed by brain, kidney, muscle, lungs, heart, spleen, liver, and blood. Lindane has a propensity to accumulate in the brain more than does β-HCH (18). Lindane also induces hepatic mixed-function oxidase systems, increasing its own metabolism. This process may minimize or reduce the accumulation of lindane in tissues (18).

Lindane has been detected in blood and CNS tissue of autopsied infants who have died after total body application of a 1% lotion (33). Initial blood concentrations of lindane were 206 ppb and declined to 1.0 ppb in 25 days. Brain concentrations were threefold that of blood in this report (33).

The accumulations of lindane in adipose tissue occur across the placenta and to newborns through breast milk (34–37). Concentrations of lindane in human breast milk were found to be five to seven times higher than concentrations in the maternal blood or in umbilical cord blood. Older women tend to harbor higher lindane concentrations of HCH and lindane in placental and umbilical cord blood than do younger women (34–36). Also noteworthy is that lindane concentrations increased in maternal blood during delivery and that, during pregnancy, higher concentrations were found in fetal blood and fetal tissue as well as placenta and amniotic fluid as compared to maternal fat tissue (34–36).

Metabolism of Lindane

The primary metabolites of lindane are chlorophenols and chlorobenzenes (Fig. 99-7) (30). Chlorinated metabolites in the urine have been found in lindane production workers. The major metabolite is trichlorophenol, which accounted for approximately 58% of lindane metabolites identified in the urine (18). Other metabolites are dichlorophenols, tetrachlorophenols, hexachlorobenzene, tetrachlorocyclohexanol, and pentachlorocyclohexene. Pentachlorophenol has also been identified as a urinary metabolite in humans after occupational exposure (18).

Clinical Toxicology of Lindane and Isomers

Human exposure that results in toxic health effects can occur by inhalation, dermal absorption, and via the gastrointestinal tract. Most studies of acute lindane inhalational poisoning have focused on anecdotal cases of home exposure from the use of vaporized lindane (37). Irritation of the eyes, throat, and upper airway may occur after short-term exposure to lindane vapors. Further reports of effects secondary to inhalation of lindane have included various blood dyscrasias: anemia, leukopenia, leukocytosis, granulocytopenia, granulocytosis, eosinophilia, thrombocytopenia, increased bone marrow megakaryocytes, and decreased bone marrow megaloblastoid erythroid series (37,38). Aplastic anemia and pancytopenia have also been reported to occur after lindane exposure (18,37,38).

Kashyap (27) reported statistically significant elevations in hepatic enzymes in 19 occupationally lindane-exposed individ-

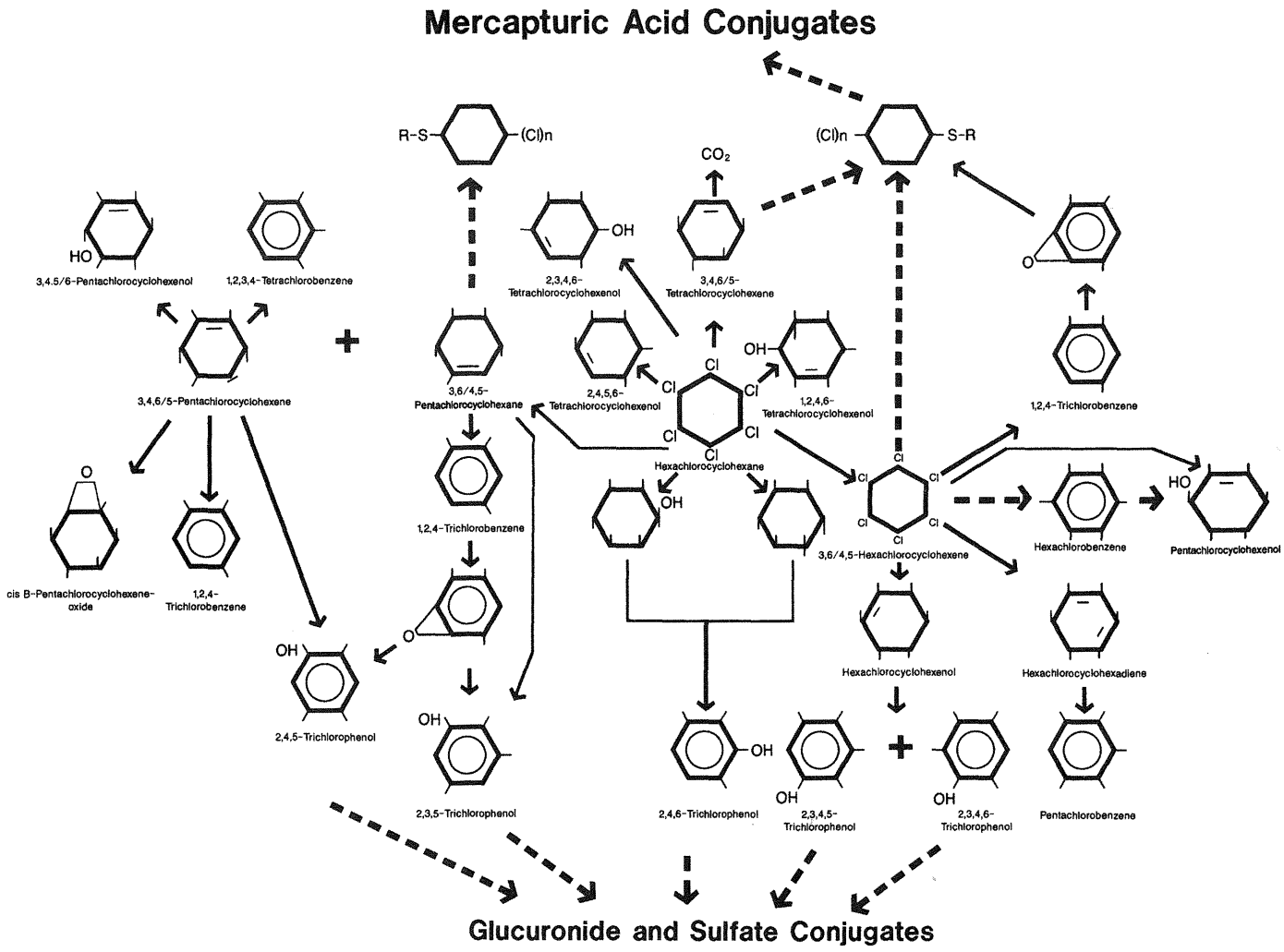


Figure 99-7. Proposed metabolism of γ-hexachlorocyclohexane. (From ref. 18, with permission.)

uals. These individuals were exposed to technical-grade HCH for 10 years in a production plant (27). The same study also reported a significant increase in the concentrations of serum immunoglobulin M. Other symptoms of exposed workers included facial paresthesias, headaches, and dizziness.

INGESTION OF LINDANE

From the 1950s through 1960s, some children experienced acute toxic effects from oral ingestion of lindane tablets used in vaporizers. Acute oral toxicity in animals manifests as ataxia, coma, and death. Acute ingestion in humans consists of abdominal pain, nausea, vomiting, excitability, seizures, muscle tremors, hyperreflexia, and coma. Rhabdomyolysis, myoglobinuria, and leukocytosis have been observed (39). Animal studies of oral dosing of lindane and technical-grade HCH have been reported to cause fatty degeneration and necrosis of the liver (18). No immunotoxic effects of HCH isomers have been detected in humans. Likewise, no studies have proved reproductive effects or carcinogenicity of the isomers of HCH in humans. In animal studies, the isomers of HCH as well as technical-grade HCH have been shown to produce liver cancer in rats and mice (18).

DERMAL ABSORPTION OF LINDANE

Most cases of lindane toxicity via dermal absorption have resulted from its use as a topical scabicide. Seizures and deaths in infants have been reported after topical application of 1% lindane lotion in large amounts (33,38). Lindane blood concentrations 46 hours after application of a 1% topical lotion to treat scabies in an infant who developed postapplication seizures were 0.10 μg per L (40). This high concentration compares to a mean blood concentration of 0.005 μg per L in most children treated with the 1% lotion. In this case, peak concentrations of lindane occur 6 hours after dermal application. Inappropriate application of excessive amounts of lindane ointment (1% scabicide) to the skin can result in clinical symptoms, including seizures (40).

Dermal absorption of organochlorine pesticide depends on the amount applied, surface area of application, breaks in the normal dermal barrier, and conditions that cause the compound to be removed from the skin, such as volatilization and dilution (41). Delayed absorption of such organochlorine pesticides as lindane, dieldrin, and aldrin has been demonstrated by the prolonged urinary excretion of these compounds up to 120 hours after dermal application (41).

NEUROTOXIC EFFECTS OF LINDANE

The neurotoxic effects of lindane exposure include seizures, headaches, dizziness, tremors, ataxia, facial paresthesias, giddiness, and coma. The mechanism of lindane neurotoxicity is believed to be inhibition of GABA-mediated neurotransmission (1,2). In the limbic system, lindane acts directly to increase excitability of neurons (42). Lindane accelerates kindling seizures, which is the sequence of changes that results from repetitive stimulation (42).

CHLORDANE AND HEPTACHLOR

Chlordane and heptachlor have been extensively used in the United States as termiticides and have been heavily applied to soils in both urban and rural settings. Its persistence in the environment is one reason that chlordane is so effective. Owing to its extensive application, chlordane can be detected in the indoor air of homes 10 to 15 years after termite treatment. It is estimated that approximately 50 million people have been exposed to chlordane in the United States, principally in the home environment (43).

Many foods contain chlordane, because it bioaccumulates up the food chain. Chlordane's persistence in soil can lead to oral and dermal exposure from ingestion of crops or from ingestion of treated soil.

In the United States, chlordane has been used almost exclusively as a termiticide by foundation injection or liquid application techniques in home environments (43). More than 200 million pounds of chlordane have been applied to the soil in the United States (43).

Chlordane is commonly detected in the groundwater runoff of hazardous-waste sites. As a component of indoor air in home environments, the chemical usually is present on dust particles and in a vapor phase. After application to the soil, chlordane can continue to be released into the indoor air of a home for years. Generally, if this is occurring, air concentrations of chlordane may exceed the National Academy of Sciences' (NAS) standard of 5 μg per cubic meter (44,45).

Production and Use of Chlordane

Chlordane, heptachlor, endrin, aldrin, dieldrin, endosulfan, and isobenzan are members of the cyclodiene class of organochlorine compounds (Fig. 99-8). Chlordane is produced by the chlorination of chlordene, which in turn is the product of the Diels-Alder reaction of hexochlorocyclopentadiene with cyclopentadiene (43). On April 14, 1988, the EPA canceled the registration and use of chlordane for commercial production, delivery, and sale in the United States.

Chemical Structure and Physical Properties

Technical-grade chlordane is a mixture of at least 50 different compounds, the major constituents being *cis*- and *trans*-chlordane, heptachlor, *cis*- and *trans*-nonachlor, and α-, β-, and γ-chlordane. Hexachlorocyclopentadiene is also a constituent (46). Seventy percent of commercial preparations comprise α- and β-chlordane (43). Of chlordane's two main isomers, *trans*- and *cis*-chlordane, the latter is more abundant (Fig. 99-9).

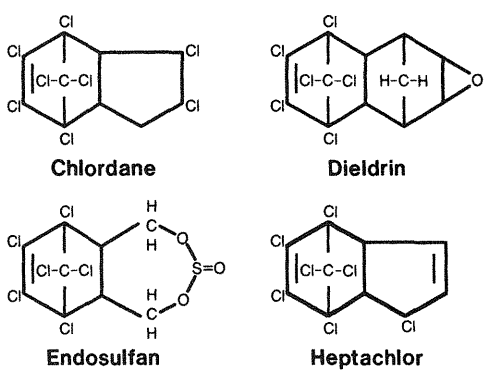
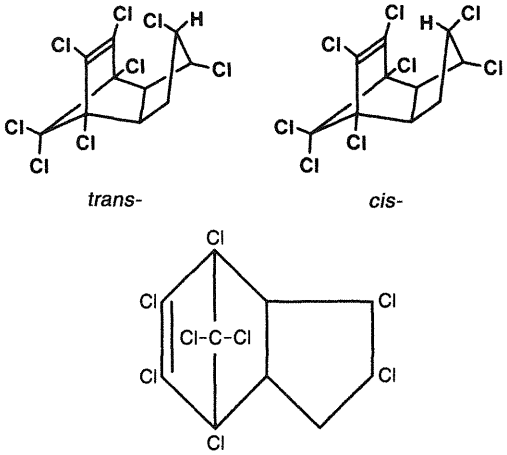


Figure 99-8. Cyclodienes.



Chemical formula	$C_{10}H_6Cl_8$
Chemical name	1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene
Synonym	1,2,4,5,6,7,8,8-Octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindan
Trade names	Chlordan; Velsicol 1068; Octachlor; Termicide C-100

Figure 99-9. Chlordane. (From ref. 43, with permission.)

The individual components of the chlordane solution usually are solids. Pure chlordane, a viscous brown liquid (as a technical product), has a molecular weight of 409.76 (43). The individual isomers have different melting points and boiling points. Chlordane is miscible with hydrocarbon solvents.

Exposure Sources

Chlordane was used previously to treat crops and to control termites. It is identified at 46 of 1,117 hazardous-waste sites on the National Priority List in the United States (43).

