PESTICIDAL ASPECTS OF CHLORDANE IN RELATION TO MAN AND THE ENVIRONMENT

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Preface

Because of the Environmental Protection Agency's statutory mandate to protect the public health and well being of its citizenry through control of economic poisons, a comprehensive effort intended to insure intensive and regular review of all economic poisons was initiated March 18, 1971, to identify those pesticides which could represent potential unreasonable adverse effects on man and his environment. Since that date comprehensive "internal reviews" have been conducted by staff of the Office of Pesticide Programs on a number of pesticides. The initial direction for this program came in a statement outlined by the Administrator of the Environmental Protection Agency on March 18, 1971.

This report on chlordane was conducted from 1971 to 1972. The chemistry and methodology section was amended in 1975. Other sections were updated in a separate report entitled: Pesticidal Aspects of Chlordane and Heptachlor in Relation to Man and the Environment - A Further Review, 1972-1975.

This review evaluates scientific data in the areas of fish, wildlife, distribution in the environment (air, soil, water), residues in crops and food items, and toxicology and epidemiology.

This review summarizes rather than interprets scientific data studied during the process of reviewing chlordane. It is not intended that this report correlate data from different sources. The review also does not present opinions on contradictory findings.

The review of chlordane covers all uses of the pesticide in the United States and should be applicable to future needs in the Agency. The review was researched and prepared by the Special Pesticides Review Group, Office of Pesticide Programs, Environmental Protection Agency.

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Pesticidal Aspects of Chlordane in Relation
To Man and the Environment

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SUMMARY

Chlordane has been registered as an insecticide for use in agriculture, homes, lawns and gardens, and structural pest control since its introduction about 25 years ago. In addition, chlordane has been registered as a herbicide primarily for the preemergence control of crabgrass. These uses have resulted in widespread application of chlordane in urban, suburban, and rural areas.

Chlordane, a chlorinated hydrocarbon pesticide, is a member of the group of cyclodiene insecticides which includes aldrin, dieldrin, heptachlor, endrin, thiodan, chlordane and telodrin. Chlordane is a term used to designate a complex mixture of products. Since 1950 technical chlordane has been manufactured by a process which is controlled so that the composition of the product is relatively constant. This consistency has permitted a more precise chemical evaluation of its formulations and residues. Chemical and instrumental analytical techniques are available and have been successful in terms of sensitivity, precision and accuracy for certain components of the chlordane mixture.

Chlordane is used primarily as a soil insecticide. Therefore, any consideration of possible environmental effects must place emphasis on the fate of chlordane in the soil. In most of the registered uses, the rates, methods of application, and the environmental conditions differ. However, while these factors may differ, the controlling factors are the characteristics of chlordane. These are persistence, relative immobility in the soil, and a low propensity for biological magnification.

The present agricultural use of chlordane accounts for approximately 25% of the annual production. Home use, including turf treatment and garden and household applications, accounts for 25% of the annual production. Professional use, primarily termite control, accounts for approximately 50% of the production.

Chlordane was at one time registered for agricultural application to more than 100 crops or uses. This involved fruits, vegetables, field crops, and noncropland applications. A significant use was for soil insect control, although foliar applications were also approved on fruits and vegetables. Foliar use has become less important in recent years.

Chlordane persists in the soil. Significant residues of chlordane can be demonstrated in the soil 10 years after a single application. Therefore, the depletion of chlordane residues is a relatively slow process. Chlordane is relatively immobile in the soil. Various workers have demonstrated that chlordane does not move when applied to the soil and that the majority of the residues are in the top few inches of soil. Several studies indicate

that contamination of water by chlordane is not a widespread problem. Waters examined in 1966 showed positive values of chlordane ranging from 5 to 75 parts per trillion. However, abusive use of chlordane could result in significant contamination of water.

Earthworms are able to concentrate chlordane from the soil. Traces of heptachlor and heptachlor epoxide have been determined in the fat of starlings. These birds are not at the top of the food chain but are commonly found in the diets of raptorial birds. Substantial levels of heptachlor epoxide have been found in the eggs of the coot, teal, and pheasant. No evidence of reproductive problems have been associated with these residues.

Residues of chlordane have been evaluated in fish from various bodies of water. In general, the values found have been less than 0.5 ppm. Fish examined from the Pacific Ocean failed to show detectable levels of chlordane. Oysters taken from the South Atlantic and Gulf of Mexico had levels of chlordane up to 10 ppb.

An examination for the presence of chlordane in water, suspended water plants, algae, chubs, bass, and clams in water from an area of extensive agricultural use indicated that the presence of chlordane was minute and no substantial buildup was evident in any of the organisms or media examined. The concentrating factor was 1.91 for algae, 1.20 for chubs, 0.9 for clams, and 0.45 for vascular plants, indicating no magnification of chlordane residues.

On the basis of results of two long-term feeding studies in rats, a no-effect level for chlordane was established by the FAO/WHO Joint Expert Committee on Pesticide Residues at 20 ppm; or 1 mg/kg/day. On the basis of the results of a 2-yr feeding study in the dog, a no-effect level for dogs was established at 3 ppm or 0.07 mg/kg/day. The acceptable daily intake for man was estimated by FAO/WHO to be 0.001 mg/kg body weight.

A tolerance of 0.3 ppm was established for 65 fruits and vegetables in 1954. This tolerance was reappraised and reconfirmed in 1965 by an advisory committee appointed by the Food and Drug Administration from a panel of experts nominated by the National Academy of Sciences National Research Council.

Chlordane is absorbed from the gastrointestinal tract, the respiratory tract, and through the skin. It is stored in adipose tissue of rats, sheep, goats, and cows and can be found in the milk.

Chlordane acts on the central nervous system, but the exact mechanism of this action is unknown. Large doses induce nausea and/or vomiting. Low level administration of chlordane produces histologic changes in the liver and kidneys of some experimental animals as well as an increase in liver microsomal activity.

Dietary levels (50-100 ppm) of chlordane in the diet produced a significant effect on reproduction in mice. However, 25 ppm chlordane had no effect on reproduction in these long-term rat and mouse reproduction studies. No evidence of teratogenesis was apparent. No specific mutagenic or teratogenic studies have been carried out on chlordane.

No carcinogenicity studies, per se, have been carried out on chlordane. However, chlordane was not shown to be tumorigenic in long-term studies in rats.

Human poisonings and fatalities have been reported from both dermal and oral exposure to chlordane. In addition, chlordane, by direct circumstantial evidence, has been implicated as a causative factor in several blood dyscrasias, including anemia, leukopenia, thrombocytopenia, and pancytopenia.

Since technical chlordane is a mixture of substances, including alpha-chlordane, gamma-chlordane, chlordene, heptachlor, hexachlor, nonachlor, and hexachlorcyclopentadiene, the pharmacological and toxicological properties may vary from experiment to experiment because of possible variation in the composition of chlordane. However, the production of chlordane was standardized in 1950 and the hexachlorocyclopentadiene content reduced to a maximum of 1%. Chlordane produced since that time is considered to be less toxic than that produced prior to 1950. In fact, the advisory committee appointed by the FDA in 1965 concluded that the standards of production would allow the constancy of the technical mixture.

In 1969 the Secretary's Commission on Pesticides and Their Relationship to the Environmental Health recommended restriction of the usage of certain persistent pesticides in the United States to specific essential uses which create no known hazard to human health or to the quality of the environment. Chlordane was included in their list of pesticides covered in this recommendation.

In a statement issued on March 18, 1971, the Administrator of the Environmental Protection Agency reported: "Active internal review is being initiated as to the registrations of products containing benzene hexachloride, lindane, chlordane, endrin, heptachlor and toxaphene, all products containing mercury, arsenic, or lead, and all others deemed necessary to review..." In accordance with this charge, the Special Pesticide Review Group has reviewed the hazards associated with the use of chlordane.

CHAPTER I

Summary of Current Pesticide Uses of Chlordane With Alternative Pesticides Available

Chlordane currently has limited use as a foliar agricultural insecticide. In general, the limitations on the foliar use of chlordane on vegetable crops include a caution not to apply after edible parts begin to form. In all instances the applications of chlordane by the foliar route include the limitation not to graze treated fields with dairy animals or animals being prepared for slaughter. In certain fruit registrations there are harvest limitations of from 14 to 30 days following foliar applications. In almost all instances chlordane is not applied directly to an edible portion of the crop. Alternatives are available except for the use of foliar applications of chlordane on pineapple to control ants.

Chlordane is registered for foliar use in home gardens on ornamentals, shade trees, and flower garden plants for a multitude of pests. The uses employ concentrations of 1-2 lb/100 gal of water for foliar applications. There are alternatives available for the home foliar uses which are less persistent and/or less toxic materials.

The major use of chlordane in agriculture is as a soil insecticide. In general, soil treatment with chlordane controls soil insects such as ants, wireworms, white grubs, Japanese beetle grubs, white-fringed beetle and cutworms. Alternatives other than the chlorinated hydrocarbons are not effective for certain of these pests. The crops include certain bush and vine fruits, citrus fruits, deciduous fruits and nuts, field, fiber and forage crops, grain crops, bananas and various vegetables. The majority of the crops for which chlordane has a registered use have a tolerance of 0.3 ppm. The maximum allowable dosage to be applied to the soil is 10 lb active ingredient (AI)/acre. However, the usual rate of application is considerably lower. The general limitation for the use of chlordane as a soil insecticide is as a preplanting soil application or when no edible portion of the crop is present above ground.

The use of chlordane as a soil treatment for the control of insects in lawns, commercial turfs and nursery plant stock may be employed up to 10 lb AI/acre. The situation relative to alternatives is essentially the same as for the agricultural soil uses described above. Use for nursery stock is extremely valuable for purposes of quarantine regulations in interstate shipment of pest-free plants.

Seed treatment application utilizes 2 oz of actual chlordane per bushel of seed. This application is effective against the following pests: seed-corn beetles, seed-corn maggots, corn rootworms and wireworms. Seed treatments are registered with the limitation that the seed not be used as food or feed. Diazinon is the only nonchlorinated hydrocarbon alternative available. The approved uses of Diazinon® are limited.

Chlordane baits are limited to soil treatments for control of grasshoppers, cutworms, crickets, and mole crickets. This use is limited to those crops for which soil treatment is allowed. The concentration of chlordane used in a bait is 1 lb AI/acre with the limitation of not contaminating edible parts of the crop.

Nonfood insecticide uses in agriculture include the treatment of agricultural premises with a 3% oil or water spray or a 6% dust for the control of adult houseflies, face flies, stable flies and mosquitoes. The limitations on the use of chlordane for agricultural premises exclude use in dairy barns and poultry houses and caution that the materials not be applied to food or not to contaminate feed or drinking water. Adequate alternates are available.

Out-of-doors spray treatments of ditchbanks, field borders, roadsides and vacant lands for the control of crickets, grasshoppers, mosquitoes, gnats, flies, ticks, and chiggers employ chlordane at rates of up to 1.5 lb AI/acre. Suitable alternate pesticides are available.