The majority of exposures to chlordane occur in the home environment owing to prior application of chlordane as a termiticide. Chlordane has been detected in the indoor air of a home up to 15 years after treatment of the home for termites (44,45). It is estimated by the EPA that more than 80 million people in the United States live in homes that have been treated with cyclodiene termiticide agents such as chlordane (43). This probably is an underestimation, because foods and food sources also contain chlordane, which bioaccumulates and produces further exposure in humans as they consume the affected food.

Chlordane and other organochlorines have been detected in surface groundwater, in drinking water, and in urban runoff water (Tables 99-5, 99-6) (43). Chlordane concentrations in surface water generally are in the low nanogram-per-liter range (ppb).

Chlordane also is detected in soil, particularly around the outside walls of treated homes in concentrations ranging from less than 1 ppb to approximately 141 ppm (45–47). Persons involved in the manufacturing of chlordane also are likely to experience high-exposure incidents.

Chlordane bioconcentrates in marine animals via contamination of water. In soil, chlordane adsorbs to organic materials (43). Owing to the fact that it does adsorb to organic materials and volatilizes slowly, chlordane does not appreciably leach from soil. Depending on the type of soil, chlordane will be present to a lesser or greater extent. Sandy soils and soils that contain a

TABLE 99-5. Drinking water and serum concentrations of organochlorine pesticides and metabolites in samples from individuals who use well water

Water (ppt)				Serum (ppb)		
HCH	Dieldrin	HCB	b-HCH	*p,p'*-DDE	Dieldrin	*p,p'*-DDT
ND	<20	ND	ND	14.5	ND	<2.0
ND	<20	0.4	0.9	24.0	ND	2.0
ND	<20	0.3	<0.7	8.6	ND	ND
ND	<20	0.3	<0.7	17.0	<1.0	3.4
ND	<20	0.5	1.8	31.5	1.2	3.3
ND	<20	<0.2	0.8	22.0	ND	<2.0
ND	<20	<0.2	<0.7	6.8	<1.0	ND
ND	ND	0.3	<0.7	21.5	ND	2.0
ND	ND	0.8	1.1	11.0	ND	ND
ND	<20	<0.2	0.9	17.2	<1.0	<2.0
		0.3	<0.7	32.0	<1.0	<2.0
		0.4	0.9	12.3	<1.0	<2.0
		0.3	0.6	11.5	ND	<2.0
		0.3	ND	7.0	ND	<2.0
		0.4	<0.7	18.0	ND	2.3
		0.3	<0.7	14.7	ND	<2.0
		<0.2	0.9	17.2	<1.0	<2.0
		0.3	0.7	9.7	ND	<2.0
		0.5	0.8	26.7	ND	2.3
		<0.2	<0.7	7.1	ND	ND
		0.7	1.2	31.6	1.4	4.6
		0.3	1.5	17.0	<1.0	<2.0
		0.4	0.7	20.8	ND	<2.0
		0.4	ND	10.8	<1.0	<2.0
		0.3	ND	3.4	ND	<2.0
		0.6	<0.7	12.9	ND	<2.0

HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; ND, not detected.
Reprinted from ref. 24, with permission.

small amount of organic materials retain chlordane less than do soils having a high organic content (43).

Chlordane is degraded in air by photooxidation. α-Chlordane is a photo-by-product of chlordane. Chlordane does not degrade rapidly in water.

Chlordane concentrations in the air of houses in urban areas range from less than the detectable limit (i.e., less than 0.1 ng per cubic meter) to 200 ng per cubic meter (45–47). Rural air concentrations of chlordane range from 0.1 to 0.8 ng per cubic meter (43). As compared to the outdoor air, chlordane concentrations in indoor air are much higher. Indoor air concentrations in houses treated with chlordane range from 0.8 to 600,000 ng per cubic meter (43–45). Indoor air sampling in previously treated homes demonstrated concentrations of γ-chlordane, α-chlordane, and *trans*-nonachlor. However, these concentrations were all lower than the 5-μg-per-cubic-meter guideline proposed by the NAS for indoor levels of chlordane.

Biological Monitoring

Biological monitoring of chlordane is via detection of chlordane or its metabolites in such human tissues and fluids as blood, adipose tissue, brain, liver, kidney, milk, and urine. Total chlordane residue levels appear to be higher in fat and liver than in the blood (47). However, attempting to correlate tissue levels with environmental levels is difficult owing to the bioaccumulative effects of chlordane.

Oxychlordane has been detected in concentrations ranging from 0.002 to 0.005 mg per L in human breast milk in a random sampling (48). In a Finnish study of human milk samples, chlordane residues averaged 0.41 mg per kg of milk fat (49). Other studies have indicated that *trans*-chlordane concentrations in skin lipids may be a biomarker of recent exposure and that oxychlordane concentration in skin lipids might be a better biomarker of previous exposure (50).

Other studies have shown that total chlordane residues in blood were between 3 and 16 times higher in persons employed as pesticide applicators and were 1.5 to 10 times higher in residents of contaminated areas in which houses had been treated with chlordane for termites (51). Other studies have shown a positive correlation between the length of exposure to airborne chlordane in treated homes and the concentration of chlordane in human milk fat (52).

Environmental Contamination and Regulation of Chlordane

Chlordane is regulated by the Clean Water Act for industrial point sources such as electroplating, steam electric production, asbestos production, timber products processing, metal finishing, paving and roofing, paint formulating, ink formulating, gum and wood processing, pesticide production, and carbon black production (43). On March 6, 1978, registration for all uses of chlordane on fruit products was discontinued (43). However, chlordane use was continued for treatment of homes for termite control until April 14, 1988, when the EPA canceled registrations for chlordane-containing termiticide products. Between July 1, 1983, and April 14, 1988, the only approved use for chlordane in the United States was for subterranean termites; for this usage, chlordane was applied as a

TABLE 99-6. Drinking water and serum concentrations of organochlorine pesticides and metabolites in samples from individuals who use city water

Water (ppt)				Serum (ppb)		
HCH	Dieldrin	HCB	b-HCH	*p,p'*-DDE	Dieldrin	*p,p'*-DDT
30	<20	0.7	5.8	68.4	ND	<2.0
68	<20	ND	ND	15.0	<1.0	ND
42	<20	0.7	0.9	7.4	ND	ND
<4	ND	<0.2	<0.7	ND	10.1	ND
ND	ND	ND	<0.7	10.9	ND	ND
ND	<20	0.4	0.8	16.8	ND	<2.0
ND	<20	0.4	1.0	20.0	0.9	<2.0
ND	<20	0.5	1.7	21.3	ND	ND
ND	<20	0.3	<0.7	17.6	ND	<2.0
ND	<20	0.9	1.1	36.1	<1.0	ND
		0.5	1.6	27.2	4.6	2.0
		0.7	1.7	22.0	1.9	4.7
		0.3	3.1	25.0	<1.0	3.0
		0.5	1.7	16.4	1.7	2.2
		0.3	0.8	14.2	<1.0	<2.0
		0.3	<0.7	23.9	<1.0	<2.0
		0.3	0.7	7.1	<1.0	<2.0
		<0.2	<0.7	3.9	ND	ND
		0.3	ND	24.3	<1.0	<2.0
		0.3	1.0	16.6	ND	<2.0
		0.4	<0.7	66.7	1.2	4.2
		0.3	ND	5.0	ND	ND
		0.2	ND	5.4	ND	ND
		0.7	0.8	21.0	ND	2.0
		0.4	<0.7	9.9	ND	<2.0
		0.4	0.8	19.0	<1.0	<2.0
		<0.2	<0.7	10.4	ND	<2.0
		<0.2	1.3	43.1	<1.0	3.4
		0.3	<0.7	12.6	ND	ND
		0.7	<0.7	20.7	ND	5.5
		1.1	1.0	20.6	1.3	3.5
		0.4	1.3	17.0	1.0	2.6
		0.5	0.8	10.6	ND	<2.0

HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; ND, not detected.
Reprinted from ref. 24, with permission.

liquid that was poured or injected around the foundation of buildings. Regulatory guidelines for chlordane are shown in Table 99-7.

Although chlordane still is produced for export, its use in the United States now is prohibited by law, and it no longer is imported into the United States.

Chlordane is stable in the atmosphere and can be transported long distances. In water, it adsorbs to sediments and also volatilizes into the atmosphere. Partitioning of chlordane into sediment is correlated with the organic content of the sediment. Thus, where the organic content of suspended sediments in water is high, chlordane concentrations from release sites will increase.

Chlordane bioconcentrates in marine and fresh-water fish. It also bioconcentrates in aquatic plants. In soil, chlordane generally remains in the top 20 cm of most soils for years. Sandy soils and soils with smaller amounts of organic content retain chlordane less well than do soils that are of high clay content and high organic content.

In the atmosphere, chlordane is degraded by photolysis and oxidation. The *trans*-chlordane isomer degrades photochemically more readily than does the *cis*-chlordane isomer, and the *trans-cis* ratio of chlordane transported over long distances in the atmosphere changes from approximately 1 in the winter to 0.5 in the summer (53).

Chlordane persists for more than 20 years in some soils, and chlordane residues in excess of 10% of the initially applied amount have been found 10 years after that initial application (54). Only a few microorganisms capable of biodegrading chlordane have been isolated, and most studies indicate that chlordane does not biodegrade rapidly in soils.

Urban air concentrations range from below detection limits to 58 ng per cubic meter. Rural background concentrations range from 0.01 to 1.0 ng per cubic meter (43). Indoor air concentrations of treated homes may exceed 1 μg per cubic meter. Chlordane injected into the soil or poured around the foundation of a house can vaporize into the indoor air of that residence, indicating that it passes through cracks or ventilation ducts and possibly through the concrete (45,55). Studies also indicate that concentrations of chlordane in treated homes can be higher in the lower level and basement areas of homes (56). Basement concentrations of chlordane have been found to be three to ten times higher than in the living areas. After misapplication of chlordane, living area samples show concentrations of 3.28 μg per cubic meter, with 40% of samples in one study exceeding 5 μg per cubic meter (57).

On April 14, 1988, the EPA terminated the use of termiticide products containing chlordane and forbade the sale or commercial use of those products within the United States.

TABLE 99-7. Regulations applicable to chlordane

Agency	Description	Value
Federal and international agencies		
WHO	Guidelines for drinking water	0.3 μg/L
WHO	Residue tolerances for sum of α and γ isomers and oxychlordane	0.02–0.5 mg/kg
WHO	Acceptable daily intake	0–0.001 mg/kg/body wt
Regulations		
OSHA	Permissible exposure limit (8-h workday)	0.5 mg/m^3
EPA	Reportable quantity (released to the environment)	1 lb
NAS	Recommended maximum indoor concentration in homes	5 μg/m^3
	Threshold planning quantity	1,000 lb
Guidelines		
Air		
ACGIH	Threshold limit value (TLV) (8-h workday)	0.5 mg/m^3
STEL		2 mg/m^3
NRC	Interim guideline for military housing	5 μg/m^3
EPA	Inhalation	1.3 mg/kg/day
Water		
EPA	Health advisories	
	1-day (10-kg child)	0.06 mg/L
	10-day (10-kg child)	0.06 mg/L
	Longer-term (10-kg child)	0.5 μg/L
	Longer-term (70-kg adult)	2 μg/L
	Maximum contaminant level goal (proposed)	0 mg/L
	Ambient water quality criteria for the following lifetime increased cancer risk levels	
	With ingestion of water, fish, and shellfish	
	10^{-5}	4.6 ng/L
	10^{-6}	0.46 ng/L
	10^{-7}	0.046 ng/L
	With ingestion of fish and shellfish only	
	10^{-5}	4.8 ng/L
	10^{-6}	0.48 ng/L
	10^{-7}	0.048 ng/L
Other		
EPA	q_1*[a] (oral)	1.3 mg/kg/day
	RfD[b] (oral)	5×10^{-5} mg/kg/day
	PADI (oral)	5.0×10^{-5} mg/kg/day
	Group B2 cancer ranking (probable human carcinogen)	
	Designated as a hazardous waste (no. U036)	
State regulations and guidelines		
	Acceptable ambient air concentration	
Connecticut		2.5 μg/m^3 (8-h avg)
Kansas		1.19 μg/m^3 (annual avg)
Kentucky		0.05 μg/m^3 (8-h avg)
Massachusetts		0.068 μg/m^3 (24-h avg)
Nevada		0.012 μg/m^3 (8-h avg)
New York		1.7 μg/m^3 (1-yr avg)
Pennsylvania (Philadelphia)		0.35 μg/m^3 (1-yr avg)
Virginia		8.0 μg/m^3 (24-h avg)
	Acceptable drinking water concentrations	
Arizona		0.5 μg/L
California		0.55 μg/L
Illinois		3 μg/L
Kansas		0.22 μg/L
Maine		0.55 μg/L
Minnesota		0.22 μg/L
New Jersey		0.5 μg/L

ACGIH, American Conference of Governmental Industrial Hygienists; EPA, U.S. Environmental Protection Agency; NAS, National Academy of Sciences; NRC, National Research Council; OSHA, U.S. Occupational Safety and Health Administration; STEL, short-term exposure limit; TLV, threshold limit value; WHO, World Health Organization.

[a] q_1* represents the upper-bound estimate of the low dose of the dose-response curve, as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually milligrams per liter of water, milligrams per kilogram of food per day, and grams per cubic meter of air).

[b] *RfD* represents an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observable-adverse-effect level (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Adapted from Agency for Toxic Substances and Disease Registry. *Toxicological profile for chlordane.* Atlanta: US Department of Health and Human Services, Public Health Service, ATSDR, 1989, with permission.

Clinical Toxicology of Chlordane

Chlordane can be absorbed systemically via oral, inhalational, and dermal routes. Acute chlordane poisoning has been reported (58–62). Animals that have been given fatal doses of chlordane exhibit symptoms of dyspnea, depressed respirations, tremors, convulsions, coma, and death. In human cases of acute chlordane ingestion, convulsions, muscle tremors, increased excitability, confusion, and coma are common (58–62). Symptoms usually begin within an hour of acute ingestion of this liquid, with manifestations of confusion followed by convulsions. Once absorbed, chlordane has a high distribution into adipose tissue. Human poisonings involving chlordane have also shown elevation of white blood cell count, pneumonias (probably secondary to aspiration), and hepatic and renal damage (58–62). Treatment is symptomatic.

SUBACUTE AND CHRONIC EXPOSURE TO CHLORDANE

Retrospective cohort mortality studies of workers in chlordane-manufacturing industries and pesticide applicators have shown no increase in mortality rates and no increase in a specific cause of death that could be attributed to chlordane exposure (63–65).

One study examined cause-specific mortality among workers occupationally exposed to chlordane or heptachlor and demonstrated no overall excess of death from cancer even in workers who were studied for 20 or more years after entry into the industry (64). Another study that examined the mortality of a cohort of 3,827 men licensed to apply pesticides in Florida showed an excess mortality from lung cancer among pesticide applicators (66). However, this study did not account for such other risk modifiers as smoking.

A retrospective mortality study of workers employed at organochlorine pesticide–manufacturing plants examined the mortality of workers employed in the manufacture of several different organochlorine hydrocarbons for use as pesticides (65). This study concluded that the standardized mortality ratio for all causes of death in each cohort was below the expected level.

Blood dyscrasias such as megaloblastic anemia and bone marrow depression have been associated with chlordane exposure in case reports (67,68). However, these case reports also identified exposures to pesticides other than chlordane, and no definitive study has indicated that chlordane is causative of blood dyscrasias.

Investigations into the health status of people living in private residences previously treated with chlordane have been undertaken (69). However, the study population was self-selected, thus indicating a bias toward involving those concerned about chlordane or who believed that they had experienced health problems related to chlordane (69). Occupational exposure to chlordane has not been associated with abnormal liver function tests or renal effects (43).

In individuals who have ingested chlordane, nausea, vomiting, abdominal pain, and diarrhea occur very early. Autopsies of individuals who have died after chlordane ingestion show inflammation of the mucosa of the upper gastrointestinal tract (43).

In animal studies of acute oral exposure to chlordane, evidence exists of hepatic microsomal enzyme induction and alteration in the activities of mitochondrial enzymes (43). Histochemical and morphological alterations in the liver also were seen.

HEMATOLOGIC EFFECTS

Anecdotal reports claim an association between blood dyscrasias and a number of the organochlorine pesticides including chlordane, lindane, and DDT (67,68). Case reports have described thrombocytopenic purpura, acute disseminated hemorrhages, aplastic anemia, hemolytic anemia, anemia, and megaloblastic anemia in individuals exposed to chlordane and heptachlor in residential environments or in professional settings in which these materials were used (69). However, confounding factors include exposure of the reported individuals to numerous other chemicals; hence, the case reports are insufficient to implicate chlordane as the sole etiologic agent for blood dyscrasias.

Studies from chlordane manufacturing showed no hematotoxic changes in workers exposed to chlordane (70). Likewise, no hematologic effects have been observed in animal models exposed to technical chlordane (71).

IMMUNOTOXICITY

Immune alterations in humans exposed to chlordane aerosols in the home or workplace for 3 days to 15 months have been reported (72). This same study also showed impaired lymphocyte proliferative responses to mitogens. However, confounding exposure factors were not eliminated.

In animal immune studies, reduced thymus weights have been observed in female rats but not male rats exposed to 28.2 mg of inhaled chlordane per cubic meter for 8 hours daily, 5 days per week, for 28 days (71). However, changes in thymus weight were not observed in female rats exposed to lower doses. Other animal studies in which chlordane was administered orally have demonstrated depressed cell-mediated immunity manifested by depressed hypersensitivity reactions and depressed mixed lymphocyte culture reactivity (73,74). Some animal studies show that chlordane interferes with cell-mediated immune proliferative responses of lymphocytes in monkeys (75).

TABLE 99-8. Residues of organochlorine compounds in human fat (mg/kg) in the United Kingdom, 1976–1977

	β-HCH	Total HCH	Heptachlor epoxide	Dieldrin (HEOD)	*p,p'*-DDE	*p,p'*-DDT	Total DDT[a]	HCB	PCB
Arithmetic mean	0–31	0.33	0.03	0.11	2.1	0.21	2.6	0.19	0.7
Range[b]	T–1.2	T–1.2	T–0.12	T–0.49	0.03–15	T–2.4	0.04–17	0.02–3.2	T–10
Standard error of mean	0.01	0.01		0.01	0.12	0.01	0.15	0.01	0.05
Median value	0.29	0.31		0.09	1.7	0.17	2.1	0.15	0.7
Geometric mean	0.24	0.27		0.09	1.5	0.15	1.9	0.15	0.6
95% Confidence interval	0.22–0.27	0.24–0.29		0.08–0.10	1.3–1.7	0.14–0.1 7	1.6–2.1	0.14–0.17	0.5–0.6

HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; PCB, polychlorinated biphenyl.
[a]Total DDT was calculated by adding to the *p,p'*-DDT found as such the *p,p'*-DDT-equivalent of the *p,p'*-DDE and *p,p'*-TDE.
[b]T is less than 0.01 (less than 0.1 for PCB).
Note: Results obtained in 236 subjects older than 5 years.
Reprinted from ref. 26, with permission.

TABLE 99-9. Concentration of organochlorine insecticides in samples of adipose tissue and liver

Adipose						Liver		
Lindane	Heptachlor epoxide	Dieldrin	*p,p'*-DDT	*p,p'*-DDE	Total equiv. DDT	Dieldrin	*p,p'*-DDE	Total equiv. DDT
0.12	0.008	0.16	0.36	2.18	2.79	0.030	0.16	0.18
0.21	0.014	0.25	0.28	1.88	2.38	0.050	0.16	0.18
0.05	0.005	0.14	0.14	0.36	0.54	0.040	0.05	0.06
0.11	0.008	0.18	0.42	2.50	3.21	0.026	0.15	0.17
0.06	0.006	0.13	0.19	1.15	1.47	0.024	0.12	0.13
0.07	0.009	0.25	0.35	1.95	2.52	0.025	0.08	0.10
0.12	0.009	0.21	0.44	2.10	2.78	0.035	0.19	0.21
0.10	0.004	0.05	0.10	0.08	0.19	0.007	0.01	0.01
0.13	0.030	0.50	0.35	2.66	3.31	0.081	0.12	0.13
0.16	0.013	0.23	0.58	2.32	3.17	0.041	0.13	0.14
0.09	0.005	0.10	0.35	1.51	2.03	0.014	0.20	0.22

Reprinted from ref. 21, with permission.

CARCINOGENESIS

Retrospective studies reveal no evidence that links carcinogenesis with exposure to chlordane (76,77). Nonetheless, an association between chronic exposure to chlordane in treated homes and an increased risk of skin neoplasms and leukemia has been suggested (69,78). The EPA considers data from laboratory animal studies sufficient to classify chlordane in the group B-2 category—that is, as a probable human carcinogen.

REPRODUCTIVE, GENOTOXIC, AND DEVELOPMENTAL EFFECTS

No data are available regarding the developmental effects in humans after exposure to chlordane. Chlordane has been tested for mutagenicity in several systems, with mostly negative results. In terms of reproductive effects, studies on humans after exposure to chlordane are limited. One study compared to control populations indicated that the incidence rates of unspecified ovarian and uterine disease were significantly elevated in women exposed to chlordane vapors in their homes as compared to the rates among control populations (78). However, this study has serious limitations.

Absorption, Metabolism, and Excretion

Human samples of adipose tissue and plasma have been assayed for the presence of organochlorine pesticides (Tables 99-8, 99-9). Because these chemicals are found commonly in human adipose tissue and plasma (in approximately 80% of the U.S. population), associating these chemicals' presence with disease is difficult. Chlordane and its metabolites can be detected in a variety of human biological tissues such as blood, brain (Table 99-10), adipose tissue, liver, breast milk (Table 99-11), kidneys, and urine. However, no information currently available correlates concentrations found in these tissues with environmental chlordane concentrations or with human health effects.

In cases of intoxication, chlordane concentrations of the blood and other tissues have been found to be highly elevated. Blood chlordane concentrations of 3.4 mg per L were associated with seizures in one child (59). The half-life of chlordane in this case was 8 days as compared to other reports of 21 days. The urinary excretion of chlordane continued up to 130 days after ingestion (59). On the basis of this and other cases, the seizure threshold for chlordane is believed to be between 2 and 4 mg per L in serum.

Chlordane is well absorbed by the oral, dermal, and inhalational routes. Blood and tissue concentrations of chlordane and chlordane metabolites will increase with the duration of exposure. Information on the absorption and distribution of chlordane comes from acute oral exposures in humans from accidental or suicidal ingestions.

Chlordane concentrates in the fatty tissues and is excreted very slowly. After a massive chlordane ingestion by a 59-year-old man, which resulted in his death, concentrations of chlordane were measured in several tissues (62). In this case, fat tissue contained 22 μg of chlordane per gram of tissue; brain contained 23.3 μg per gram; kidneys, 14.1 μg per gram; liver, 59.9 μg per gram; and spleen, 19.2 μg per gram. In a child who drank technical-grade chlordane, the concentration in adipose tissue was measured. One-half hour after the exposure, the chlordane concentration was approximately 3.1 mg per kg of fat tissue, which peaked at 35 mg per kg of fat 8 days after ingestion (79).

Values for the concentration of the metabolite of chlordane, oxychlordane, in human adipose tissue have ranged from 0.03 to 0.5 mg per kg of fat tissue, with an average concentration of 0.11 to 0.19 mg per kg (80). The usual chlordane metabolites found in humans are heptachlor, oxychlordane, and heptachlor epoxide (Fig. 99-10).

One excretion route of metabolites of chlordane is through breast milk. Oxychlordane, *trans*-nonachlor, and heptachlor epoxide have been identified in human breast milk. *Trans*-nonachlor has been reported to be present in human breast milk in concentrations of 0.027 to 0.210 μg per mL, heptachlor epoxide in concentrations of 0.001 to 0.067 μg per mL, and oxychlordane in concentrations of 0.011 to 0.160 μg per mL.

TABLE 99-10. Mean concentrations of organochlorine insecticides in human brain tissues

	Dieldrin (ppm)		Total equivalent DDT (ppm)	
	White matter	Gray matter	White matter	Gray matter
Arithmetic mean	0.009	0.006	0.033	0.025
Standard deviation	0.002	0.001	0.005	0.004
Geometric mean	0.0061	0.0047	0.0023	0.020
Confidence limits ($p = .05$)	0.0047–0.0080	0.0037–0.0059	0.018–0.031	0.015–0.026

Reprinted from ref. 21, with permission.

TABLE 99-11. Mean values of samples taken at different times during breast feeding (pesticide levels in parts per million of whole milk)

Samples	Prefeeding mean ± SD (range)	Postfeeding mean ± SD (range)	Random mean ± SD (range)
Urban			
No. samples	43	42	45
% Lipid	2.7 ± 1.6 (0.3–9.7)	4.8 ± 1.8 (0.7–8.6)	3.3 ± 1.6 (0.8–7.9)
HCH	0.006 ± 0.004 (0.001–0.016)	0.010 ± 0.006 (0.002–0.025)	0.007 ± 0.005 (0.001–0.027)
γ-HCH	0.001 ± 0.002 (0.000–0.007)	0.001 ± 0.002 (0.000–0.009)	0.001 ± 0.002 (0.000–0.006)
Dieldrin	0.010 ± 0.008 (0.002–0.038)	0.012 ± 0.008 (0.002–0.041)	0.007 ± 0.005 (0.002–0.024)
DDE	0.023 ± 0.013 (0.005–0.067)	0.039 ± 0.019 (0.011–0.077)	0.029 ± 0.022 (0.006–0.127)
DDT	0.011 ± 0.009 (0.002–0.033)	0.017 ± 0.011 (0.003–0.051)	0.010 ± 0.008 (0.002–0.037)
Total DDT	0.036 ± 0.020 (0.008–0.096)	0.060 ± 0.028 (0.015–0.136)	0.042 ± 0.030 (0.009–0.179)
Rural			
No. samples	42	42	53
% Lipid	2.8 ± 1.3 (0.3–5.9)	4.8 ± 1.5 (0.7–9.2)	2.6 ± 1.3 (0.3–6.2)
HCH	0.006 ± 0.003 (0.001–0.015)	0.009 ± 0.004 (0.002–0.024)	0.006 ± 0.003 (0.002–0.019)
γ-HCH	0.000 ± 0.001 (0.000–0.003)	0.001 ± 0.002 (0.000–0.003)	0.000 ± 0.001 (0.000–0.002)
Dieldrin	0.006 ± 0.004	0.009 ± 0.006	0.008 ± 0.005

HCH, hexachlorocyclohexane.
Reprinted from ref. 29, with permission.

The elimination half-life has been reported to be 21 days in one study, 34 days in another, and 88 days in yet another study (62,79,81). Only small amounts of chlordane are excreted in the urine after ingestion. The fat-serum partition ratio for chlordane in exposed workers was found to be 660:1 (82).