Application of household uses of chlordane has been reported as one of the significant uses. The limitations preclude the use of chlordane in areas where food is exposed in order to reduce the occurrence of residues on food. Chlordane is used for household control of ants, ticks, mosquitoes, house flies, roaches, spiders, scorpions and other general pests using either a 6% dust or a 3% spray application, usually as a spot treatment. Adequate alternate insecticides are not available for all cockroach species.

Chlordane is used as a 5% dust or a 0.5% dip or spray on dogs for the control of lice, fleas, ticks, and mange. Limitations preclude use on young animals or the excessive use of sprays and dips. Alternatives for mange control are limited to BHC and lindane.

Chlordane is registered as a herbicide for the preemergence control of crabgrass on lawns. The recommended dosage of chlordane for this treatment is 65-87 lb AI/acre. Several herbicides are very effective substitutes for this use of chlordane.

The major use of chlordane in the United States is as a soil treatment around and under buildings for the control of termites. The usual rate of application is 4 gal of a 1% chlordane solution per 10 linear feet along the inside and outside of foundation walls and partitions. Aldrin, dieldrin and heptachlor are the only alternatives available for termite control.

Chlordane is registered as a mosquito larvicide at a rate of 0.2-0.4 lb AI/acre in water. It is registered as a mosquito adulticide at a rate of 1 lb AI/acre. Paris green is an effective alternate for use as a mosquito larvicide. Chlordane is used in sewage treatment for the contol of Psychoda larvae at a rate of 0.5 gal (90% concentrate)/3000 gal liquid sewage.

Table 1 presents the currently registered chlordane uses by use pattern and the registered alternative pesticides (substitutes) where available. The conclusions and effects of proposed actions are presented in subsection I.B.

Table 1. Summary of Registered Chlordane Uses and Alternatives

I.A.

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Foliage Applications				
Agricultural Crops				
Blackberry Blueberry	Strawberry root weevil adults	2		Apply before fruit starts to form and after harvest.
Grape	Thrips	2	Dibrom Guthion Parathion	
Strawberry	Strawberry crown borer	2		
	Strawberry root weevil adults	2	Malathion Parathion	
	Spittelbug	2	Carbaryl Diazinon Malathion Methoxychlor Parathion Thiodan	
Cotton	Boll weevil	1.5	Azodrin Carbaryl Endrin EPN Guthion Methyl parathion Methyl trithion	Do not apply after bolls open. Do not graze dairy animals or animals being finished for slaughter on treated fields.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Cotton fleahopper	1.5	Bidrin	
			Carbaryl	
			DDT	
			Dibrom	
			Endrin	
			Guthion	
			Malathion	
			Methyl Parathion	
			Parathion	
			Phosphamidon	
			Trichlorofon	
	Darkling beetle	1.5	Carbaryl	
			DDT	
			Endrin	
	Fall armyworm	1.5	Carbaryl	
			DDT	
			Endrin	
			Methyl Parathion	
			Strobane	
			Toxaphene	
	Grasshoppers	1.5	Carbaryl	
			Malathion	
			Methyl Parathion	
			Strobane	
			Toxaphene	
	Tarnished plant bugs	1.5	Bidrin	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Thrips	1.5	Carbaryl DDT Endrin Guthion Malathion Methyl parathion Parathion Phosphamidon Strobane Toxaphene	
Citrus	Grasshoppers (outer foliage to drip line)	2	Toxaphene	14 days. Apply to trunk and larger branches and to outer foliage at drip line.
Apples	Codling moth	8	Carbaryl Parathion Malathion	30 days
	Oriental fruit moth	8	Carbaryl	
	Plum curculio	8	Carbaryl	
	Bagworms		Parathion Malathion	
	Thrips Flea beetles	8	Diazinon	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Apricots Nectarines Peaches	Plum curculio	8	Carbaryl Dieldrin Guthion EPN Malathion Methoxychlor Parathion	30 days 30 days 30 days
	Catfacing insects	8	Carbaryl Dieldrin Guthion Parathion	
Pears	Plum curculio	8	Carbaryl Parathion	30 days
	Thrips	8	Diazinon Malathion	
	Flea beetles	8	Diazinon	
Pineapples	Ants	2	Aldrin Dieldrin	Do not feed bran or husks to livestock.
Corn (field)	Corn earworm	1.5	Carbaryl Diazinon Parathion Toxaphene	Do not feed treated forage to dairy animals or animals being finished for slaughter.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Corn silk fly	1.5	Parathion	No restriction of grain.
Small Grains (Barley, Oats, Rye, Wheat)	Armyworms	2	Carbaryl Malathion Methyl parathion Parathion (except on rye) Toxaphene	Do not apply after heads begin to form. Do not graze treated fields. No restriction on use of grain.
Rice	Armyworms	2		Do not apply after heads start to form. Do not graze treated forage. No restriction on use of grain.
Flax	Crickets	3	None	Do not apply after blossoms appear. Do not feed treated forage to dairy animals being finished for slaughter. No restriction on the use of treated grain.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Asparagus	Asparagus beetle (post-cutting use)	1.0	BHC Carbaryl Malathion Rotenone	Post-cutting only
Beans	Flea beetles	2	Carbaryl Methyl parathion Methoxychlor	Do not apply to green or snap bean after pods begin to form.
	Green stink bugs	2	Carbaryl Dibrom Guthion Methyl parathion	Do not apply to green or snap beans after pods begin to form.
Beets	Cutworms (climbing and surface)	2	Dylox Phosdrin	Do not apply after seedling stage if tops are to be used as food.
	Flea beetles	2	Carbaryl Malathion Methoxychlor Methyl parathion Parathion	
	Armyworms	2	Dylox Malathion Methyl parathion	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Blackeye peas (Cowpeas)	Flea beetle	2	Carbaryl Methoxychlor Carbaryl Guthion Dylox Parathion	Do not apply after pods start to form.
Broccoli Brussels sprout Cabbage Cauliflower Collards	Cabbage worms	2	Carbaryl Dibrom (except kohlrabi) Guthion (except collards, kale and kohlrabi)	Do not apply after edible parts start to form.
Kale			Lannate (cabbage, broccoli, cauli-flower only) Parathion	
Kohlrabi			Phosdrin (except kohlrabi) Thiodan Toxaphene	
	Flea beetle	2	Carbaryl Methoxychlor Methyl parathion Parathion Rotenone Thiodan	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Celery	Armyworms	2	Malathion Lindane Phosdrin	Do not apply after celery begins to bunch or after one-half grown.
Cole Crops	Flea beetles	2	Diazinon	
	Green stink bugs	2	Dibrom Methyl parathion Parathion Thiodan	Do not apply after edible parts start to form.
	Harlequin bugs	2	Carbaryl Dibrom Parathion Thiodan	
Carrots	Carrot rust fly	2	Parathion	No time limitation
Corn, sweet	Corn earworms	1.5	Carbaryl Diazinon Lannate Parathion Thiodan Toxaphene	Apply primarily to silks. Do not feed treated forage to dairy animals or animals being finished for slaughter.
	Corn silk fly	1.5	Parathion	No restriction on the use of corn as human food.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Cucumbers Melons Squash	Cucumber beetle	1.5	Carbaryl Lindane Malathion Methoxychlor Parathion Rotenone Thiodan	Do not apply after edible parts start to form. May be injurious to some varieties.
	Squash bug	1.5	Carbaryl Lindane Parathion Thiodan	
	Squash vine borer	1.5	Carbaryl Lindane Malathion	
Eggplants	Flea beetle	2	BHC Carbaryl Dibrom Lindane Parathion Methoxychlor Thiodan	Do not apply after edible parts start to form.
	Serpentine leafminer		BHC Dibrom Guthion Parathion	Do not apply after edible parts start to form.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Lettuce	Armyworms	2	Dibrom Dylox Lannate Methyl parathion Parathion Phosdrin	Do not apply after edible parts start to form.
	Lygus bugs	2	Carbaryl Parathion Phosdrin	
	Serpentine leafminer		Dizainon Dimethoate Dibrom Parathion	
	Spotted cucumber beetle	2	Parathion Phosdrin	
Okra	Serpentine leafminer		Parathion Toxaphene	Do not apply after edible parts start to form.
	Stink bugs	2	Carbaryl Parathion Phosdrin	
Onion	Thrips	2	BHC Diazinon Dibrom Guthion Malathion Parathion Phosdrin	Do not apply to green or spring onions.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Peas	Pea Leafminer	1.5	Parathion Toxaphene	
Peppers	Climbing cutworms	2	Carbaryl	Do not apply after edible parts are starting to form.
	Flea beetles	2	Carbaryl Parathion	
	Serpentine leafminers	2	Malathion Lindane Diazinon	
Potato	Potato flea beetle	1.5	Carbaryl Diazinon Dibrom Dieldrin Parathion Phosphamidon Rotenone Thiodan	No time limitation.
	Colorado potato beetle	1.5	Carbaryl Dibrom Diazinon Guthion Phosphamidon Thiodan	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Serpentine leafminer	1.5	Diazinon Dibrom Dimethoate Guthion Parathion	
Tomato	Flea beetles	2	BHC Carbaryl Dibrom TDE Thiodan Toxaphene	Do not apply after fruit begins to form.
	Leafminer	2	Carbaryl Dibrom TDE Thiodan Toxaphene	
	Leafminer	2	BHC Diazinon Dibrom Dimethoate Guthion Parathion Phosphamidon	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Home Gardens				
Flower Garden Plants Ornamentals and Shade Trees (foliar)	Ants	1 lb actual/ 50 gal water	Diazinon	
	Bagworms	1 lb actual/ 100 gal water	Bidrin Carbaryl Diazinon Dimethoate Dylox Malathion Toxaphene Trithion	
	Black vine weevil adults	1 lb actual/ 100 gal water	Dieldrin Heptachlor Thiodan	
	Crickets Earwigs	1 lb actual/ 100 gal water	Dieldrin* Dieldrin*	
	Elm leaf beetles	1 lb actual/ 100 gal water	Carbaryl Dieldrin Di-Syston* Lead arsenate Metasystox-R(R) TDE Thiodan Toxaphene	

*Soil application

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Fullers rose beetle	1 lb actual/ 100 gal water	Lindane	
	Grasshoppers Imported fire ant (mound treatment)	100 gal water 1 lb actual/ 50 gal water	Dieldrin Heptachlor* Mirex bait*	
	Lacebugs	1 lb actual 100 gal water	Carbaryl Demeton Dimethoate Di-Syston* Malathion Methoxychlor TDE Pyrethrins	
	Leafminers	1 lb actual/ 100 gal water	Bidrin Dimethoate Dylox Lindane Malathion Phosphamidon	
	Leafrollers	1 lb actual/ 100 gal water	BHC Carbaryl Diazinon Dimethoate Pyrethrins TDE	