ALDRIN AND DIELDRIN

Aldrin and dieldrin are cyclodiene pesticides that are chemically related. Aldrin is rapidly converted to dieldrin in the environment, and their toxicities are similar. Aldrin and dieldrin were used from the 1950s through the 1970s but were still manufactured through 1990. Both have been used in agricultural settings for control of disease vectors such as insects and as a soil insecticide. Dieldrin has also found use in the past as a veterinary dip for sheep. The use of both of these chemicals was banned in 1975; the manufacture of dieldrin was terminated in 1987 and that of aldrin in 1990.

Aldrin is prepared by the Diels-Alder reaction using hexachlorocyclopentadiene. Dieldrin is prepared by the oxidation of aldrin with an organic acid or hydrogen peroxide and a tungsten oxide catalyst. The insecticide dieldrin contains 85% 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo,exo-5,8-dimethanonaphthalene, or HEOD (83).

Exposure Sources

Aldrin is readily converted to dieldrin in the environment. Dieldrin is persistent and resists biodegradation, and thus bioaccumulates throughout the food chain. Aldrin readily volatilizes from soil. Dieldrin, however, volatilizes more slowly because it adsorbs to soil. In soil, aldrin is converted to dieldrin by epoxidation. Aldrin and dieldrin do not leach to appreciable degrees into groundwater.

Human exposure to aldrin and dieldrin has occurred through dermal and inhalational routes during pesticide application. However, owing to the persistence and bioaccumulation of these chemicals, human exposure also occurs through the food chain.

Air and drinking water are minor exposure sources. A study of U.S. drinking water samples revealed that fewer than 17% contained dieldrin, with very low concentrations of 4 to 10 ng per L of water (84).

Because aldrin is converted to dieldrin, soil concentrations of dieldrin are higher than those of aldrin. Dietary exposure to aldrin and dieldrin is the most significant source of exposure for the general population, and food is the main source of the human adipose tissue concentration of dieldrin in humans (Tables 99-12 through 99-16) (84).

Infants are the population at greatest risk from aldrin and dieldrin exposure in the diet. The concentration of dieldrin in breast milk is another factor that places infants at risk of exposure. Breast milk is one of the major excretion routes for organochlorine compounds, and exposure to infants from human milk sources can be significant (28,29). Dieldrin has been found in the breast milk of 80% of nursing mothers sampled (84). Transplacental transfer is possible, and concentrations in fetal tissue probably occur. Placental-fetal transfer of aldrin and dieldrin has also been documented (34–36).

Homes treated for termite control with aldrin and dieldrin are another source of exposure. Indoor air in these homes contains aldrin in varying concentrations, depending on the sampling. In one study, the aldrin concentration ranged between 77 and 102 ng per cubic meter within the first 7 days of treatment and fell to a low of 36 ng per cubic meter by 1 year after treatment (84). The concentration in crawl spaces of treated homes was much higher.

Chemical and Physical Forms

The chemical structures of cyclodienes aldrin and dieldrin are depicted in Figure 99-11.

Absorption, Metabolism, and Excretion

Aldrin and dieldrin can be absorbed by inhalational, dermal, and gastrointestinal routes. Rapid conversion of aldrin to the dieldrin epoxide takes place once absorption has occurred. Aldrin rarely is found in blood or tissue owing to this rapid conversion.

Dieldrin is stored in the fat and, during such periods of stress as weight loss and high fever, can be mobilized to the plasma, where it can be metabolized. The half-life of dieldrin in humans is 266 days (84). A correlation has been found between dieldrin concentrations in human breast milk and the pesticide treatment of homes. The distribution of dieldrin between blood and tissue of humans is shown in Figure 99-12. In human volunteers ingesting dieldrin, dieldrin concentrations in blood and fat tissue increased

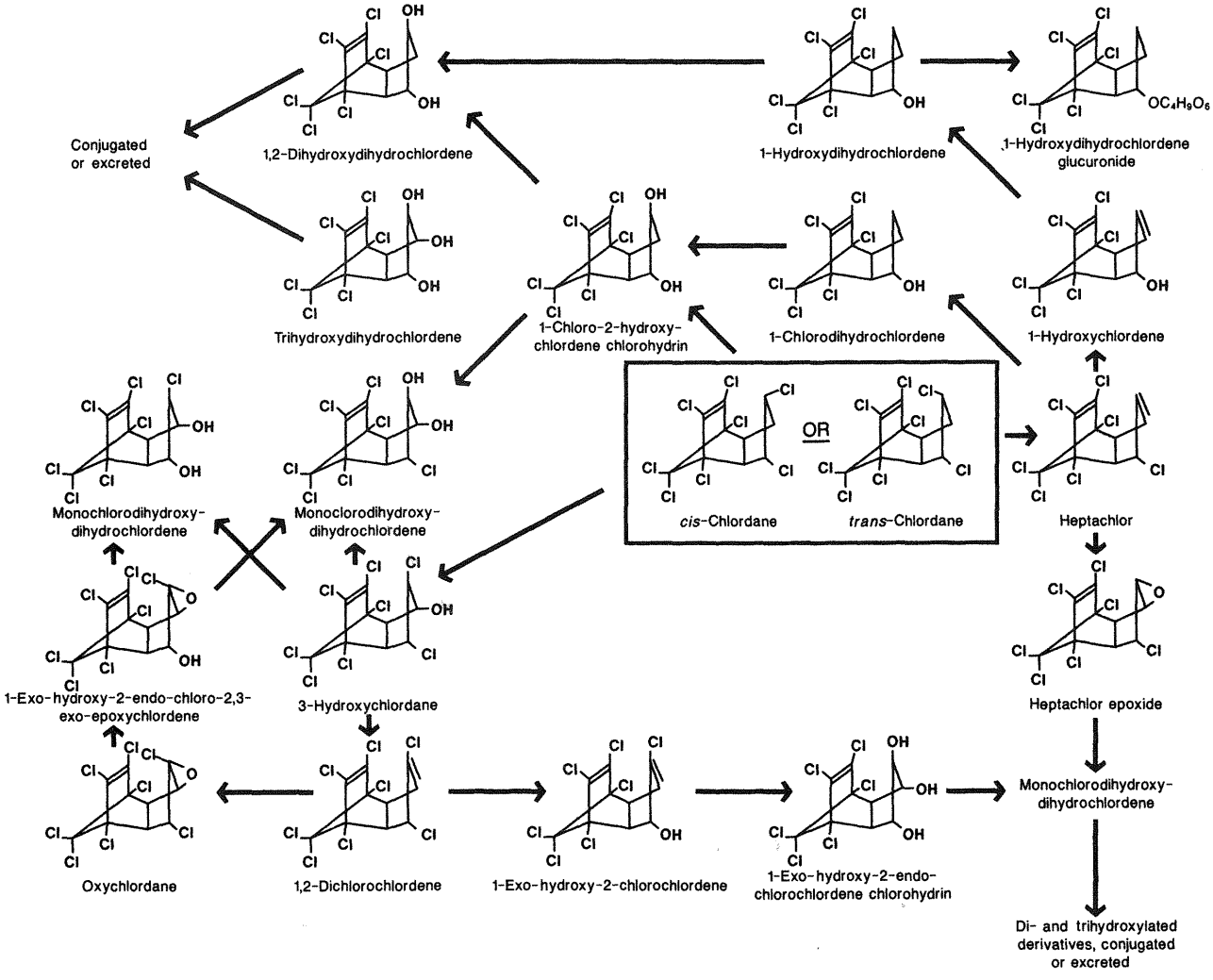


Figure 99-10. Metabolic pathways of chlordane. (From A Nomeir, N Hajjar. Metabolism of chlordane in mammals. *Rev Environ Contam Toxicol* 1987;100:1–22, with permission.)

in a dose-related fashion, the fat tissue–blood ratio being 136:1 (84). In this same study, after dieldrin administration was terminated, the biological half-life decreased exponentially and was approximately 369 days, with a range of 141 to 592 days. The biotransformation of aldrin to the dieldrin epoxide occurs primarily in the liver (Fig. 99-13). Ackerman (85), in 1980, noted that the concentration of dieldrin in humans reaches a constant concentration and that the amount ingested and absorbed equals the amount metabolized and excreted after a period. With the increasing concentration of dieldrin in the liver, the rate of metabolism increases.

The biological half-life of dieldrin in the blood of workers who were occupationally exposed was estimated to be approximately 266 days in reports in which the subjects were studied for 3 years after an occupational exposure (86,87). Hunter and Robinson (86) reported an estimated half-life of 369 days for dieldrin.

Clinical Toxicology

The clinical toxicology of aldrin and dieldrin can essentially be ascribed to dieldrin, as aldrin is rapidly metabolized to dieldrin after its absorption in the human body. Once aldrin has been converted, dieldrin is distributed extensively into tissue spaces and accumulates in adipose tissue. Dieldrin is metabolized hepatically, and metabolites are excreted in bile and feces. Major toxicity involves the CNS. Toxic exposure produces tremors, giddiness, hyperexcitability, seizures, and coma (88). Dieldrin inhibits GABA neurotransmission in a manner similar to that of other cyclodiene pesticides.

In animal studies, the median lethal dose for species of all laboratory animals ranged from 40 to 70 mg of aldrin per kg of body weight and 40 to 90 mg of dieldrin per kg of body weight (84). Also in animal studies, it was determined that weight loss resulted in immobilization of dieldrin from the fat stores, increased the blood levels peripherally, and produced toxic manifestations. No deaths have been reported from human intoxication during the manufacture of aldrin or dieldrin. Most deaths occur as a result of intentional or accidental exposure to concentrated amounts of the pesticides.

In occupational settings, aldrin and dieldrin have produced symptoms of headache, dizziness, ataxia, and muscle twitching (84). Occupational exposure to aldrin and dieldrin in pesticide workers showed that the average dieldrin blood level of those studied over a 4-year period was 0.035 μg per mL (87). Sprayers and pesticide applicators in India showed symptoms of intoxication that included headache, tremors, and seizures (84).

The mechanism of action of dieldrin in the CNS is at the level of the synapse, causing increased neuronal excitability. Evidence indicates that dieldrin produces impairment of memory and emotional disturbances in humans, which may be due to the effect of the chemical on the limbic system. In general, the cyclodiene insec-

TABLE 99-12. Individual donor information (urban)

	Average residue levels (ppm)				
HCH	γ-HCH	Dieldrin	DDE	DDT	Total DDT
0.003	0.002	0.013	0.012	0.021	0.034
0.002	0.003	0.011	0.010	0.013	0.024
0.002	Tr	0.008	0.009	0.017	0.027
0.002	0.001	0.009	0.017	0.011	0.030
0.009	Tr	0.013	0.033	0.020	0.057
0.005	0.005	0.017	0.026	0.019	0.048
0.010	0.002	0.024	0.026	0.007	0.036
0.009	0.007	0.011	0.019	0.021	0.042
0.009	0.001	0.008	0.024	0.007	0.034
0.002	Tr	0.005	0.023	0.005	0.031
0.015	0.001	0.015	0.055	0.029	0.090
0.008	Tr	0.009	0.020	0.004	0.026
0.012	0.001	0.009	0.046	0.022	0.073
0.016	0.001	0.024	0.057	0.028	0.092
0.007	Tr	0.005	0.014	0.005	0.021
0.012	0.003	0.015	0.041	0.013	0.059
0.011	0.003	0.011	0.044	0.037	0.086
0.004	Tr	0.007	0.026	0.008	0.037
0.006	Tr	0.010	0.047	0.015	0.067
0.006	Tr	0.012	0.029	0.007	0.039
0.007	0.002	0.012	0.050	0.012	0.068
0.010	Tr	0.005	0.039	0.014	0.057
0.005	0.002	0.008	0.034	0.027	0.065
0.006	Tr	0.003	0.023	0.006	0.032
0.003	0.001	0.024	0.024	0.014	0.041
0.010	0.001	0.007	0.029	0.009	0.041
0.004	0.001	0.003	0.012	0.003	0.016
0.005	0.001	0.007	0.036	0.013	0.053
0.004	Tr	0.007	0.034	0.010	0.048
0.003	0.001	0.002	0.011	0.004	0.016
0.017	Tr	0.012	0.073	0.027	0.108
0.006	Tr	0.004	0.025	0.006	0.034
0.012	Tr	0.007	0.039	0.011	0.054
0.011	Tr	0.009	0.041	0.009	0.055
0.007	Tr	0.003	0.016	0.005	0.023
0.007	Tr	0.003	0.037	0.006	0.047
0.010	Tr	0.008	0.034	0.012	0.050
0.011	Tr	0.005	0.025	0.007	0.035
0.013	Tr	0.007	0.043	0.009	0.057
0.007	0.004	0.005	0.024	0.006	0.033
0.006	Tr	0.003	0.022	0.004	0.029
0.010	Tr	0.005	0.034	0.009	0.047
0.008	0.001	0.008	0.022	0.007	0.032
0.008	Tr	0.021	0.028	0.008	0.039
0.004	Tr	0.006	0.013	0.004	0.018

HCH, hexachlorocyclohexane; Tr, trace amount.
Reprinted from ref. 29, with permission.

ticides mimic the action of picrotoxin: Dieldrin has been shown to bind to the picrotoxin receptor in rodent brain synaptosomes (89).

No evidence of hepatic injury was noted in exposed individuals manifesting serum concentrations of dieldrin (range, 4 to 350 ppb) (87). Hepatic enzyme activity levels were found to be normal in 233 pesticide applicators exposed occupationally to aldrin, dieldrin, endrin, and kelodrin for 4 to 12 years (87). Studies have concluded that long-term exposure to aldrin and dieldrin do not produce liver disease detectable by enzyme elevation or hepatic enzyme induction. Blood concentrations of dieldrin are normally lower than 10 ng per mL. Concentrations between 10 and 100 ng per mL probably are indicative of overexposure (90). Dieldrin blood concentrations from 100 to 200 ng per mL indicate significant and potentially serious exposure. Concentrations exceeding 200 ng per mL may be associated with toxic effects.

Carcinogenesis

The available data on aldrin and dieldrin are inadequate to establish a clear relationship between these compounds and cancer in humans. However, malignant tumors of the liver have been observed in animal studies involving these chemicals (91). Mortality studies of workers engaged in the manufacturing of aldrin, dieldrin, and endrin revealed excess cancer incidence.

Environmental Regulations of Aldrin and Dieldrin

The WHO recommends the following guidelines for aldrin and dieldrin concentrations:

- Food (extraneous residue limit): 0.02 to 0.2 mg per kg of product

TABLE 99-13. Mean levels of organochlorine pesticides in milk of individual donors exposed to indoor air concentrations of organochlorine pesticides (values expressed in nanograms per gram of whole milk)

Donor no.	No. of sample	HCH	γ-HCH	Chlordane	Heptachlor	Heptachlor epoxide	Dieldrin	DDE	DDT	Total DDT
1	4	12	1	2	Tr	3	14	27	8	38
2	6	15	2	2	Tr	3	14	50	5	61
3	7	3	2	32	Tr	2	10	15	3	20
4	6	4	1	2	Tr	2	9	18	3	23
5	2	13	4	3	Tr	7	26	104	23	139
6	6	7	1	2	Tr	3	21	28	6	37
7	6	10	2	2	1	5	10	33	5	42
8	1	5	1	2	Tr	1	19	40	5	50
9	3	5	1	1	Tr	2	19	17	3	22
10	14	15	1	4	2	11	13	48	10	63
11	4	9	1	1	1	2	7	17	4	23
12	7	5	1	3	1	2	9	18	5	25
13	4	8	Tr	2	1	2	8	16	3	21
14	4	4	1	8	Tr	3	16	44	8	57

HCH, hexachlorocyclohexane; Tr, trace amount.
Reprinted from ref. 23, with permission.

- Food (maximum residue limit): 0.02 to 0.1 mg per kg
- Drinking water: 0.03 μg per L
- Acceptable daily intake: 0.1 μg per kg of body weight (sum of aldrin and dieldrin)

The Occupational Safety and Health Administration established an 8-hour time-weighted average (TWA) atmospheric permissible exposure limit for aldrin of 0.25 mg per cubic meter and for dieldrin of 0.25 mg per cubic meter, with a skin notation for each compound (OSHA 1985).

In 1974, the EPA suspended all use of aldrin and dieldrin, and all food uses were canceled in 1975 (84). Specific precautions regarding the termiticide use of aldrin and dieldrin were instituted in 1981, and a label improvement program was initiated to reduce potential risk due to the possibility of misapplication in termiticide use. Label changes indicated precautions concerning application of these chemicals near water supplies, heating ducts, and intake ducts in dwellings and around structures having crawl spaces underneath (84). New labels also warned against annual applications (84).

Effluent limitations of zero discharge were established by the EPA in 1986, under the National Pollutant Discharge Elimination System, for both existing and new sources. Tolerances for residues of aldrin and dieldrin in or on various raw agricultural commodities are set at 0, 0.02, 0.05, or 0.1 ppm under section 408 of the Pesticide Residue Amendment to the Federal Food, Drug and Cosmetic Act as administered by the EPA. Aldrin (Waste Number P004) and dieldrin (Waste Number P037) are listed as hazardous wastes under the Resource Conservation and Recovery Act.

Aldrin and dieldrin are listed as toxic pollutants under section 307 of the Federal Water Pollution Control Act. They are regulated as hazardous substances with a reportable quantity of 1 pound (0.454 kg) for each, under section 102 of the Comprehensive Environmental Response, Compensation, and Liability Act for releases from vessels and facilities.

The American Conference of Governmental Industrial Hygienists has adopted TWA threshold limit values for exposure to aldrin and dieldrin of 0.25 mg per cubic meter. The American Conference of Governmental Industrial Hygienists' recommendation includes a "skin" notation to indicate the potential for absorption of the compound by the dermal or airborne route or by direct contact. The TWA limit for aldrin was chosen to prevent hepatic injury and to maintain the dieldrin load at a sufficiently low level to prevent systemic poisoning.

The National Institute for Occupational Safety and Health has recommended a permissible exposure limit for both aldrin and dieldrin of 0.25 mg per cubic meter and has recommended the designation of 100 mg of aldrin per cubic meter and 450 mg of dieldrin per cubic meter as those concentrations that are immediately dangerous to life or health.

TABLE 99-14. Dieldrin levels in donors for whom aldrin was the most recent pesticide used in the home

	Dieldrin levels (ng/g whole milk) in months after treatment[a]							
Donor no.	2 mo	3 mo	4 mo	5 mo	6 mo	7 mo	8 mo	9 mo
2	26	9	12	14	11	14		
6			19	21	26	31	21	8
9						16	24	16

[a]Note decline in concentration over time.
Reprinted from ref. 23, with permission.

TABLE 99-15. Chlordane levels in one breast-milk donor exposed to home pesticide spraying

Sample no.	Sampling time relative to treatment	Chlordane (ng/g whole milk)
1	3 days prior	Tr
2	1 week after	63
3	3 weeks after	66
4	7 weeks after	64
5	11 weeks after	26
6	15 weeks after	2
7	19 weeks after	2

Tr, trace amount (<1 ng/g).
Reprinted from ref. 23, with permission.

TABLE 99-16. Hexachlorobenzene, heptachlor, and heptachlor epoxide levels in breast milk of an individual after home application of pesticides (values expressed in nanograms per gram of whole milk)

Sample no.	Sampling time relative to treatment	HCH	Heptachlor	Heptachlor epoxide
1	3 months prior	3	—	1
2	2 months prior	8	Tr	4
3	1 month prior	7	Tr	3
4	1 day after	6	13	2
5	3 days after	22	2	4
6	1 week after	18	Tr	8
7	2 weeks after	17	Tr	8
8	3 weeks after	13	2	13
9	4 weeks after	22	3	29
10	5 weeks after	23	4	29
11	7 weeks after	21	2	21
12	9 weeks after	18	1	16
13	12 weeks after	17	Tr	7
14	15 weeks after	9	Tr	3

HCH, hexachlorocyclohexane; Tr, trace amount.
Reprinted from ref. 23, with permission.

The NAS has issued a health advisory for a level of 0.0031 ppb for chronic exposure in drinking water. The drinking water equivalent level for dieldrin is 2 μg per L and the draft drinking water equivalent level for aldrin is 0.9 μg per L. On the basis of estimates of carcinogenic potential, a level of 0.02 μg per L of drinking water corresponds to a cancer risk level of 1×10^{-5}.

In 1980, the EPA established a National Ambient Water Quality Criterion of 0.074 μg of aldrin per L and of 0.071 μg of dieldrin per L for human health (84). This was founded on a 1:1,000,000 risk for cancer and was based on estimates for the ingestion of contaminated water and contaminated organisms in the water. The International Agency for Research on Cancer in 1987 classified aldrin and dieldrin in group 3, as a possible human carcinogen, on the basis of limited evidence in animals as human data are lacking (84). Aldrin is also listed as a probable human carcinogen on the weight of experimental evidence under the EPA Proposed Guidelines for Carcinogen Risk

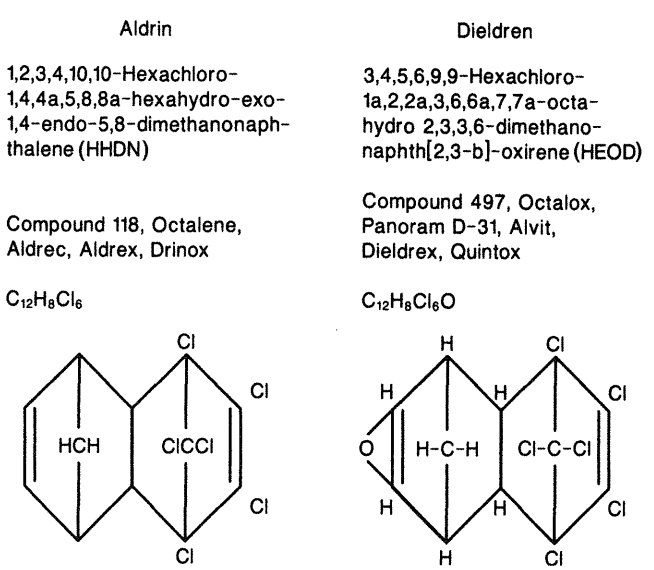


Figure 99-11. Chemical structures of aldrin and dieldrin. (From ref. 84, with permission.)

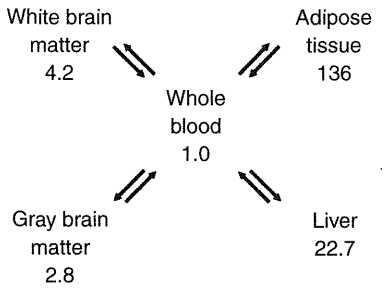


Figure 99-12. Relationship of the distribution of dieldrin among blood and certain tissues in humans. (From ref. 21, with permission.)

Assessment released in 1984 (84). Evidence of the carcinogenicity of this substance from animal studies appears sufficient, although human studies have been inadequate. Dieldrin also is classified by the EPA as a probable human carcinogen, with sufficient evidence in animals and inadequate evidence in humans.

ENDRIN

Endrin, a stereoisomer of dieldrin, is a cyclodiene organochlorine pesticide with a formula of $C_{12}H_8Cl_6O$ and a molecular weight of 380.93. The technical product is approximately 85% endrin. Endrin, a white, crystalline solid introduced in 1951, is one of the most toxic of the cyclodiene compounds and produces dizziness, seizures, tremors, and confusion in acute toxic-

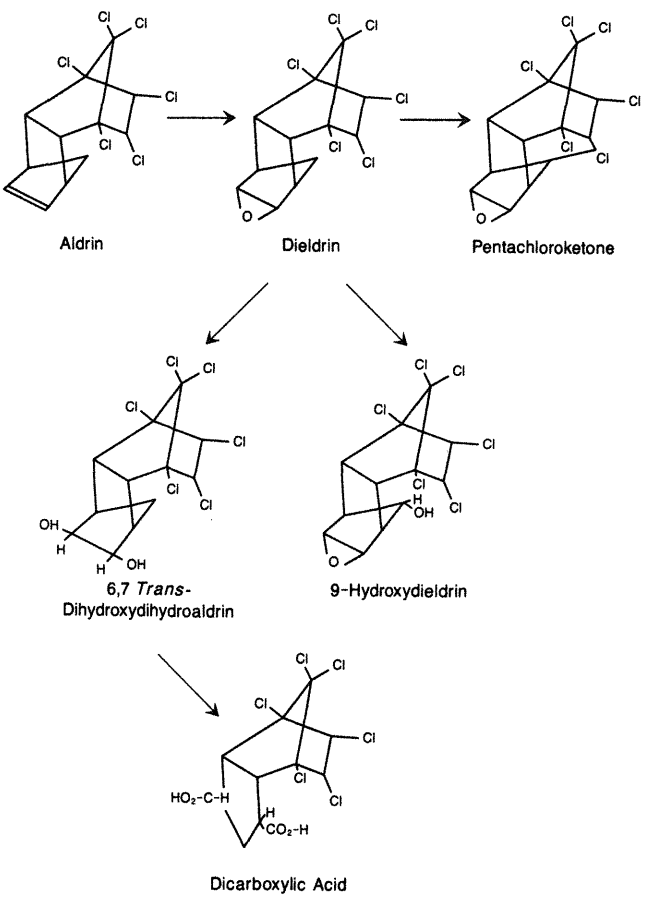


Figure 99-13. Metabolism of aldrin and dieldrin. (From ref. 84, with permission.)

ity (92). Toxicity has also been associated with hyperthermia and decerebrate rigidity (46).

Endrin is rapidly metabolized in animals and humans and does not accumulate in human tissues after exposure. In animals, endrin is metabolized to water-soluble compounds and is excreted mainly in the feces. The threshold limit value of endrin is 0.1 mg per cubic meter, which was set to prevent systemic toxicity. The short-term exposure limit for endrin is 0.3 mg per cubic meter. Endrin is toxic to animals in oral overdose studies (90). The half-life of endrin is 2 to 6 days. Endrin and a metabolite, anti-12-hydroxyendrin, can be found in the stool of humans. Anti-12-hydroxyendrin can also be found in the urine of occupationally exposed individuals and can be used as a biological monitoring marker. Endrin has not been found to be carcinogenic or teratogenic or to cause reproductive effects in animals studied.

An outbreak of endrin poisoning from contaminated food in Pakistan in 1984 resulted in a 10% mortality rate from seizures (92). Seizures occurred within 2 hours after the contaminated food was ingested and, in some instances, status epilepticus occurred. Endrin serum concentrations in these individuals ranged from 1.5 to 49.4 ppb. Nonfatally affected patients recovered within a few days.