*Soil application

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Soil Application				
Agricultural Crops				
Blackberry	Cutworms	2.5-4	Heptachlor	Preplanting soil application or when no fruit is present.
	Root weevil larvae	10	Heptachlor	
	Japanese beetle bugs White grubs Wireworms White fringed beetle grubs	2.5-4	Heptachlor	
Blueberry	Cutworms Japanese beetle grubs White grubs Wireworms White fringed beetle grubs	2.5-4	Dieldrin Heptachlor	Preplanting soil application or when no fruit is present.
Grape	Cutworms Japanese beetle grubs White grubs Wireworms White fringed beetle	2.5-4	Dieldrin Heptachlor	
Boysenberry Dewberry Huckleberry Loganberry Raspberry Youngberry	Cutworms Japanese beetle grubs White grubs White fringed beetle grubs Wireworms	2.5-4	Heptachlor (registered on Boysenberry, dewberry and raspberry only)	Preplanting soil application or when no fruit is present.
Strawberry	Brachyrhinus weevil	10	Aldrin Dieldrin	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Cutworms	2.5-4	Aldrin Dieldrin Lindane Toxaphene	
	Earwigs	2.5		
	Mole crickets	2.5	Diazinon	
	Strawberry root weevil	10	Dieldrin Aldrin Parathion	
	White grubs Wireworms	2.5-4	Aldrin Dieldrin	
Pineapple	Ants	2	Aldrin	Do not feed bran or husk to livestock.
Cotton	White fringed beetle	5	DDT	Preplanting soil application.
Citrus	Argentine ant	2	Heptachlor	Soil treatment. Apply when no food is present.
	Little fire ant	2		
	Termites	2	Dieldrin	
Peaches Apple, Pear, Plum Quince, Apricot, Cherry, Nectarine, Prune	Plum curculio	2	Aldrin	Soil application when no fruit is present.
	General soil parts	2	Heptachlor	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Corn(field)	Asiatic garden beetle larvae	2.5-4		Preplanting soil application.
	Cornfield ants	2-4	Heptachlor	
	Corn root aphid	2-4	Heptachlor	
	Corn rootwroms	2-4	Bux Carbofuran Dasanit Di-Syston Dyfonate Heptachlor Phorate Parathion	
	Cutworms	2.5-4	Aldrin Carbaryl Diazinon Heptachlor Parathion Toxaphene	
	Green June beetle larvae	2.5-4	Heptachlor	
	Japanese beetle larvae White grubs		Aldrin Heptachlor Parathion	
	Seed corn beetles	2.5-4	Aldrin Heptachlor Thimet (Iowa and Illinois Only)	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Seed corn maggot White fringed beetle	2.5-4	Aldrin Heptachlor	
	Wireworms	2.5-4	Aldrin Diazinon Heptachlor Parathion	
Small Grains (Barley, oats, rye, wheat)	Red harvester ants and Cutworms Wireworms White grubs	.5/colony	CS_2 (mound treatment) Heptachlor	Preplanting soil application.
Soybeans	Cutworms	2.5-4	Diazinon Heptachlor	Preplanting soil application.
	Japanese beetle grubs White grubs	2.5-4	Heptachlor Parathion	
	Wireworms	2.5-4	Heptachlor	
	White fringed beetle grubs	2.5-4	Heptachlor	
Flax		2.5-4		Preplanting soil application
Peanuts		2.5-4		Preplanting soil application.
Sugar beets	Sugar beet root maggot	4	Diazinon Di-syston (limited to 2 states) Phorate	Preplanting soil application.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Wireworms	2.5-4	Diazinon Dyfonate Parathion	
Tobacco	Wireworms (transplant solution)	1.5	Aldrin Diazinon Dieldrin Heptachlor Lindane	Transplanting treatment
	Wireworms (broadcast)	2.5-4	Aldrin Diazinon Dieldrin Dyfonate Heptachlor Lindane	Preplanting soil application.
	White grubs (broadcast	2.5-4	Aldrin Dieldrin Parathion	
	White fringed beetle grubs (broadcast)	2.5-4	Aldrin Dieldrin Heptachlor	
Hops		2.5-4		Preplanting soil application.
Sorghum		2.5-4		

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Asparagus	Cutworms	2.5-4	BHC Lindane Calcium arsenate bait	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs	2.5-4	BHC Lindane	
	White grubs	2.5-4	BHC Aldrin Lindane EDB (wireworms only) Parathion	
	White fringed beetle grubs	2.5-4		
Beans	Cutworms	2.5-4	Diazinon Heptachlor Parathion Toxaphene	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs	2.5-4	Parathion	
	White grubs	2.5-4	Heptachlor Parathion	
	Wireworms	2.5-4	Diazinon Heptachlor Parathion	
	White fringed beetle grubs	2.5-4	Heptachlor	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Beets	Cutworms	2.5-4		Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs	2.5-4		
	White grubs	2.5-4		
	Whiteworms	2.5-4	Parathion	
	White fringed beetle grubs	2.5-4		
Blackeyed peas (cowpeas)	Cutworms	2.5-4	Diazinon	
	Japanese beetle grubs	2.5-4		Preplanting soil application or at time of planting or transplanting.
	White grubs	2.5-4		
	Wireworms	2.5-4	Diazinon Parathion	
	White fringed beetle grubs	2.5-4		
Cucurbits	White fringed beetle grubs	2.5-4	Aldrin Dieldrin	
Eggplant	Cutworms	2.5-4	Aldrin BHC Dieldrin Lindane Toxaphene	
	Japanese beetle grubs White grubs	2.5-4	Aldrin BHC Dieldrin Lindane	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Wireworms	2.5-4	Aldrin BHC Dieldrin EDB Lindane Parathion	Preplanting soil application or at time of planting or transplanting.
	White fringed beetle grubs	2.5-4	Aldrin Dieldrin	
Broccoli* Brussels sprout Cabbage Cauliflower Collards Kale Kahlrabi	Cabbage maggots	2.5-4	Aldrin Diazinon Dieldrin Dyfonate** Heptachlor (furrow, transplant, water, and drench. Cabbage only.)	Preplanting soil application or at time of planting or transplanting.
Cucurbits	Cutworms	2.5-4	BHC Aldrin Diazinon Dieldrin Lindane	Preplanting soil application at time of planting or transplanting.

* Aldrin and dieldrin are not registered for use on collards, kale, and kohlrabi.
* Diazinon is not registered on kohlrabi.
EDB registered for use on broccoli and cauliflower only.
**Seed crop only.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Japanese beetle grubs	2.5-4	Aldrin BHC Dieldrin Lindane	
	White grubs	2.5-4	Aldrin BHC Dieldrin Lindane	
	Wireworms	2.5-4	Aldrin BHC Dieldrin Diazinon Lindane Parathion	
Lettuce	Cutworms	2.5-4	Aldrin BHC Diazinon Dieldrin Heptachlor (lettuce only) Lindane Parathion Toxaphene	Preplanting soil application or at time of planting or transplanting.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Japanese beetle grubs White grubs Wireworms	2.5-4	Aldrin BHC Dieldrin Heptachlor (lettuce only) Lindane Parathion	
	Mole crickets	2	Aldrin Diazinon	
	Root maggots	1.5	Aldrin Diazinon Dieldrin Heptachlor (lettuce only) Lindane	
Celery	Carrot rust fly	2	Diazinon	Preplanting soil application or at time of planting or transplanting.
	Cutworms	2.5-4	Aldrin BHC Diazinon Lindane Parathion Toxaphene	
	Japanese beetle grubs White grubs	2.5-4	Aldrin BHC Lindane Parathion	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Mole crickets	2	Aldrin Diazinon	
	Wireworms	2.5-4	Aldrin BHC Diazinon Lindane Parathion	
	White fringed beetle grubs	2.5-4		
Corn (sweet and pop)	See field corn			
Garlic Onions Leeks	Onion maggots	1	Diazinon Dieldrin Ethion Dyfonate Parathion Trithion Diazinon Parathion	Preplanting soil application or at time of planting or transplanting.
Okra	Wireworms	2.5-4	BHC EDB Lindane Parathion	Preplanting soil application or at time of planting or transplanting.
Peas	Wireworms	2.5-4	Diazinon Parathion	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Parsnips	Cutworms	2.5-4	Dieldrin	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs	2.5-4	Dieldrin	
	White grubs			
Mustard greens	Cutworms	2.5-4	BHC Diazinon Lindane	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs		BHC	
	White grubs		Lindane	
	Wireworms		Diazinon	
	White fringed beetle grubs	2.5-4		
Pepper	Cutworms	2.5-4	Aldrin BHC Dieldrin Diazinon Heptachlor Lindane Toxaphene	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs	2.5-4	Aldrin BHC Dieldrin Lindane Parathion	
	White grubs	2.5-4	Aldrin BHC Dieldrin Heptachlor Lindane Parathion	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Wireworms	2.5-4	Aldrin BHC Diazinon Dieldrin EDB	
Pepper	Wireworms	2.5-4	Heptachlor Lindane Parathion	Preplanting soil application or at time of planting or transplanting.
	White fringed beetle	2.5-4	Aldrin	
Potatoes	Colorado Potato Beetle	1.5	Diazinon Carbaryl	No limitation.
	Potato flea beetle	1.5	Malathion Carbaryl Diazinon	No limitation.
	Serpentine leafminer	1.5	Malathion Diazinon	No limitation.
Radish	Cutworms	2.5-4	Diazinon Dieldrin	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs White grubs	2.5-4	Dieldrin Parathion	
	Wireworms	2.5-4	Dieldrin Diazinon Parathion	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	White fringed beetle grubs	2.5-4	Dieldrin	
Rutabaga	Cutworms	2.5-4	Heptachlor Parathion	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs White grubs Wire worms	2.5-4	Heptachlor Parathion Heptachlor Parathion	
	White fringed beetle grubs	2.5-4	Heptachlor	
Spinach	Cutworms	2.5-4	BHC Diazinon Lindane Parathion	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs White grubs Wireworms	2.5-4	BHC Parathion Lindane BHC Diazinon Lindane Parathion	
	White fringed beetle grubs	2.4-5		
Turnips	Cutworms	2.4-5	Diazinon Parathion	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs	2.5-4	Parathion	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	White grubs Wireworms	2.5-4	Parathion Diazinon	Preplanting soil application or at time of planting or transplanting.
	White fringed beetle grubs	2.5-4		
Sweet potato	Flee beetle larvae	2.5-5	Diazinon Dyfonate Parathion	Preplanting soil application or at time of planting or transplanting.
	White grubs	2.5-5	Parathion	
Tomato	Cutworms	2.5-4	Aldrin BHC Diazinon Dieldrin Heptachlor Lindane Parathion Toxaphene	Preplanting soil application or at time of planting or transplanting.
	Japanese beetle grubs White grubs	2.5-4	Aldrin BHC Dieldrin Heptachlor Lindane Parathion	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Wireworms	2.5-4	Aldrin BHC Diazinon Dieldrin Heptachlor EDB Lindane Parathion	
	Wireworms (transplant treatment)	.75		Transplant treatment.
	White fringed beetle grubs	2.5-4	Aldrin Dieldrin Heptachlor	Preplanting soil application or at time of planting or transplanting.
Watermelons Pumpkins Melons Squash	Cucumber beetle Squash bug Squash vine borer	2.5	Thiodan Carbaryl	Do not apply after edible parts start to form.

Soil Insects

General claims for wireworms, white grubs, Japanese beetle grubs, white fringed beetle and cutworms are acceptable for soil treatment of all crops listed in the "EPA Compendium of Registered Pesticides."