ISOBENZAN

Isobenzan (telodrin) is a cyclodiene compound with a formula of $C_9H_4Cl_8O$ and a molecular weight of 411.79 (46). The technical product is greater than 95% isobenzan. The compound, a light brown crystalline powder, is soluble in other organic solvents although insoluble in water. It was produced between the years 1958 to 1965 and had limited agricultural use (90). Little is known about the human toxicology of isobenzan. Available human data indicate that this substance's clinical toxicologic effects are related to CNS stimulation and seizures, as is true of other organochlorine compounds. Other symptoms associated with isobenzan include headaches, dizziness, irritability, paresthesias, and drowsiness (46).

Exposure of the general population to isobenzan has been limited. Clinical cases of seizures have been reported after serious exposures (90). A mean blood concentration of 0.023 ng of isobenzan per mL (range, 1.017 to 0.030 ng per mL) was found in nine workers who experienced intoxication.

Isobenzan is well absorbed by the gastrointestinal tract. It accumulates in adipose tissue and has one identified metabolite, telodrin lactane. Isobenzan also crosses the placenta. Its biological half-life is reported to be 2.8 years (90).

ENDOSULFAN

Endosulfan (see Fig. 99-8) is a mixture of two isomers, α- and β-endosulfan. Introduced in 1956, it has a formula of $C_9H_6Cl_6O_3S$ and a molecular weight of 406.95 (46). Its common names include *benzoepin, cyclodane, malix, thimul, thiosulfan,* and *thionex.* The α isomer constitutes 70% of the mixture and the β isomer approximately 30% (46). Endosulfan is a brownish, crystalline powder that smells like sulfur dioxide. It is soluble in organic solvents and insoluble in water.

The primary source of human exposure is through residues on food and on tobacco (93). Endosulfan contamination is not widespread in the environment. The β isomer of endosulfan has a higher affinity for soil and thus a longer half-life in the environment. The soil half-life of the α isomer is 60 days, whereas the half-life of the β isomer is 900 days (93). Both isomers resist photodegradation.

Clinical toxicologic effects have been described in cases of ingestion and occupational exposures. After ingestion of endosulfan, symptomatology begins within a few hours, and death has been reported within 2 hours (93,94). The clinical syndrome consists of vomiting, agitation, pulmonary edema, seizures, dyspnea, and cyanosis (94). Occupational exposure has been associated with anxiety, headaches, dizziness, stupor, confusion, and seizures.

CHLORDECONE, KELEVAN, AND MIREX

The chemical formula for mirex is $C_{10}Cl_{12}$, which has a molecular weight of 545.51 (Fig. 99-14) (95). Mirex is a white, crystalline solid that melts at 485°C. It is insoluble in water but soluble in benzene, carbon tetrachloride, and xylene. It is a very stable compound in the environment and bioaccumulates up the food chain.

Introduced in 1955, mirex once was used extensively for the control of fire ants in the southern United States (95). The EPA began phasing out the use of mirex for this purpose in the mid-1970s. The substance has been detected in fat samples collected in geographic areas known to have been treated with the chemical (46). Mirex has also been used as a fire retardant, under the name *dechlorane,* in plastics, rubber, paint, paper, and electrical products (95). Most of the mirex produced between 1959 and 1975 was used in the United States.

Human environmental exposures to mirex occurred from food ingestion and from contaminated soil. Mirex is excreted in human breast milk. Adipose tissue concentrations ranging from 0.16 to 6.0 mg per kg of fat have been found in autopsy samples from persons residing in the southeastern United States (95). The mean blood concentration of mirex in pregnant women in Mississippi was 0.5 μg per L. Mirex resists metabolism in humans and animals. Cases of human poisoning have not been reported. Mirex was not fetotoxic in animal studies and was not a teratogen. It crosses the placenta in animal studies and is carcinogenic in mice and rats.

Chlordecone (Kepone) is a tan to white solid having a chemical formula of $C_{10}Cl_{10}O$ and a molecular weight of 490.61 (Fig. 99-15) (46). It is soluble in acetone and less soluble in benzene and similar petroleum solvents. Technical-grade chlordecone is 88% to 99% pure, with minor contamination by hexachlorocyclopentadiene (96).

Chlordecone production began in 1965 but was terminated in July 1975 after its manufacturing plant had been in operation for 16 months (46). No effective occupational control of chlordecone exposure had been determined, and workers were being excessively contaminated. The clinical syndrome of chlordecone toxicity was insidious, and its onset involved some weight loss, tremor of the muscles of the upper extremities, muscle weakness, abnormal eye movements, slurring of speech, mental status changes, chest pain, arthralgias, dermatitis, and abnormal liver function tests (46,97). After manufacturing of chlordecone was initiated, blood levels of this substance in residents of the community in close proximity to the plant were found to be as

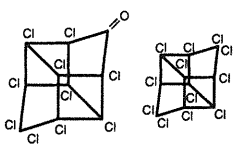


Figure 99-14. Chlordecone and mirex.

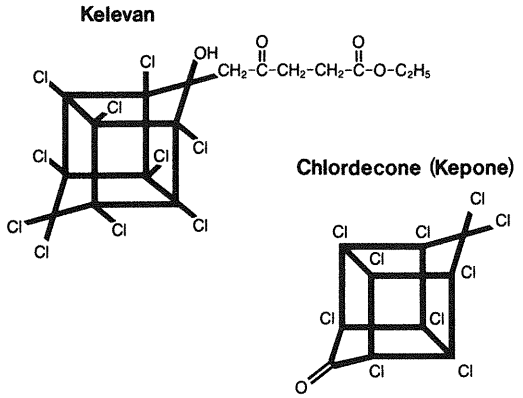


Figure 99-15. Kelevan and chlordecone (Kepone).

high as 0.033 ppm (46,97,98). Chlordecone is a known neurotoxin and can produce peripheral neuropathy.

Chlordecone is environmentally very stable. Human exposure to chlordecone has occurred via food residues owing to its bioaccumulation. It is excreted in human breast milk. Occupational exposure occurred in its production plant in 1975, with large amounts of chlordane contaminating the surrounding environment. Chlordecone blood concentrations in workers exhibiting health effects averaged 2.53 mg per L (98). Those exposed workers who were not ill had average blood concentrations of 0.60 mg per L. Chlordecone's half-life ranges from 63 to 148 days. Cholestyramine was found to enhance gastrointestinal elimination of this toxin in exposed individuals.

Chlordecone and kelevan are chemically related pesticides. Kelevan (Despirol, Elevat), a condensation product of chlordecone and ethyl levulinate (96), is a solid white powder with a molecular weight of 634.79 (see Fig. 99-15). Technical-grade kelevan is 94% to 98% pure, with minor contamination by chlordecone. Once absorbed by animals or humans, it is metabolized to chlordecone.

TOXAPHENE

Toxaphene, introduced in 1948, is a mixture of chlorinated bicyclic terpenes (chlorinated camphenes) containing 67% to 69% chlorine. Toxaphene is a yellow, waxy solid with a chemical formula of $C_{10}H_{10}Cl_{18}$ (Fig. 99-16). It is well absorbed dermally and via the gastrointestinal tract. Environmentally, toxaphene vaporizes from soil but can be adsorbed to soil with a half-life of up to 12 years. Toxaphene bioaccumulates in aquatic organisms (99). It is soluble in organic solvents but insoluble in water. In the environment, toxaphene is photodegraded by ultraviolet light and, in soil, is degraded by the action of bacteria (99).

Clinical toxicity from toxaphene occurs from occupational exposures and ingestion of the product. Cases of poisoning have manifested as seizures and respiratory depression (96). In occupational settings, inhalation of the product has been associated with decreased pulmonary function and dyspnea. Toxaphene exposure has resulted in death in some instances. Symptoms occur within 30 minutes to a few hours after ingestion. The main clinical manifestations of toxicity are convulsions, hyperthermia, tremors, and confusion (46).

Toxaphene is considered to be a potential human carcinogen, whereas in mice and rats it is a proved carcinogen. The threshold limit value is 0.5 mg per cubic meter, with a notation warning against dermal contact.

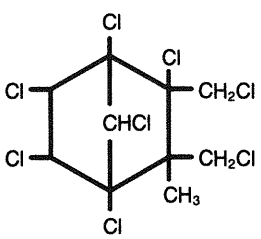


Figure 99-16. Toxaphene.

DICOFOL AND METHOXYCHLOR

Dicofol is a chlorinated hydrocarbon pesticide used mainly as an acaricide on grain crops (Fig. 99-17). The chemical's generic name is 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethanol, and it is marketed as Kelthane, Acarin, and Mitigan. Dicofol has a molecular weight of 370.5 and is a white solid with a melting point of 79°C. The technical product is a light brown, viscous oil with a density of 1.45. Dicofol is insoluble in water but soluble in most aliphatic and aromatic solvents. It is highly lipophilic. This chemical is hydrolyzed by alkali to dichlorobenzophenone and chloroform (46).

Dicofol is manufactured by the chlorination of bis(4-chlorophenyl)carbinol. It is registered for use on vegetables, fruits, and a variety of field crops and is used widely in nurseries and greenhouses. It is relatively stable, although when heated or in contact with strong acids, it decomposes to hydrogen chloride, the vapors of which may cause acute health problems. The chemical is also structurally similar to DDT (46).

Dicofol is stable in the environment after application. Residues decrease rapidly, but trace amounts of the chemical can be found in soil up to a year after application. Human toxicity information is limited, as human exposures have demonstrated very little clinical toxicity. Animals given toxic doses have symptoms referable to CNS stimulation.

Methoxychlor [1,1,1-trichloro-2,2-bis(*p*-methoxyphenyl) ethane], having the chemical formula $C_{16}H_{15}C_{13}O_2$, has a molecular weight of 345.65 (see Fig. 99-17) (46). It is marketed as Marlate. The compound is a clear crystal in its pure state and a gray powder in its technical state (46). It was first introduced in 1945 as a wettable powder, dust, and concentrate. Like dicofol, methoxychlor has a low order of animal toxicity but, in sufficient doses, can produce seizures. Human volunteers ingesting up to 2 mg per kg per day for 8 weeks showed no health effects. In humans, dermatitis may occur from contact with either dicofol or methoxychlor. No cases of systemic intoxication from methoxychlor have been reported in humans.

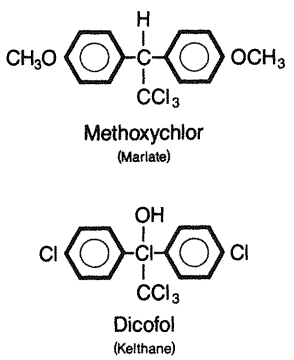


Figure 99-17. Methoxychlor (Marlate) and dicofol (Kelthane).

ORGANOCHLORINE PESTICIDE CONCENTRATIONS IN HUMAN TISSUES

The period from the 1950s to 1970s witnessed heavy use of many organochlorine pesticides. The concentration of DDT in human adipose tissue during this time averaged approximately 5 ppm (24). At the same time, the adipose concentrations of DDT and DDE in combination averaged 15 ppm (24). After the ban on DDT was issued, a gradual reduction of adipose tissue concentrations of both DDT and DDE occurred. By the late 1960s, the average concentration ranged from 1 to 2 ppm of DDT and approximately 9 ppm for all DDT- and DDE-related pesticides (24).

Because pesticides had been used extensively throughout southern Florida, the presence of organochlorine pesticides in the serum of 59 female residents of Dade County, Florida, was surveyed and compared with pesticide content in the drinking water (24). Ten organochlorine pesticides and their metabolites were analyzed in this monitoring program: HCH, β-HCH, heptachlor, oxychlordane, heptachlor epoxide, *trans*-nonachlor, DDE, dieldrin, *o,p'*-DDT, and *p,p'*-DDT. In the subjects, HCH, β-HCH, *p,p'*-DDE, dieldrin, and *p,p'*-DDT were detected. Serum concentrations of most of these organochlorine compounds were in the parts-per-billion range (see Table 99-6). For all five compounds detected in the subject pool, each was undetectable in at least some subjects and ranged to various maximum concentrations as follows: HCH to 1.1 ppb, β-HCH to 5.8 ppb, DDE to 68.4 ppb, dieldrin to 10 ppb, and DDT to 5.5 ppb. When subjects were compared with individuals who consumed well water as opposed to city water, no significant difference in serum levels of organochlorine pesticide metabolites was noted (see Table 99-7) (24).

Organochlorine pesticide residues were studied in human adipose tissue in the United Kingdom between the years 1976 and 1977. These samples were taken from adipose tissue during autopsies on 236 individuals older than 5 years (26). The ranges of these compounds in adipose tissue were as follows: β-HCH ranged from undetectable to 1.2 mg per kg; heptachlor epoxide, from lower limits of detection to 0.12 mg per kg; dieldrin, from undetectable to 0.49 mg per kg; DDE, from 0.03 to 15 mg per kg; DDT, from 0.04 to 17 mg per kg; and total chlorinated biphenyls, from undetectable to 10 mg per kg (26). The concentrations of these organochlorine compounds were similar to those observed in other studies carried out in the 1960s. Results of the 1976 and 1977 study in the 236 subjects and the organochlorine pesticide residues found in human fat are summarized in Table 99-8.