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Home Gardens				
Flower garden plants	Mole crickets	1 lb actual/ 100 gal water	Diazinon	
Ornamentals and Shade trees (soil)	Narcissus bulbflies	1 lb of 6% dust/ 75 ft of row	Dieldrin Dylow Heptachlor	
	Seed corn maggots	1 level tsp 40% wp per lb	Dieldrin*	
	Black vine weevil larvae	5 lb actual/ acre (soil treatment	Aldrin* Dieldrin* Heptachlor* Thiodan*	

*Soil applications

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Table 1. (continued)

Lawns and Ornamental Turf Soil and Surface Applications		Registered Alternatives									
Insect Pest		Aldrin	Aspon	Carbaryl	Diazinon	Dieldrin	Ethion	Dursban	Heptachlor	Toxaphene	Trithion
Ants	1.5	X		X	X	X			X		
Asiatic garden beetle larvae	2.5-5					X			X		
Boxelder bugs	1				X				X		
Chiggers	1.5				X	X			X		
Chinch bugs	2	X	X	X	X	X	X	X	X		X
Cicada killers	5				X						
Wild bees	5				X						
Cutworms	5			X	X	X			X		
Earthworms	10										
Earwigs	1			X	X	X			X		
European chafer larvae	2.5-5	X				X			X		
Green June beetle larvae	2.5-5	X				X			X		
Japanese beetle larvae	2.5-5	X				X			X	X	
Lawn moths (sod webworm)	3	X	X	X	X	X	X	X	X	X	
Mosquito adults	.2-.4			X					X		
Ticks	1.5			X	X	X			X		
White fringed beetle larvae	2.5-5										
White grubs	5-10	X				X			X		
Wireworms	5-10					X			X		
Imported fire ants	1.5	X				X			X		

X - Registered

Note: Chlordane is registered for control of moles in lawns.

Table 1. (continued)

Seed Treatments

Crop Treatment	Insect Pest		Registered Alternatives: Aldrin	Diazinon	Dieldrin	Heptachlor	Lindane	BHC	Chlordane Limitations
Beans	Seed corn beetle	2 oz. actual	X	X	X	X	X	X	Do not use for
Blackeyed peas	Seed corn maggot	insecticide	X		X			X	food, feed, or
Corn	Corn rootworm	per bushel	X	X	X	X	X	X	oil purposes
Cotton	Wireworms		X		X	X	X		
Cowpeas	(Temporary		X		X		X	X	
Oats	protection against)		X		X	X	X		
Peas			X	X	X		X	X	
Rice			X		X	X	X	X	
Rye			X		X	X	X	X	
Sorghum			X		X	X	X	X	
Soybeans			X	X	X	X	X	X	
Wheat			X		X	X	X		

X - Registered

Baits - Chlordane baits limited to soil treatments are acceptable for use against grasshoppers, cutworms, crickets, and mole crickets. This type application may be used only in accordance with approximate "Summary" clearance and limitations on crops so specified. In general, toxaphene baits are registered for many of the same uses as chlordane baits. Use of 1 lb of actual insecticide per acre. Do not contaminate edible parts.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Agricultural Premises				
(excluding dairy barns and poultry houses)				
	Housefiles		Ciodrin Dibrom Diazinon DDVP Dimethoate Lindane Malathion	3% spray (in oil or water). Use as a residual surface spray. Do not apply to feed stuffs. Do not contaminate feed or drinking water.
			Methoxychlor Synergized pyrethrins Ronnel	6% dust. Thorough application to interior and exterior surfaces. Do not apply to feed stuffs. Do not contaminate feed or drinking water.
Outdoor Treatments				
Ditch Banks, Field Borders, Roadsides, Vacant Lands	Chiggers	1.5	Lindane Toxaphene	Do not feed or graze dairy animals or animals being finished.
	Ticks	1.5	Gardona Lindane Toxaphene	
	Flies Gnats Mosquitoes	.2-.4	Lindane Ronnel Carbaryl (Mosquito only)	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Grasshoppers	1	Carbaryl Dieldrin Lindane Toxaphene	
	Crickets		Dibrom Heptachlor Malathion	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Dosage Rate	Baygon	Diazinon	Dieldrin	Heptachlor	Lindane	Malathion	Pyrethrum powder	Ronnel	Chlordane Limitations
			Registered Alternates								
Household and Commercial Uses											
Sprays and Dusts											
	Ants	6% Dust	X	X	X	X	X	X	X	X	Do not use in serving areas while food is exposed. Do not use in the edible product areas of food processing plants, restaurants, or other areas where food is processed or served.
	Boxelder bugs	3% spray		X	X	X	X	X			
	Brown dog ticks		X	X	X	X	X	X		X	
	Carpet beetles			X	X	X	X	X		X	
	Centipedes		X		X	X	X	X			
	Crickets		X		X	X	X				
	Houseflies		X	X	X	X	X	X		X	
	Mosquitoes		X	X	X	X	X	X		X	
	Roaches		X	X	X	X	X	X	X	X	
	Waterbugs		X	X	X	X	X	X	X	X	Spot treatment.
	Scorpions		X	X	X	X	X	X			
	Spiders		X	X	X	X	X	X	X	X	
	Silverfish		X	X	X	X	X	X		X	
	Wasps		X		X	X	X				

X - Registered

Crop or Site of Application	Insect Pest	Dosage Rate	Registered Alternates	Chlordane Limitations
Dogs	Lice Fleas Ticks	5% Dust .25 or .5% dip or spray. Shampoos	BHC Carbaryl DDVP (jet use only) Lindane Malathion Pyrethrins (synergized) Rotenone	Do not use on young animals. Do not apply .25% solution more than once per week. Do not apply .5% solution more than once every 2 weeks.

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
	Sarcoptic Mange	5% Dust, .5% or .25% dip or spray		
Herbicide				
Preemergence Crabgrass Control		65-87 lb/acre	Benefin Betesan Dacthal Siduron Zytron	
Termite Control				
Buildings Household and Industrial Oil·Treatment	Termites	1-3% Solution	Aldrin Dieldrin Heptachlor	
Special Uses				
Mosquito Adulticide and Larvicide		Adulticide: 1 lb AI/acre Larvicide: 0.2-0.4 lb AI/acre	Carbaryl Malathion Naled Pyrethrins Parathion Paris green Flit MLO	

Table 1. (continued)

Crop or Site of Application	Insect Pest	Maximum or Usual Dosage Rate (lb actual insecticide/acre)	Registered Alternatives	Chlordane Limitations
Sewage Treatment for Psychoda flies		One treatment consists of 1/2 gal of product containing 1 lb chlordane/gal Two treatments one week apart, then 1-2 treatments per month during summer months.	Mevinphos plus DDVP	

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I.B. Discussion of Registered Uses of Chlordane and its Alternatives - The Special Pesticide Review Group has studied the toxicological hazard to man and the environment associated with the use of chlordane as a pesticide in the United States. In making this study, the Group has consulted pesticide experts in EPA and other Federal agencies and has evaluated the information received in response to the Federal Register notice on October 6, 1971 on chlordane and heptachlor (36FR19453). The Group considered, but was not able to fully evaluate, the social and economic effects which would result from the cancellation of specific uses of chlordane as a pesticide.

In an effort to evaluate the environmental and human health effects of chlordane, broad use patterns were established within the Special Pesticide Review Group. Basically, the outdoor uses may be grouped into four broad categories 1) foliar; 2) soil treatment; 3) seed treatment; and 4) special uses. The significant uses of chlordane include application to agricultural crops, home gardens, ornamental plants, lawns, and for termite control. Other broad categories include indoor applications for household pests and for use on dogs. These broad use patterns present distinctly different degrees of hazard to human health, wildlife, and the environment.

Seed treatments present the lowest order of hazard to human health, wildlife, and the environment of the four outdoor categories. The treatment procedure usually involves the application of the pesticide directly at a relatively low dosage rate at a location remote from the field. This seed treatment is usually carried out by a commercial seed treatment firm. However, in some instances the pesticide is placed directly into the furrow along with the seed. In either instance, the furrow is covered with soil, keeping the pesticide localized.

Soil applications of chlordane present the next lowest order of hazard. Granulated formulations of chlordane are generally used in this procedure. These granules are usually applied to agricultural crops as a band over the row for soil insect control, especially in cornfields. The treated bands are at least 7 in wide. The applicator is usually mounted on a planter, and the band of granules is dropped just ahead of it and the press wheel of the planter. The press wheel may make a slightly concave hand over the row. Most agricultural granules contain 10 to 20% AI. Following are the significant advantages for use of granules of a pesticide as far as minimizing environmental contamination: (1) dosages of pesticides in granular form may be kept at a minimum because drift is minimized, and; (2) minimizes contamination of the edible portion of the crop because of the more specific placement or application before the crop emerges.

Foliar applications present the highest degree of hazard of the three methods of application of chlordane, both in terms of environmental contamination, and also in terms of human hazard resulting from residues in food or feed crops. Pesticides may be applied to plant foliage in the form of either dusts or sprays. In the latter, wettable powders or emulsifiable concentrates are mixed with water and are applied by ground or aerial equipment.

Dusts or sprays for foliar applications have the following characteristics: (1) They are subject to drift, thus contaminating food crops or water outside of the desired area of application; (2) much of the applied pesticide does not reach the target area; and, (3) deposits of pesticide are left on the foliage of treated crops, thus contaminating edible portions.

Of the methods described for the application of chlordane, seed treatment and soil applications offer the least possibility for environmental contamination or for the production of residues in food or feed. Foliar applications, on the other hand, have a great propensity for contamination of food, feed, or the environment.

The following broad use patterns were established for the systemic review of chlordane:

I.B.1. <u>Foliar Application</u> -

I.B.1.a. <u>Agricultural Crops</u> - All foliar applications of chlordane on agricultural crops except ant control on pineapple in Hawaii have adequate alternate pesticides. Although some of the alternatives present a greater acute toxicity hazard, most represent less long-term hazard to man and the environment than chlordane when used as a foliar spray on agricultural crops. At the present time, there are no Federal or State recommendations for agricultural use of chlordane as a foliar treatment in the continental United States. Loss of most agricultural foliar uses would create no adverse economic impact.

I.B.1.b. <u>Home Gardens and Ornamentals</u> - There were no significant requests to continue foliar applications of chlordane for home gardens, ornamentals, shade trees, and flower garden plants. All foliar uses of chlordane to home gardens and ornamentals have adequate alternate pesticides. At the present time, there are no Federal or State recommendations for use of chlordane as a foliar treatment on home gardens or ornamentals. Loss of all home garden and ornamental foliar uses of chlordane would create no adverse economic impact.

I.B.1.c. <u>Herbicide for Crabgrass Control</u> - Chlordane is registered as a preemergence herbicide for the control of crabgrass on lawns. The rates of chlordane recommended for this use are 65 to 87 lb/acre. There are a number of more widely recommended alternates including benefin, siduron, dacthal, betasan, and zytron and elimination of this high quantity use of chlordane would minimize the human and environmental hazard of this pesticide. The application rate is in effect a biological sterilizing dose and will probably restrict most animal life in the soil for considerable periods of time after application. Loss of this use will present no adverse economic impact.