Other studies performed in the 1960s in autopsy samples showed mean concentrations of dieldrin of 0.0061 ppm in the white matter of the brain, gray matter concentrations of 0.0047 ppm, liver concentrations of 0.03 ppm, and fatty tissue concentrations of 0.17 ppm (21). Figures 99-4 and 99-12 depict the distribution of DDT and dieldrin, respectively, in blood and other tissues in humans, as prepared from this study (21). Dieldrin has a greater tendency to be stored in liver and brain tissue relative to adipose tissue, as compared with DDT-related compounds. Concentrations of organochlorine pesticides typically found in adipose tissue, liver, and brain tissue are shown in Tables 99-9 and 99-10 (21).

Assays for oxychlordane metabolites were conducted in adipose tissue samples collected from postmortem examination and surgical procedures in the 1960s and 1970s (80). In 27 specimens, oxychlordane concentrations ranged from 0.03 to 0.40 ppm (80).

Isomers and metabolites of a variety of organochlorines—including *p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE, β-HCH, dieldrin, and heptachlor epoxide—have been found in persons who have had no occupational exposure. Serum pesticide concentrations in the parts-per-billion range were detected by Morgan and Lin (13) in a population studied between 1967 and 1973. These concentrations were compared with various clinical chemistries in more than 2,600 subjects (13). DDT and DDE serum concentrations were found to be higher in those subjects living in the southern United States. No evidence was found of abnormal hematologic studies (13).

The presence of organochlorine pesticide residue concentrations in human breast milk was studied in western Australia from 1979 to 1980 (see Table 99-11) (29). In this study, 267 samples of human breast milk were supplied by 140 donors from urban and rural areas and were analyzed for organochlorine pesticides. The organochlorine pesticides detected were aldrin, lindane, HCH, dieldrin, and DDT. Aldrin and lindane were found in trace amounts, whereas DDT-related compounds measuring 0.078 to 0.046 ppm were found. The levels of HCH ranged from 0.025 to 0.008 ppm and of dieldrin ranged from 0.005 to 0.009 ppm. A comparison of this study's results with those of a previous study conducted from 1970 to 1971 showed that, except for dieldrin concentrations (which were increasing), organochlorine pesticide concentrations in human breast milk were decreasing. The Australian government imposed controls on the use of organochlorine pesticides in western Australia in 1971. During the years 1978 to 1979, a decrease in pesticide concentrations was documented in most countries in which limitations had been placed on the use and application of chlorinated pesticides in the environment. Endeavors to correlate the pesticide concentrations in human tissues and the use of pesticides or the exposure to pesticides have been unsuccessful. The results of the 1979 to 1980 Australian study demonstrate that restricting the use of organochlorine pesticides reduces the human tissue content of these pesticides. Individual information on samples from the urban donors of human breast milk in this 1979 to 1980 study are shown in Table 99-12 (29).

Indoor air concentrations of organochloride pesticides, particularly chlordane, contribute to the total body burden of the residues found in humans (47). Sampling and analysis of indoor air for chlorinated pesticides has revealed low concentrations of chlordane and nonachlor (44,45). Concentrations of γ-chlordane, α-chlordane, and *trans*-nonachlor were found in the various homes sampled. In one study, 12 homes were sampled from November 1985 to October 1986 (45). The outdoor air concentrations of chlordane and *trans*-nonachlor were very low, the average outdoor air concentration of γ-chlordane being 0.5 ng per cubic meter (45). In contrast, the indoor air concentration of γ-chlordane ranged from 29 ng per cubic meter and averaged seven times higher than the outdoor air concentration. Interestingly, in this study, homes in which the windows were closed versus those in which windows were open did not show substantially different concentrations of indoor air (45). These homes had been treated with subsurface slab injection of chlordane for termites. Large cracks in the foundation probably were responsible for the high concentration of chlordane in indoor air (45).

Another 1985 study correlated home treatment with organochlorine pesticides to the presence of such pesticides in human breast milk (23). Fourteen subjects supplied breast milk in this study and answered questions regarding treatment of their houses with organochlorine pesticides. Most houses had been treated with applications of heptachlor and aldrin. This study concluded that a connection existed between the concentrations of pesticides and other metabolites in human breast milk and the use of such pesticides for spraying inside or outside the home (23). The mean concentrations of the organochlorine pesticides found in human breast milk from these donors are shown in Table 99-13. The subjects were chosen from among those whose houses had been recently treated with organochlorine pesticides. Table 99-14 indicates the concentrations of dieldrin in breast milk donors and the decline in dieldrin concentrations months after

the application of dieldrin in the home environment (23). Table 99-15 shows chlordane concentrations in one of the subjects (expressed as nanograms per gram of whole breast milk) relative to the time of chlordane treatment in the subject's house. Table 99-16 shows concentrations of HCH, heptachlor, and heptachlor epoxide relative to treatment times in the home environment (23). These data demonstrate that spraying of homes with organochlorine pesticides is related to increased concentrations of pesticides in human breast milk (23).

The occupational permissible exposure limit of chlordane is 500 μg per cubic meter for a 40-hour work week. The NAS in 1979 considered this concentration to be unacceptable in the home environment because of continuous exposure 24 hours per day and recommended a concentration of chlordane of 5 μg per cubic meter as acceptable in the home environment (44). The NAS also recommended a concentration of 2 μg per cubic meter for heptachlor in homes (44).

Chlordane was measured in 474 family housing units at seven U.S. Air Force installations from the 1980 to 1981 (44). Chlordane had been used in these homes for treatment of termites by subsurface slab injection or exterior application, and 86% of these homes had chlordane air concentrations of less than 3.5 μg per cubic meter, whereas 12% had concentrations between 3.5 and 6.5 μg per cubic meter, and 2% had indoor air concentrations exceeding 6.5 μg per cubic meter (44).

REFERENCES

1. Gant DB, Eldefrawi ME, Eldefrawi AT. Cyclodiene insecticides inhibit GABA receptor-regulated chloride transport. *Toxicol Appl Pharmacol* 1987;88:313–321.
2. Lawrence LJ, Casida JE. Interactions of lindane, toxaphene and cyclodienes with brain-specific t-butylbicyclophosphorothionate receptor. *Life Sci* 1984;35:171–178.
3. Agency for Toxic Substances and Disease Registry. *Toxicological profile for p,p'-DDT, p,p'-DDE, p,p'-DDD.* Atlanta: US Department of Health and Human Services, Public Health Service, ATSDR, December 1989.
4. Coulston F. Reconsideration of the dilemma of DDT for the establishment of an acceptable daily intake. *Regul Toxicol Pharmacol* 1985;5:332–383.
5. Saxena MC, Siddiqui MKJ, Seth TD, Krishna Murti CR. Organochlorine pesticides in specimens from women undergoing spontaneous abortion, premature or full-term delivery. *J Anal Toxicol* 1981;5:6–9.
6. Mattison DR. Pesticides in human breast milk: changing patterns and estimates of cancer risk. Presented at the thirty-eighth annual meeting, San Antonio, TX, March 20–23, 1991.
7. Curtie RA, Kadis VW, Breitkreitz WE, Cunningham GB, Bruns GW. Pesticide residues in human milk, Alberta, Canada—1966–70, 1977–78. *Pestic Monit J* 1979;133:52–55.
8. Griffith FD, Blanke RV. Pesticides in people: blood organochlorine pesticide levels in Virginia residents. *Pestic Monit J* 1975;8:219–224.
9. Polishuk ZW, Ron M, Wassermann M, Cucos S, Wassermann D, Lemesch C. Pesticides in people: organochlorine compounds in human blood plasma and milk. *Pestic Monit J* 1977;10:121–129.
10. Radomski JL, Deichmann WB, Rey AA, Merkin T. Human pesticide blood levels as a measure of body burden and pesticide exposure. *Toxicol Appl Pharmacol* 1971;20:175–185.
11. Radomski JL, Astolfi E, Deichmann WB, Rey AA. Blood levels of organochlorine pesticides in Argentina: occupationally and nonoccupationally exposed adults, children and newborn infants. *Toxicol Appl Pharmacol* 1971;20:186–193.
12. Dale WE, Curley A, Hayes WJ Jr. Determination of chlorinated insecticides in human blood. *Ind Med Surg* 1967;36(4):275–280.
13. Morgan DP, Lin LI. Blood organochlorine pesticide concentrations, clinical hematology and biochemistry in workers occupationally exposed to pesticides. *Arch Environ Contam Toxicol* 1978;7:423–447.
14. Hunter DJ, Hankinson SE, Laden F, et al. Plasma organochlorine levels and the risk of breast cancer. *N Engl J Med* 1997;337(18):1253–1258.
15. Krieger N, Wolff MS, Hiatt RA, et al. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. *J Natl Cancer Inst* 1994;86:589–599.
16. Safe SH. Xenoestrogens and breast cancer. *N Engl J Med* 1997;337(18):1303–1304.
17. Baumann K, Angerer J, Heinrich R, Lehnert G. Occupational exposure to hexachlorocyclohexane, part I. *Int Arch Occup Environ Health* 1980;47:119–127.
18. Agency for Toxic Substances and Disease Registry. *Toxicological profile for hexachlorocyclohexane.* Atlanta: US Department of Health and Human Services, Public Health Service, ATSDR, December 1989.
19. Baumann K, Behling K, Brassow HL, Stapel K. Occupational exposure to hexachlorocyclohexane, part 3. *Int Arch Occup Environ Health* 1981;48:165–172.
20. Nigam SK, Karnik AB, Majumder SK, et al. Serum hexachlorocyclohexane residues in workers engaged at a HCH manufacturing plant. *Int Arch Occup Environ Health* 1986;57:315–320.
21. de Vlieger M, Robinson J, Crabtree AN, van Dijk MC. The organochlorine insecticide content of human tissues. *Arch Environ Health* 1968;17:759–767.
22. Pines A, Cucos S, Ever-Hadani P, Ron M. Some organochlorine insecticide and polychlorinated biphenyl blood residues in infertile males in the general Israeli population of the middle 1980s. *Arch Environ Contam Toxicol* 1987;16:587–597.
23. Stacey CI, Tatum T. House treatment with organochlorine pesticides and their levels in human milk—Perth, Western Australia. *Bull Environ Contam Toxicol* 1985;35:202–208.
24. Barquet A, Morgade C, Pfaffenberger CD. Determination of organochlorine pesticides and metabolites in drinking water, human blood serum, and adipose tissue. *J Toxicol Environ Health* 1981;7:469–479.
25. Dale WE, Curley A, Cueto C Jr. Hexane extractable chlorinated insecticides in human blood. *Life Sci* 1966;5:47–54.
26. Abbott DC, Collins GB, Goulding R, Hoodless RA. Organochlorine pesticide residues in human fat in the United Kingdom 1976–7. *BMJ* 1981;283:1425–1428.
27. Kashyap SK. Health surveillance and biological monitoring of pesticide formulators in India. *Toxicol Lett* 1986;33:107–114.
28. Takahashi W, Saidin D, Takei G, Wong L. Organochloride pesticide residues in human milk in Hawaii, 1979–80. *Bull Environ Contam Toxicol* 1981;27:506–511.
29. Stacey CI, Perriman WS, Whitney S. Organochlorine pesticide residue levels in human milk: Western Australia, 1979–1980. *Arch Environ Health* 1985;40:102–108.
30. Brassow HL, Baumann K, Lehnert G. Occupational exposure to hexachlorocyclohexane, part 2. *Int Arch Occup Environ Health* 1981;48:81–87.
31. Milby TH, Samuels AJ, Ottoboni F. Human exposure to lindane: blood lindane levels as a function of exposure. *J Occup Med* 1968;10:584–587.
32. Ramachandran M, Banerjee M, Grover A, Zaidi S. DDT and HCH residues in the body fat and blood samples from some Delhi hospitals. *Ind J Med Res* 1984;80:590–593.
33. Davies JE, Dedhia HV, Morgade C, Barquet A, Maibach HI. Lindane poisonings. *Arch Dermatol* 1983;119:142–144.
34. Saxena MC, Siddiqui MKJ, Bhargava AK, Krishna Murti CR, Kutty D. Placental transfer of pesticides in humans. *Arch Toxicol* 1981;48:127–134.
35. Saxena MC, Siddiqui MKJ. A comparison of organochlorine insecticide contents in specimens of maternal blood, placenta, and umbilical cord blood from stillborn and live-born cases. *J Toxicol Environ Health* 1983;11:71–79.
36. Roncevic N, Pavkov S, Galetin-Smith R, et al. Serum concentrations of organochlorine compounds during pregnancy and the newborn. *Bull Environ Contam Toxicol* 1987;38:117–124.
37. Morgan DP, Stockdale EM, Roberts RJ, Walter AW. Anemia associated with exposure to lindane. *Arch Environ Health* 1980;35:307–310.
38. Berry DH, Brewster MA, Watson R, Neuberg RW. Untoward effects associated with lindane abuse [Letter]. *Am J Dis Child* 1987;14:125.
39. Jaeger U, Podczeck A, Haubenstock A, et al. Acute oral poisoning with lindane-solvent mixtures. *Vet Hum Toxicol* 1984;26:11–14.
40. Pramanik AK, Hansen RC. Transcutaneous gamma benzene hexachloride absorption and toxicity in infants and children. *Arch Dermatol* 1979;115:1224–1225.
41. Feldmann RJ, Maibach HI. Percutaneous penetration of some pesticides and herbicides in man. *Toxicol Appl Pharmacol* 1974;28:126–132.
42. Joy RM, Albertson TE. Lindane and limbic system excitability. *Neurol Toxicol* 1985;2:193–214.
43. Agency for Toxic Substances and Disease Registry. *Toxicological profile for chlordane.* Atlanta: US Department of Health and Human Services, Public Health Service, ATSDR, 1994.
44. Wright CG, Leidy RB. Chlordane and heptachlor in the ambient air of houses treated for termites. *Bull Environ Contam Toxicol* 1982;28:617–623.
45. Anderson DJ, Hites RA. Chlorinated pesticides in indoor air. *Environ Sci Technol* 1988;22:717–720.
46. Hayes WJ. Chlorinated hydrocarbon insecticides. In: *Pesticides studied in man.* Baltimore: Williams & Wilkins, 1982:172–283.
47. Mussalo-Rauhamaa H. Partitioning and levels of neutral organochlorine compounds in human serum blood cells and adipose tissue and liver tissue. *Sci Total Environ* 1991;103:159–175.
48. Barnett R, D'Ercole A, Cain J, et al. Organochlorine pesticide residues in human milk samples from women living in northwest and northeast Mississippi, 1973–1975. *Pestic Monit J* 1979;13:47–51.
49. Mussalo-Rauhamaa H, Pyysalo H, Antervo K. Relation between the content of organochlorine compounds in Finnish human milk and characteristics of the mothers. *J Toxicol Environ Health* 1988;25:1–19.
50. Sasaki K, Kawasaky Y, Sekita K et al. Disposition of β-hexachlorocyclohexane, *p,p*-DDT and *trans*-chlordane administered subcutaneously to monkeys (*Macaca fascicularis*). *Arch Environ Contam Toxicol* 1992;22:25–29.
51. Wariishi M, Nishiyama K. Observations on the progress of chlordane contamination in humans by blood and sebum analysis. *Arch Environ Contam Toxicol* 1989;18:501–507.
52. Taguchi S, Yakushiji T. Influence of termite treatment in the home on chlordane concentration in human milk. *Arch Environ Contam Toxicol* 1988;17:65–72.