I.B.2. <u>Soil Applications</u> - The effective alternatives for several of the significant soil uses of chlordane include the chlorinated hydrocarbons, aldrin, dieldrin, and heptachlor. Alternatives other than the chlorinated pesticides are not registered for all uses nor are they likely to give equivalent control of insects such as ants, seed corn maggots, wireworms, grubs, cutworms, and termites. This is especially true for certain soil applications for agricultural crops, lawns, and termite control. These uses are reported to account for almost all of the poundage of the total chlordane used in the United States at the present time.

Another consideration in the review of chlordane is the current status of the registrations of aldrin and dieldrin. Actions against the registered uses of aldrin and dieldrin could result in an increased use of chlordane. This may increase the impact upon man and his environment.

I.B.2.a. Agricultural Crops - Under present conditions, 8-10,000 acres of citrus in California require soil treatment for ant control each year. The Argentine ant and the gray ant in California do not cause any direct damage or injury to the citrus tree but their presence in large numbers in the aerial parts of the tree significantly decrease the effectiveness of natural enemies against certain primary citrus pests. The Argentine and gray ants destroy adult parasites and the larvae of predators. The primary problem of the endemic fire ant in California is direct injury to young citrus trees.

The University of Idaho reports chlordane as an effective soil treatment for control of the sugar beet wireworm in potato fields. Chlordane was also reported to have a lesser acute toxicity hazard than two other insecticides on sugar beet wireworms.

An administrative report of the Economic Research Service, U.S. Department of Agriculture (May 26, 1972, appended) explains that the total cost to United States farmers for discontinuing the use of chlordane in 1971 would have been $1.84 million ($1.56 million for substitute insecticides and $0.28 million for production losses). The added cost for the substitute insecticides ranged from a low of $0.18 per acre for cotton to a high of $6.77 per acre for corn. The added cost for substitute insecticides in potato, tomato, vegetable and strawberry production is estimated at $2.50 per acre. The per-acre value of production losses are $23.00 for vegetables, $31.00 for citrus, and $75.00 for strawberries.

Production of cabbage has decreased substantially in the chlordane-resistant maggot areas of Maine, primarily because of the high cost of Diazinon® in relation to the value of cabbage and to the poor control obtained with this pesticide. In many instances a single application of chlordane is sufficient for wireworm control for several years while other more toxic materials require several annual treatments.

Increased use of chlordane may result from the cancellation of the soil insect control uses of other chlorinated hydrocarbon pesticides such as aldrin and dieldrin. Present evidence suggests that any added soil use of chlordane could increase its impact upon the environment.

I.B.2.b. Home Gardens - Alternatives other than chlorinated hydrocarbon pesticides are not registered for all uses nor are they likely to give equal control of insects such as ants, wireworms, grubs, cutworms and various other soil pests. Increased use of chlordane could result from the cancellation of soil insect control uses for other chlorinated hydrocarbon insecticides such as aldrin and dieldrin.

I.B.2.c. Lawns, Commercial Turf and Nursery Plant Stock - Alternatives other than the chlorinated hydrocarbon pesticides are neither registered for all uses nor likely to give equal control of pests such as ants, wireworms, grubs, cutworms and other soil insects. Increased use of chlordane could result from the cancellation of soil insect control uses for other chlorinated hydrocarbon insecticides sucy as aldrin and dieldrin. Loss of the currently registered insecticidal uses of chlordane as a soil application to lawns, commercial turf and nursery plant stock will have a significant impact.

There have been numerous indications of the need to continue the uses of chlordane for control of soil insect pests on lawns, commercial turf and nursery plant stock. For example, the State of New York recommends the use of chlordane at a rate of 4 lb AI/acre for the control of scarabaeid grubs which will be sufficient for four seasons of protection. The best available substitute as recommended by the State of New York is Diazinon^{R} which must be applied at the rate of 6-8 lb AI/acre on an annual basis.

It has been estimated that the loss of chlordane and heptachlor for turf use would result in damage estimated at approximately $0.50 per square foot in Pennsylvania. One acre of lost turf would cost approximately $20,000 to replace or renew. Turf grass is a primary agricultural industry in Pennsylvania and the loss of chlordane for soil insect control would be significantly damaging to the agricultural industry of that State.

The State of Mississippi has indicated that the cancellation of chlordane would leave no pesticide available for certification for movement of nursery stock under the provisions of the imported fire ant, white-fringed beetle and Japanese beetle quarantine progran involving interstate commerce of live plants. New York State also recommends the use of chlordane to control white grubs and strawberry root weevils in the New York State Tree Nursery. Chlordane is used to protect against damage from soil insects on crops that are valued in excess of $15,000 per acre with experimental trees being valued at upward of $5 - $10 apiece.

The States of Virginia, West Virginia, North Carolina and South Carolina recommend chlordane to control insects in nursery beds of tree seedlings needed to replant cut over timber areas. Total cost of the replanting procedures in North Carolina is approximately $50-$70 per acre. This forestry based industry has been reported to provide an estimated 227,000 jobs in North Carolina. The South Carolina State Commision of Forestry recommends chlordane for control of white grubs of May and June beetles and grubs of Japanese beetle in their forest tree nurseries. Without chlordane they would expect to lose practically all of the tree seedlings. The State of Vermont has estimated that damage to lawns due to the Japanese beetle larvae and mole tunneling would be approximately 50% of the turf in that state.

In addition to the above statements found to give specific information of value in considering use of chlordane on lawns, there have been numerous indications of the need to continue use of chlordane for control of lawn pests.

I.B.3 Seed Treatments - Alternatives other than the chlorinated hydrocarbons are not registered for all uses nor are they likely to give control equal to that available with chlordane. Diazinon is the only nonchlorinated hydrocarbon alternate pesticide available. The registered uses for diazinon are limited. Loss of the seed treatment uses of chlordane would have a significant impact.

I.B.4 Baits - Chlordane baits are indicated to be essential because no other materials in baits have the registered spectrum of pest activity. Toxaphene is one pesticide which might be used as an alternate to retain the spectrum of activity established for chlordane. Loss of the currently registered uses of chlordane in bait formulations would have a significant impact.

I.B.5. Agricultural Premises (excluding dairy barns and poultry houses). Chlordane is registered for control of a number of pests in agricultural premises, excluding dairy barns and poultry houses, and may be applied in areas where animal feed is stored. There are no suitable alternate pesticides for control of certain pests infesting agricultural premises.

The uses of chlordane on agricultural premises are similar to the household uses of chlordane in that they are for the control of insects in and around farm buildings, excluding dairy barns and poultry houses. When used as intended, these uses should not contaminate food or feed or present an undue health hazard.

I.B.6. Outdoor Treatments - This use includes ditchbanks, field borders, roadsides, and vacant lands. It is recognized that this use is actually a "foliar use" and general comments of I.B.1 are applicable.

I.B.7 Household and Commercial Uses - This use covers the use of sprays and dusts for control of cockroaches, ants, ticks, and a number of other household and commercial buildings pests. The insecticide treatments for pest control are usually applied inside the buildings as well as those areas near food processing or serving.

The concentrations and use directions for chlordane are regulated by interpretation number 19 of the Regulations for the Enforcement of the Federal Insecticide, Fungicide, and Rodenticide Act. Petroleum distillate solutions, diluted or concentrated, water emulsions, dusts, and pressurized dispensers which deliver a coarse spray are allowed. Pressurized dispensers may not contain over 3% chlordane while the concentrates may contain up to 72%. Dusts may not contain more than 6% chlordane. The directions for liquid formulations and pressurized sprays under all circumstances provide for applications as a coarse, wet spray or by the use of a paintbrush or similar means.

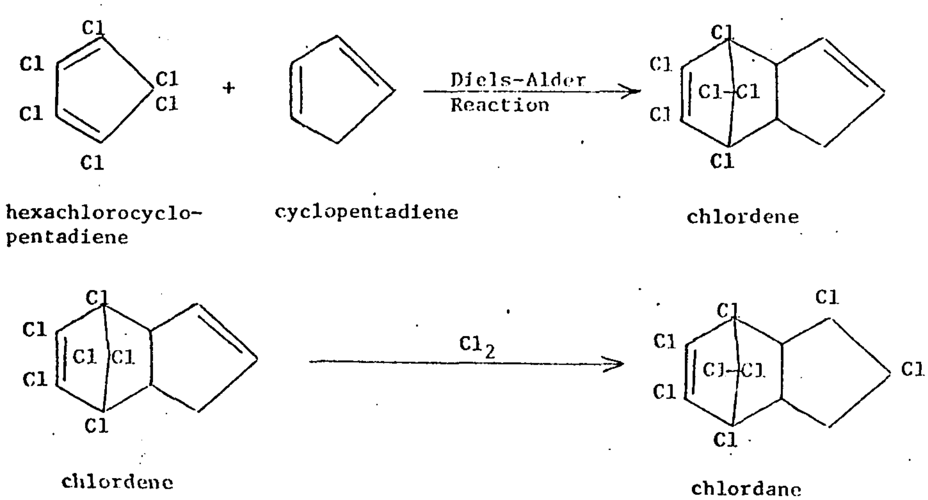
The use of chlordane to control Psychoda larvae in sewage plants constitutes a direct, although minimal, contamination of water. Psychoda fly larvae congregate on and clog the filter beds of sewage treatment plants. Chlordane is currently used at a rate of one-half lb AI poured over the bed for a period of one minute during which time approximately 3,000 gal of water will pass the filter. This gives an immediate dilution to 20 ppm of chlordane in the water. If the effluent enters a stream flowing at a rate of 500,000 gal of water per minute, it is diluted to 0.125 ppm in the first minute and to 0.04 ppm by the third minute.

CHAPTER II

Chemistry and Methodology

II.A. Chemistry - Chlordane is a member of a group of polycyclic chlorinated hydrocarbons called "cyclodiene insecticides" which include heptachlor, aldrin, Thiodan[R] (endosulfan), and Telodrin[R] (isobenzan). The first insecticide of the cyclodiene group to be developed was chlordane (M-410, German designation) which has been industrially manufactured in the United States since approximately 1947.

II.A.1. Synthesis - The carbon structure of the cyclodienes is obtained by Diels-Alder addition of an olefin to a chlorinated diene. For the manufacture of chlordane, hexachlorocyclopentadiene is reacted with cyclopentadiene to form chlordene ($C_{10}H_6Cl_6$) and this adduct is chlorinated to approximately 65% as is described in Table 1. The registered mixture of chlorinated products is called technical chlordane. The synthesis of chlordane is illustrated as follows:



II.A.2. Composition - The term chlordane has been used to designate a complex mixture of chlorinated hydrocarbons, a single chemical substance, and a mixture of isomeric forms (Food and Drug Administration Advisory Committee, 1965). Technical chlordane consists of the alpha and gamma isomers of 1,2,4, 5,6,7,8-octachlor-4, 7-methano-3a,4,7,7a tetrahydroindane (chlordane), heptachlor, nonachlor, isomers of chlordene, and other related compounds. The alpha isomer and the gamma isomer of chlordane (Velsicol notation) are known as cis-chlordane and trans-chlordane, respectively. According to Ingle (1965) technical chlordane is manufactured by a rigidly controlled process. Composition of preparations obtained by this process are consistent, but technical chlordane contains a number of compounds.

Table 1. Approximate Composition of Technical Chlordane*

(A)	Diels-Alder Adduct (DAA) of Pentachlorocyclopentadiene and cyclopentadiene $C_{10}H_7Cl_5$	2 ± 1%
(B)	Chlordene isomers in order of GLC retention time $C_{10}H_6Cl_6$	
	(1) Isomer-1, chlordene-AA: hexachlorocyclopentadiene (Hex) and "Cyclo"	1 ± 1%
	(2) Isomer-2	7.5 ± 2%
	(3) Isomers-3 and 4 (combined)	13 ± 2%
(C)	Heptachlor $C_{10}H_5Cl_7$	10 ± 3%
(D)	Chlordane isomers $C_{10}H_6Cl_8$	
	(1) Alpha-chlordane (cis-chlordane)	19 ± 3%
	(2) Gamma-chlordane (trans-chlordane)	24 ± 2%
(E)	Nonachlor $C_{10}H_5Cl_9$	7 ± 3%
(F)	Other Constituents	
	Hexachlorocyclopentadiene (C_5Cl_6) (Hex) Maximum	1%
	Octachlorocyclopentene (C_5Cl_8)	1 ± 1%
	$C_{10}H_{7-8}Cl_{6-7}$	8.5 ± 2%
	Constitutents of lower GLC retention time than C_5Cl_8, including Hex	2 ± 2%
	Constituents of higher GLC retention time than nonachlor	4 ± 3%

*The foregoing approximations are based upon unadjusted values derived from gas-liquid chromatography. Apparent values obtained are typically influenced by conditions of analysis and the chromatographic systems employed, and the relative response sensitivity of the components.

Source: Velsicol Chemical Corporation.

The composition of technical chlordane has been essentially, but not completely, determined. Reports in the literature based on early work state that technical chlordane contains 60-75% alpha- and gamma- isomers of chlordane and 25-40% subsidiary products. (Riemschneider, 1963; Melinkov, 1971; Metcalf, 1971; Buchel, 1970). According to data from Velsicol Chemical Corporation, as presented in Table 1, technical material contains a total of 38-48% of alpha and gamma chlordane.

Chromotographic techniques were used to detect seven components in technical Chlordane (Thruston, 1965; U.S. Department of Health Education and Welfare, 1970). Saha and Lee (1969) and Bevenue and Yeo (1969) described 14 distinct chromatographic components from technical and formulated chlordane. Saha and Lee (1969) and Polen (1966) using various analytical techniques confirmed the identity of the major components of technical chlordane, but the assignment of structures to some of the major components appeared to differ from structures assigned by others (Hill, 1970).

Brooks (1974) has written an extensive review of the chemistry of chlorinated insecticides including technical chlordane and its components.

Riemschneider (1963) reported technical chlordane contained four isomers of octachlor-adducts, 2-heptachloro-derivatives, 1-nonachloro and 1-decachloro derivative in addition to hexachlorodicyclopentadiene. Evidence has been presented by Reimschneider (1963) confirming the structure of the intermediate hexachlorodicyclopentadiene and the special assignment of isomers of the chlordane synthesis. The major isomers of chlordane have the endo-configuration in the carbon skeleton. The alpha isomer is an endo-isomer in which the two chlorine atoms are in a cis-configuration and the gamma isomer is an endo-configuration in which the chlorine atoms are assigned in the trans-configuration. Different nomenclature systems have been used in the past, leading to confusion.

Technical chlordane, with a viscosity of 75-120 centistokes at 130°F., is a light yellow oil; d^{20} 1.59-1.63; N_d^{20} 1.57-1.58. The product is practically insoluble in water (Gunther *et al.*, 1968) but highly soluble in organic solvents. The aromatic hydrocarbons, ketones, esters and chlorinated solvents are completely miscible with chlordane. The chlorine content is 64-67%. The melting points of the cis- and trans- isomers are very close (Benson, 1971).

cis-chlordane	107.0 - 108.0°
trans-chlordane	103.0 - 105.0°

Chlordane is relatively volatile with a vapor pressure of approximately $1x10^{-5}$ (25°C). The FDA Advisory Committee (1965) considered these aspects of the manufacture, production and identification of synthesis products of chlordane and noted that the standards of production were such as to allow the constancy of the technical mixture. This constancy has allowed adequate analyses to be made of the formulation and residues present. In the case of technical chlordane, despite difficulties inherent with a mixture of components, the current analytical means for residue determination are apparently successful, in terms of sensitivity, precision, and accuracy.

II.A.3 Chemical Reactions - Chemical reactions of chlordane are many and varied and a complete analysis of them is beyond the scope of this review. Some of these reactions have been described in the extensive reviews by Melnikov (1971) and Buchel (1970) in Wegler (1970) and Reimschneider (1963). Benson (1969) indicated that the chlorine atoms are relatively unreactive toward base. The hydrogen and chlorine atoms are not in the proper trans-planar positions for low energy elimination reactions. The four chlorine atoms attached to the aliphatic positions are protected from displacement reaction by the bicyclic bridge system. Benson indicated that the two chlorines on the olefin are also generally unreactive towards base. These chemical conditions generally coincide with the reactions that have been obtained both *in vivo* and *in vitro* with chlordane isomers. However, other data obtained photolytically (Crosby, 1969), and chemically (Chau, 1970) indicate the relative stability of chlorine atoms on the bicyclic ring.

Chau (1970) has demonstrated that prolonged contact with chromous chloride solution causes dechlorination of the methylene bridge of heptachlor and chlordene. Thus, the photolysis results of Crosby (1969) and Chau (1970) suggest the chlorinated bicyclic ring is not a completely stable entity and may undergo partial degradation,

II.A.4. Photodecomposition - Light is an important environmental force that may induce chemical transformation. With some noticeable exceptions, including plant photosynthesis, photoperiodism and color photography, most photochemical reactions to sunlight are energized by the ultraviolet (UV) components at wave lengths shorter than 400 nm.

Light intensity, including UV, is strongly affected by season, climate, latitude and other factors. The atmosphere effectively absorbs UV light, with 287 nm being the minimum wavelength ever recorded on the earth's surface; 300 nm probably represents the practical UV limit at most locations. The total intensity at wavelengths below 313 nm increases sixfold from a December minimum of 30 $\mu W/cm^2$ to a June maximum of 180 $\mu W/cm^2$ and doubles for each kilometer rise in elevation.

Korte examined the photodecomposition of some components of chlordane in acetone solution, and observed a high conversion of heptachlor, heptachlor epoxide, beta-dihydro-heptachlor and chlordane to cage-type compounds. Trans-chlordane did not yield a product even after 100 hr (Hill, 1970).

Benson et al. (1971) found that chlordane, cis-chlordane, heptachlor and heptachlor epoxide were converted on photolysis to cage-type compounds, and isolated them. The materials were irradiated in acetone solution using filters and as thin films by sunlight or by UV lamps. Although both cis and trans-isomers were degraded at similar rates, under the conditions employed only the cis-isomer formed a photo-product which was apparently a half-cage compound formed through hydrogen migration and carbon-to-carbon bond formation. The photoisomerization of cis-chlordane was apparently similar to that produced by photoisomerization of dieldrin. Photolysis of technical chlordane for 70 hr resulted in a complex mixture of products.

Trans-chlordane does not photolyze to a half-cage compound but does disappear very slowly on irradiation; trans-nonachlor behaves similarly. Also beta-dihydroheptachlor failed to yield an isolatable compound. Crosby (1969) studied the photolytic decomposition of aldrin and dieldrin and described a dechlorinated product resulting from the loss of chlorine from the olefinic portion of the presumably stable bicyclic ring. Although the photolytic alteration of technical chlordane under actual field conditions, in sunlight from various areas, has yet to be reported, it seems reasonable to assume that similar products would be obtained following ultraviolet degradation of chlordane.

II.B. <u>Methods of Analysis</u> - A number of methods have been used for the determination of residues of organochlorine compounds and most of these can be used for determining residues of technical chlordane. A gas chromatographic procedure given in the <u>Pesticide Analytical Manual</u>, Volume I (U.S. Department of Health, Education and Welfare, 1971). The history of the multiple residue technique was discussed in a review article by Burke (1971). The section on gas liquid chromatography discusses this further.

II.B.1.a. <u>Colorimetric and Total Chlorine Methods, and Color Reactions</u> - These methods were commonly used about 1950-1965 but have largely been superseded by gas chromatographic methods.

Following extraction of material from biological samples, various methods have been used for quantitative determinations of total residues of chlorine-containing compounds. Chlordane forms several colored derivatives. When an alcoholic solution of chlordane is heated with KCH and p-aminophenol, a red-brown color is obtained; with pyridine and ethylcellosolve, a red color; with pyridine and ethylene glycol, a red violet color; with diethanolamine, a violet color. These color reactions were demonstrated by Ard (1948), Davidow (1950), Ordas <u>et al.</u> (1956), Malina (1965), and Faucheux (1965). In general, plant and wax components, which qualitatively interfere with colorimetric measurements of several of the more commonly used cyclodiene insecticides, reduce the sensitivity of colorimetric methods for chlordane. Measurement of total chlorine by sodium biphenyl reduction was considered to be the most reliable quantitative method for chlordane, but it is not specific. Excellent agreement has been obtained with this method in several laboratories using chlordane formulations (Meyer, 1962). A field test developed by Chisholm <u>et al.</u> (1962) to examine termite treatments uses a color produced with 2-phenoxyethanol.

II.B.1.b. <u>Bioassay</u> - Chlordane residues may be determined semi-quantitatively by bioassay. Several insect species have been used, including housefly (Stansbury and Dahm, 1951), mosquito (Hartzell <u>et al.</u>, 1954), and a parasite of the oriental fruit moth, <u>Marcrocentrus</u> spp. (Fleming <u>et al.</u>, 1951). Recently, Sadar and Guilbault (1971) suggested the use of the enzyme system, hexokinase, as a substrate for the determination of several chlorinated pesticides. This enzyme system has a rather unique sensitivity to certain chlorinated insecticides, including chlordane, heptachlor, aldrin and DDT, but not dieldrin, kelthane or DDT analogues. At best, bioassays have been shown to be non-specific and relatively insensitive.

II.B.1.c. <u>Thin-Layer Chromatography</u> - Thin-layer chromatography, featuring various solvent systems and adsorbents, has been used to separate chlordane isomers from extraneous biological materials. Systems for organochlorine compounds are discussed in the <u>Pesticide Analytical Manual</u>, Volume 1, (U.S. Department of Health, Education and Welfare, 1971). In general, this procedure has been used as a qualitative tool in combination with gas liquid chromatographic techniques. Means for detection of material on thin-layer chromatograms are as varied as the solvent systems employed and generally require the same reagents and methods used in the colorimetric methods.

Faucheux (1965) suggested the use of diphenylamine-zinc chloride as a chromogenic reagent with a sensitivity of 5 mg. He reviewed the use of several reagents including N,N-dimethyl-phenylenediamine HCG; methanolamine-$AgNO_3$; 2-phenoxyethanol-$AgNO_3$; bromphenol blue-$AgNO_3$; Iodine; H_2SO_3; bromo-fluorescein-$AgNO_3$.