53. Oehme M. Dispersion and transport paths of toxic persistent organochlorines to the arctic levels and consequences. *Sci Total Environ* 1991;106:43–53.
54. Beeman R, Matsumara F. Metabolism of *cis*- and *trans*-chlordane by soil microorganism. *J Agric Food Chem* 1981;29:84–89.
55. Wallace L. Comparison of risk from outdoor and indoor exposure to toxic chemicals. *Environ Health Perspect* 1991;95:7–13.
56. Anderson D, Hites R. Indoor air: spacial variations of chlorinated pesticides. *Atmosphere Environ* 1989;23:2063–2066.
57. Fensk ER, Sternbach T. Indoor air levels of chlordane in residences in New Jersey. *Bull Environ Contam Toxicol* 1987;39:903–910.
58. Barnes R. Poisoning by the insecticide chlordane. *Med J Aust* 1967;1(19):972–973.
59. Aldrich FD, Holmes JH. Acute chlordane intoxication in a child. *Arch Environ Health* 1969;19:129–132.
60. Derbes VH, Dent JH, Forrest WW, Johnson MF. Fatal chlordane poisoning. Council on Pharmacy and Chemistry. *JAMA* 1955;158:1367–1369.
61. Dadey JL, Kammer AG. Chlordane intoxication. *JAMA* 1953;153:723–726.
62. Kutz FW, Strassman SC, Sperling JF, Cook BT. A fatal chlordane poisoning. *J Toxicol Clin Toxicol* 1983;20:167–174.
63. Wang HH, MacMahon B. Mortality of pesticide applicators. *J Occup Med* 1979;21:741–744.
64. Wang HH, MacMahon B. Mortality of workers employed in the manufacture of chlordane and heptachlor. *J Occup Med* 1979;21:745–748.
65. Ditraglia D, Brown DP, Namekata T, Iverson N. Mortality study of workers employed at organochlorine pesticide manufacturing plants. *Scand J Work Environ Health* 1981;7:140–146.
66. Blair A, Grauman DJ, Lubin JH, Fraumeni JF. Lung cancer and other causes of death among licensed pesticide applicators. *J Natl Cancer Inst* 1983;71:31–37.
67. Furie B, Trubowitz S. Insecticides and blood dyscrasias: chlordane exposure and self-limited refractory megaloblastic anemia. *JAMA* 1976;235:1720–1722.
68. Mendeloff AI, Smith DE. Clinicopathologic conference: exposure to insecticides, bone marrow failure, gastrointestinal bleeding, and uncontrollable infections. *Am J Med* 1955;(August):274–284.
69. Epstein S, Ozonoff D. Leukemias and blood dyscrasias following exposure to chlordane and heptachlor. *Teratog Carcinog Mutagen* 1987;7:527–540.
70. Fishbein W, White J, Isaacs H. Survey of workers exposed to chlordane. *Ind Med Surg* 1964;10:726–727.
71. Khasawina A, Hardy C, Clark G. Comparative inhalation toxicity of technical chlordane in rats and monkeys. *J Toxicol Environ Health* 1989;28:327–347.
72. McConnachie P, Zahalsky A. Immune alterations in humans exposed to the termiticide technical chlordane. *Arch Environ Health* 1992;47:295–301.
73. Barnett J, Holcomb D, Menna J, et al. The effect of prenatal chlordane exposure on specific anti-influenza cell-mediated immunity. *Toxicol Lett* 1985;25:229–238.
74. Barnett J, Soderberg L, Menna J. The effect of prenatal chlordane exposure on delayed hypersensitivity response of balb/c-mice. *Toxicol Lett* 1985;25:173–183.
75. Chuang L, Liu Y, Killam K, et al. Modulation by the insecticides heptachlor and chlordane of the cell mediated immune proliferative responses of the rhesus monkeys. *In Vivo* 1992;6:29–32.
76. Brown D. Mortality of workers employed at organochlorine pesticide manufacturing plants—an update. *Scand J Work Environ Health* 1992;18:155–161.
77. Cantor K, Blair A, Everett G, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992;52:2447–2455.
78. Menconi S, Clark J, Langenberg P, et al. A preliminary study of potential human health effects in private residences following chlordane applications for termite control. *Arch Environ Health* 1988;43:349–352.
79. Curley A, Garretson L. Acute chlordane poisoning: clinical and chemical studies. *Arch Environ Health* 1969;18:211–215.
80. Biros FJ, Enos HF. Oxychlordane residues in human adipose tissue. *Bull Environ Contam Toxicol* 1973;10:257–260.
81. Olanoff L, Bristow W, Cololough J. Acute chlordane intoxication. *J Toxicol Clin Toxicol* 1983;20:291–306.
82. Garretson L, Guzelian PS, Blanke R. Subacute chlordane poisoning. *J Toxicol Clin Toxicol* 1984;22:565–571.
83. Hunter CG, Robinson J. Pharmacodynamics of dieldrin (HEOD), part 1. *Arch Environ Health* 1967;15:614–626.
84. Agency for Toxic Substances and Disease Registry. *Toxicological profile for aldrin/dieldrin.* Atlanta: US Department of Health and Human Services, Public Health Service, ATSDR, May 1989.
85. Ackerman L. Humans—overview of human exposure to dieldrin residues in the environment and current trends of residue levels in tissue. *Pestic Monit J* 1980;14:64–69.
86. Hunter CG, Robinson J. Pharmacodynamics of dieldrin (HEOD): ingestion by human subjects for 18 to 24 months and postexposure for eight months. *Arch Environ Health* 1969;18:12–21.
87. Jager K. *Aldrin, dieldrin, endrin and telodrin—an epidemiological and toxicological study of long-term occupational exposure.* New York: Elsevier Science, 1970:121–131.
88. Patel TB, Hy B, Rao VN. Dieldrin poisoning in man: a report of 20 cases observed in Bombay State. *BMJ* 1958;19:919–922.
89. Bloomquist JR, Soderlund DM. Neurotoxic insecticides inhibit GABA-dependent chloride uptake by mouse brain vesicles. *Biochem Biophys Res Commun* 1985;133:37–43.
90. Jong de G. Long-term health effects of aldrin and dieldrin. *Toxicol Lett* 1991;[Suppl]:1–206.
91. Ribbens PH. Mortality study of industrial workers exposed to aldrin, dieldrin and endrin. *Int Arch Occup Environ Health* 1985;56:75–79.
92. Rowley D, Rab M, Hardjotanojo W, Liddie J. Convulsions caused by endrin poisoning in Pakistan. *Pediatrics* 1987;79(6):928–934.
93. World Health Organization. *Endosulfan: environmental health criteria 40.* Geneva: World Health Organization, 1984.
94. Shemesh Y, Bourvine A, Gold D, Bracha P. Survival after acute endosulfan intoxication. *J Toxicol Clin Toxicol* 1988;26:265–268.
95. World Health Organization. *Mirex: environmental health criteria 44.* Geneva: World Health Organization, 1984.
96. World Health Organization. *Kelevan: environmental health criteria 66.* Geneva: World Health Organization, 1986.
97. Taylor J. Neurological manifestations in humans exposed to chlordecone: follow-up of results. *Neurotoxicology* 1985;6:231–236.
98. World Health Organization. *Chlordecone: environmental health criteria 43.* Geneva: World Health Organization, 1984.
99. World Health Organization. *Camphechlor: environmental health criteria 45.* Geneva: World Health Organization, 1984.

CHAPTER 100
Fumigants

John A. Lowe and John B. Sullivan, Jr.

Fumigants are pesticides that exist as gases or vapors at specified temperatures and pressures (generally room temperature and ambient pressures). Fumigation is used to control a variety of pests, including insects in stored grain products, wood-destroying insects, and nematodes or fungi in soil (1). The advantages of fumigation are the speed with which it works, its ability to reach places that sprays cannot reach (i.e., within building materials or deep within soil), and the possible lower cost as compared to that of repeated spraying. Disadvantages are the need for specialized equipment and the requirement of training to use fumigants safely (2). Fumigants span several different classes of chemicals; however, nearly all the chemicals used as fumigants are highly toxic, both to pest species and to nontarget organisms (Table 100-1). Chemicals formerly used as fumigants are carbon tetrachloride, carbon disulfide, and hydrogen cyanide. Other chemicals with important commercial uses as fumigants [e.g., 1,2-dibromo-3-chloropropane (DBCP); ethylene dibromide (EDB); 1,3-dichloropropene (1,3-D); methyl bromide; and aluminum phosphide] have been associated with significant chronic and acute health effects in humans and laboratory animals. Carbon tetrachloride and methyl bromide potentially affect stratospheric ozone and the ability of the atmospheric ozone layer to protect the earth's surface from ultraviolet radiation.

Many fumigants epitomize the balance of economic benefits and estimated health risks associated with chemical use. Classic examples of this balance include such chemicals as EDB and DBCP, which have served vital roles in increasing crop yields by controlling soil-borne nematodes. Use of these compounds has resulted in potential widespread exposures of humans through groundwater contamination in agricultural areas and, in the case of DBCP, adverse effects in workers. EDB and DBCP have been demonstrated to be carcinogens in laboratory animals; hence, they represent a potential human cancer risk. The estimated cancer risk associated with these chemicals in groundwater has significantly influenced decisions to prohibit their use in agriculture in the United States. Over time, greater reliance has been placed on methyl bromide as a soil and object fumigant. However, production and use of methyl bromide eventually will cease by the early twenty-first century, principally owing to its ozone-depleting effects. Ultimately, the loss of methyl bromide presents an opportunity to move away from heavy reliance on a single chemical that has discouraged an in-depth

Clinical Environmental Health and Toxic Exposures

Second Edition

John B. Sullivan, Jr., M.D.

Associate Dean for Clinical Affairs,
Associate Professor of Emergency Medicine,
University of Arizona Health Sciences Center,
Tucson, Arizona

Gary R. Krieger, M.D., M.P.H., D.A.B.T.

Associate Adjunct Professor of Toxicology,
University of Colorado School of Pharmacy;
Department of Molecular and Environmental Toxicology,
University of Colorado Health Sciences Center,
Denver, Colorado

LIPPINCOTT WILLIAMS & WILKINS
A **Wolters Kluwer** Company
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Anne M. Sydor
Developmental Editor: Leah Ann Kiehne Hayes/Sarah Fitz-Hugh
Supervising Editor: Mary Ann McLaughlin
Production Editors: Erica Broennle and Allison Spearman, Silverchair Science + Communications
Manufacturing Manager: Ben Rivera
Cover Designer: Mark Lerner
Compositor: Silverchair Science + Communications
Printer: Courier Westford

530 Walnut Street
Philadelphia, PA 19106 USA
LWW.com

1st edition entitled Hazardous Materials Toxicology: Clinical Principles of Environmental Health, 1992

Library of Congress Cataloging-in-Publication Data
Clinical environmental health and toxic exposures / editors, John B. Sullivan, Jr., Gary R. Krieger. -- 2nd ed.
p. cm.
Rev. ed. of: Hazardous materials toxicology / editors, John B. Sullivan, Jr., Gary R. Krieger. Baltimore : Williams & Wilkins, c1992.
Includes bibliographical references and index.
ISBN 0-683-08027-X
1. Environmental toxicology. 2. Environmental health. I. Sullivan, John B. (John Burke) II. Krieger, Gary R. III. Hazardous materials toxicology.
[DNLM: 1. Hazardous Substances--toxicity. 2. Environmental Exposure. 3. Environmental Health. 4. Risk Factors. WA 465 C641 1999]
RA1226.C56 1999
615.9'02--dc21
DNLM/DLC
for Library of Congress 99-33986
CIP

10 9 8 7 6 5 4 3 2 1