II.B.1.d. Gas Liquid Chromatography - Gas liquid chromatography is the method of choice for the qualitative and quantitative estimation of chlordane residues in foods (U.S. Department of Health, Education and Welfare, 1971); Noren and Westdb, 1968; Duggan and Cook, 1971), air (Yobs, 1971a), water (Lamar *et al.*, 1966; Feltz *et al.*, 1971; Carver, 1971), human tissue (Weirsma and Sands, 1971; Yobs, 1971b), fish (Inglis et al., 1971); and wildlife (Dustman et al., 1971). With GLC techniques contamination in small samples may be measured rapidly with high levels of sensitivity. In general, this method of detection is at least 10 times more sensitive than the colorimetric methods previously employed. This is emphasized by the analysis of 1 mg of fish tissue with a precision of 20% and 25 mg samples analyzed with a precision of +5% (Seba and Land, 1969).

The Pesticide Analytical Manual, Volume I Section 302.44c (U.S. Department of Health, Education and Welfare, 1971) gives the procedure used by the Food and Drug Administration for determination of residues of chlordane. Technical chlordane contains several significant components, and the residue of chlordane usually contains these components in proportions different from those in technical chlordane. The procedure considers all peaks representing the residue. Calculation may be based on the total area of the peaks or by "peak height addition". Procedures are also given for extraction and cleanup for the preparation of samples (Chapter 2); for the cleanup on Florisil, technical chlordane elutes with the first fraction (Eluant A, using 20% methylene chloride in hexane).

Thompson (1970), examining the *in vitro* weathering of technical chlordane, showed that not all peaks in the GLC tracing disappear at the same rate. Because of various rates of volatilization of components in the technical chlordane, the use of signal peaks versus the whole spectrum might well account for the lower values obtained with GLC than with total chlorine analysis.

Other systems of solvent partitioning have been used. Solvent partitioning with mixtures of hexane and methanol or ethanol are effective (Saha, 1971). Noren and Westoo (1968) described a method of analysis using a combination of dimethylformamide (containing 8% water) -- hexane partitioning extraction with a recovery for fortified samples ranging from 83% to 92%. The sensitivity of the extraction when using approximately 10 g samples of fat appeared to be 10 ppb.

The advent of GLC techniques with the use of sensitive detectors has enabled the chemist to extend the range of analyses to the submicrogram levels. However, this technique has introduced some of the following problems 1) coordination of recent data with those obtained with older methods, primarily colorimetric analyses; 2) in the case of chlordane GLC assays usually result in lower numerical values than the total chlorine assays; 3) establishment of a uniform GLC system for residue determination.

Alpha-Chlordane, gamma-chlordane, and particularly oxychlordane and heptachlor epoxide are difficult to separate on most GLC columns. Conder et al. (1972), report that a column containing 1.5% OV 17 plus 1.95% OV 210 will separate all four materials.

Su (1973) determined heptachlor epoxide, oxychlordane and certain other pesticides in the presence of PCB's using the Coulson electrolytic conductivity detector in the non-catalytic reductive mode at 660°C, and the column used by Conder et al. (1972). PCB's are not detected under these conditions.

II.B.2. Interference - Naturally occurring chlorinated materials usually pose no problem in the determination of chlorinated pesticides by the total chlorine method (Hylin et al., 1969). Although some chlorine-containing materials have been found in certain fungi, the possible occurrence of fungal contamination in samples for chlorinated organic assays is small. The possible interferences with polychlorinated biphenyl contaminants appear to be significant.

II.B.3. Confirmatory Methods - Because GLC detection systems (electron capture or flame ionization) are sensitive but cannot provide an unequivocal identification based on retention times, various confirmatory methods have been employed (some in combination with the GLC).

II.B.3.a. GLC - Mass Spectrometry - The use of GLC - mass spectrometry for the qualitative and quantitative estimation of pesticide residues is one of the most significant advancements in residue analysis in recent years. Francis Biros discusses applications of this technique in a chapter entitled "Applications of Combined Gas Chromatography - Mass Spectrometry to Pesticide Residue Identifications in Advances in Chemistry Series 104: Pesticides Identification at the Residue Level (American Chemical Society, 1971).

Using the combination of GLC-mass spectrometry, Biros and Walker (1970) showed that the peak with the retention time of heptachlor epoxide was in fact heptachlor epoxide. An unidentified peak was later found to be the metabolite designated as oxychlordane.

Without highly specific confirmatory techniques such as mass spectrometry these residues would not be readily identified. Possible errors have been made in the past on the identification of some GLC peaks.

II.B.3.b. Neutron Activation - Bogner (1966) reported on the potential use of neutron activation analysis for the qualitative determination of chlorinated pesticides; primarily the high cost of instrumentation has precluded the wide acceptance of neutron activation analysis.

II.B.3.c. P-values - Another confirmatory method employs the extraction of solute between two immiscible solvents. Using this technique Beroza et al. (1969), developed p-values which they have defined as the fraction of a pesticide which is distributed in the non-polar phase (usually upper) of equal volumes of a solvent pair. This method has been used as a tool in cleanup and for confirmatory identification of a pesticide and for selecting solvents for partition cleanup procedures. The p-values for gamma-chlordane have been reported with 6-solvent pairs (Beroza et al., 1969).

II.B.3.d. Carbon-Skeleton Chromatography - When chlordane is pyrolytically dechlorinated (hydrogenated, and chromatographed), the method is called "carbon-skeleton chromatography" (Asai et al., 1967). The confirmatory technique of carbon-skeleton chromatography lacks sensitivity (10 μg of sample) and materials having the same carbon-skeleton, e.g., heptachlor, heptachlor epoxide, etc., cannot be differentiated. Carbon-skeleton chromatography has been used successfully to confirm the identity of peaks of GLC which have resulted from interferences by polychlorinated biphenyls (Asai et al., 1971) and in certain instances will serve as a confirmatory method.

II.B.3.e. Derivatization - A sensitive means for the confirmative determination of chlordane has been shown to be derivatization. (Chau and Cochrane, 1969a, 1969b; Cochrane, 1969; Cochrane and Chau, 1970). The reaction of chlordane with Potassium tert-butoxide/tert-butanol with subsequent silylation achieves routine confirmation of chlordane at a level of 10 ppb when 10 gram samples are used. It was found that cis-chlordane was converted rapidly to 3-chlorochlordene and trans-chlordane was converted slowly to 2-chlorochlordane. In combination with GLC simple derivatization is useful in the qualitative confirmation of residues.

II.B.4. Formulation Analysis - The Association of Official Analytical Chemists (AOAC) methods for technical chlordane formulations are the total chlorine method and the colorimetric methods (Association of Official Analytical Chemists, 1970).

A method for determining the impurity hexachlorocyclopentadiene (Hex) in technical chlordane is also given. (AOAC, 1975, par 6.229 - 6.232).

A product AG Chlordane consisting of at least 95% of the alpha and gamma isomers of chlordane has been developed, but it is not registered. Malina (1972, 1973) has developed an AOAC infrared method for alpha-chlordane and gamma-chlordane, and a GLC method for heptachlor in AG Chlordane (Association of Official Analytical Chemists, 1973).

CHAPTER II

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CHAPTER III

Fate and Implications of Chlordane in the Ecosystem

III.A. The Fate of Chlordane in the Soil - Chlordane persists in the soil. Under experimental conditions and actual field application of pesticides chlordane has been shown to persist for extended periods of time, will not migrate, and is apparently bound to soil particles. Dependent upon the soil and climatic conditions, chlordane will dissipate. However, complete removal of the residue is a slow process. Control of some insect species in the soil is obtained for considerable lengths of time under most conditions.

Analyses of agricultural lands extensively treated with chlorinated pesticides do not show the residues as might be expected from results obtained with experimental plots. For example, there is no indication of why only 10% of the agricultural soils in Canada show only minute residues of chlordane after extensive treatments with heptachlor which contains considerable quantities of γ-chlordane. The possibilities exist that 1) the material is in the soil and bound so tightly that it cannot be extracted and analyzed or 2) under field conditions, after agricultural application, dissipation is more rapid than is anticipated from experimental conditions, or 3) the material is metabolized to products which are not recognized with the available methods of analysis.

III.A.1. Build-up and Persistence in the Soil - Chlordane is recommended for use and is used extensively for soil insect control. Studies have been carried out to determine the duration and extent of soil contamination, either under experimental or field conditions. In a series of experiments, Lichtenstein and Polivka (1959) reported the persistence of chlordane in the soil in Wisconsin. Using bioassay techniques they demonstrated that approximately 15% of active insecticide materials persisted 12 yr after application to turf soils. They further demonstrated that chlordane was more persistent than heptachlor in the soil. This could be due to the differences in the vapor pressure of the two compounds: chlordane, 1X10-5 mm/Hg; heptachlor, 3X10-4 mm/Hg (Edwards, 1966). (Tables 1, 2, 3 and Figure 1).

Chlordane, when applied at dosages of 8 to 10 lb/acre for the control of European chafer, provides complete control for at least seven to eight growing seasons (Gambrell *et al.*, 1968; Shorey *et al.*, 1958). When chlordane was applied to Hawaiian soils for the control of subterranean termites it was found that the material begins to degrade slowly within 4 yr although after 6 yr it was active as a termite insecticide. In the last three experiments, bioassay was used as a means of evaluating chemical effectiveness and no indication was given to the concentration of chlordane in the soil.

In a more recent study, Lichtenstein *et al.* (1970) determined that approximately 18% to 20% of an applied dose of chlordane was present in the soil 10 yr after application. Following the application of approximately 7.5 lb/acre, a residue of 0.925 ppm was observed after 10 yr.

TABLE 1. Insecticide Vapor Pressures vs. Disappearance from Soils

Insecticide	Average % insecticide in soil after 1 yr	Vapor pressure at 20°C (mm Hg)
DDT	80	$1.0\text{x}10^{-7}$ Slightly Volatile
Dieldrin	75	$1.0\text{x}10^{-7}$
Lindane	60	$9.4\text{x}10^{-6}$ Moderately volatile
Aldrin	26	$6.0\text{x}10^{-6}$ Volatile
Chlordane	55	$1.0\text{x}10^{-5}$
Heptachlor	45	$3.0\text{x}10^{-4}$

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TABLE 2. Persistence of Some Chlorinated Hydrocarbon Insecticides in Soil

Chemical	Average dose in lb AI/acre	Time for 95% disappearance (years)
Aldrin	1-3	1-6 (3)
Chlordane	1-2	3-5 (4)
DDT	1-2½ (10)	4-20 (10)
Dieldrin	1-3	5-25 (8)
Heptachlor	1-3	3-5 (3½)
Lindane	1-2½ (5)	3-10 (6½)
Telodrin	¼-1	2-7 (4)

a. Figures in parenthesis are doses which may be used for particular pests in unusual circumstances.

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TABLE 3. Persistence (ppm) in soil after 1 and 2 yr.

Insecticide	1 yr	2 yr
Aldrin	25	5
Heptachlor	45	10
Chlordane	55	15
Lindane	60	--
Dieldrin	75	40
DDT	80	50

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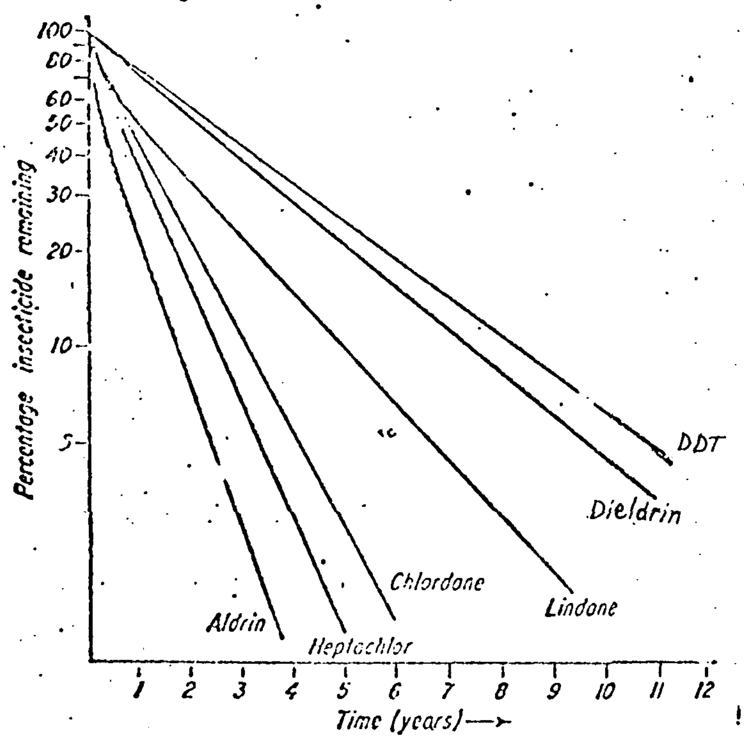

Figure 1. Breakdown of chlorinated hydrocarbon insecticides in soil

Note: Regression based on all available data.

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Chlordane was more persistent than heptachlor whether the soil was cultivated or planted in alfalfa. Cultivation reduced the residue level of heptachlor but not chlordane.

Degradation of a chemical in the soil is a function of many conditions. Generalizations on the persistence of chlordane in the soil on the basis of experimental work in another area with different soil types is not valid (Bess et al., 1966). The penetration of chlordane into the soil is primarily dependent upon the soil type and the organic matter content. Other factors such as moisture, pH, silt, and clay content play a lesser role in the penetration and stability (Carter and Stringer, 1970).

The reduction of residues of chlordane is a relatively slow process. Only 45% of the initial dose of chlordane was removed from the soil 1 yr after application; approximately 3 to 5 yr are required to remove 95% of the residue of chlordane (Edwards, 1966).

Lichtenstein et al. (1971) found that, under the conditions of their study, chlordane does not move when applied to the soil. Ninety-five percent of the residue was found in the top 6 in of soil, with 52% of the residue being in the top 2 to 4 in layer.

Chlordane was applied to soil at a rate of 145.7kg/hectare (Nash and Woolson, 1968). Thirteen years after the initial application, approximately 11% of the total material applied to the soil was present as a residue. Out of 9 chlorinated pesticides examined, chlordane was the least mobile and tended to remain in the upper soil layers. Except for dieldrin and endrin, cyclodiene insecticides were present in quantities of less than 11% of the administered dosage.

Onsager et al. (1970), demonstrated that the loss of chlordane from a loam soil was proportional to the amount applied. When application rates varied from 1.25 to 20 lb /acre, residues after 30 months in the soil were observed ranging from 0 to 48% of the initial concentration.

Chlordane was applied at 8 and 10 lb/acre and approximately 18 to 30% of the applied dose was found as a residue after 12 yr (Steward and Fox, 1971). Penetration of the pesticide was generally into the top 0 to 4-in layer of the loam soil although some penetration of 6 to 8 inches was observed.

Studies have been carried out in Canada on residues of chlordane in soils from various sections (Saha et al., 1968). In agricultural soils in Northeast Saskatchewan, only one of 20 soil samples examined contained a measurable level of chlordane (0.02 ppm). Sixteen of the 20 soil samples had residues of other cyclodiene pesticides.

In the Atlantic provinces of Canada, Duffy and Wong (1967) were able to detect chlordane in less than 10% of the agricultural lands and only at concentrations below 1 ppm. For many years the land had been exposed to heptachlor which was contaminated with high concentrations of γ-chlordane.

A more recent survey of the build-up of chlordane soils in Saskatchewan indicated that chlordane was present in 17% of the soils sampled (Saha and Sumner, 1971). Seven of 41 samples were positive for chlordane with 3 of the samples showing residue levels of 0.01 to 0.1 ppm; 3 samples showing residue levels of 0.11 to 0.5 ppm; and one sample showing a residue level of 3.91 ppm. These soils were sampled from farms having an extensive history of cyclodiene insecticide applications.

Samples of soil from six states in 1967 showed the most commonly occurring pesticides to be members of the DDT group, dieldrin, or chlordane (Wiersma et al., 1971). Only 5.4% of all samples had chlordane residues. Soils from four of the six states showed levels of chlordane less than 0.01 - 0.02 ppm.

Gish (1970), in an examination of residues in soils from eight states, showed that only one area had small residues of γ-chlordane which presumably came from contamination resulting from heptachlor application.

Attempts have been made to reduce residue levels in soil with cultivation (Lichtenstein et al., 1971) or by treatment with activated charcoal (Lichtenstein et al., 1968; Ahrens and Kring, 1968). This technique does not appear to be practical on a commercial scale and, on the basis of surveys of agricultural croplands in the U.S. and Canada, is probably not necessary.

III.A.2. Translocation into Plants - Chlordane, when applied to soil for control of soil insects, will translocate to certain plants, primarily root crops.

Onsager et al. (1970), reported that 2 yr after application of chlordane to a loam soil small residues were found in sugar beets. The concentrations were proportional to those applied to the soil.

Winnett and Reed (1968) applied chlordane to a loam soil at a level of 4 to 6 lb/acre. Residues of 75 to 100 ppb were detected in potatoes during the first year of planting. No residues were found after 1 yr. No indication was given as to the concentration of chlordane in the soil.

[illegible] et al. ([illegible]) applied chlordane at 10 lb/acre and also found residues the first year in carrots, sweet potatoes and rutabagas. Several other crops were found to contain no residues. In general, it has been found that root crops will absorb small quantities of chlordane. Carrots, radishes, turnips and onions have been observed to absorb low levels of pesticides from the soil. Boyd (1971) demonstrated that chlordane was easily translocated from soil to alfalfa, but only in the first year after application.

Harris and Sans (1967) found that although residues of insecticides were present in high levels in soil, the quantities translocated to crops were not above tolerance levels set for Canadian agriculture. Although translocation did occur, it appeared to be rather small. Lichtenstein et al. (1970) observed that in carrots, the crop which generally absorbs the greatest quantity of pesticide from the soil, approximately 10 to 15% of the soil residue levels were found in the edible portion. Boyd (1971) reported that the relationship of the soil residue to the crop residue was not consistent or predictable. Soil containing an average of 0.38 ppm in the top one quarter-inch, and soil containing 1.32 ppm in the top one quarter-inch, both gave approximately the same residue in the alfalfa. Caro (1969) was not able to establish a relationship between the concentration of pesticide in the soil and that taken up by plants.

III.B. Build-up of Chlordane in the Water - Several studies have indicated that contamination of water by chlordane is not a widespread problem. Waters examined in 1966 showed positive values of chlordane ranging from 5 to 75 ppt. The sensitivity of the method was reported to be 1 to 5 ppt. (Green et al., 1966). Water from Galveston Bay was essentially free of chlordane residue in 1964 following a mosquito control program in which chlordane was used (Casper, 1967). Large amounts of chlorinated pesticides applied to crops in the Mississippi River Delta showed as residues of cyclodiene insecticides in only two areas close to manufacturing and formulating plants (Barthel et al., 1969).

Schafer et al. (1969), examined drinking water, originating from the Mississippi and Missouri rivers, for chlordane and other pesticides. They observed that chlordane did not appear to be a si nificant contaminant of drinking water. Levels above 0.25 ppb were found in 14 of 63 samples of drinking water examined. Twelve of the 14 samples were from one location (Kansas City). Twelve of 28 samples taken from the Kansas City area were positive for chlordane. Examination of raw water showed that 11 of 46 samples had traces of chlordane. Again the majority of the samples were from the Kansas City area and all were not uniformly contaminated. Although the study showed a large proportion of samples containing chlordane (>0.25 ppb) most of the samples were from one area which apparently had a local contamination. The chlordane concentration of the Kansas City water samples was in excess of 0.25 ppb. Abusive use of pesticides will result in residue levels in water as evidenced by Shea (1970) who described the high chlordane content of a stream into which a commercial applicator had dumped a pesticide.

Measurements of chlordane content in rainwater in the United Kingdom at a sensitivity of 1-2 ppt showed that no detectable levels of chlordane were evident (Tarrant and Tatton, 1968). Significant quantities of BHC, DDT and its analogues, and dieldrin were observed in rainwater at all times of the year and in all locations in the United Kingdom.

In vitro studies indicate that chlordane residues in water will not be a significant problem. Bowman et al. (1964), examining the fate of several chlorinated pesticides in a static, nonmoving water system concluded that the nonpolar materials will co-distill with water and thus be removed more quickly than the more polar pesticides. They demonstrated chlordane was removed more readily than other chlorinated pesticides including lindane, DDT, dieldrin and heptachlor epoxide. Although these studies do not correlate all of the factors occurring in nature, it is conceivable that co-distillation phenomena in the aquatic environment will result in a reduction of the residues of chlorinated insecticides which might otherwise occur. Further in vitro studies by Bevenue and Yeo (1969a, 1969b) show that when chlordane is exposed to water or water vapor, various changes occur, and some of the components are removed with a short period of time. This study indicates that heptachlor, a natural component of technical chlordane, disappears when exposed to water for 14 days. This study confirms the observations by Bowman et al. (1964) that heptachlor in aqueous solutions is more volatile and is removed faster than γ-chlordane. The relationship of chlordane to heptachlor in water is similar to that observed in soil, where because of differences in the vapor pressure, heptachlor is less persistent.

It has been demonstrated that chlordane residues probably will not occur in drinking water or water supplies within the United States except under conditions of misuse. However, if contamination does occur the removal of contaminants can be accomplished with charcoal (Weber and Gould, 1966). It has been found that levels of pesticides in the range of 1 to 100 ppb can be effectively removed from water by activated charcoal filtration.

III.C. Air - The atmospheric contamination by chlordane does not appear to be a major environmental problem. Tabor (1966) reported the presence of chlordane in air over agriculture and nonurban areas at levels approximating 30 ngm/m^3. Chlordane was not found in air over urban areas where it had been used for mosquito abatement programs. In the fall season, when agricultural use of chlordane ended, atmospheric contamination was not observed in agricultural areas. Jeigier (1969) observed that detectable levels of chlordane were found in the atmosphere of apartments, stores and cafeterias which had been treated by professional pest control operators for insect control. Levels of 0.8-0.92 mg/m^3 were frequently observed during the spray operations. Calculations indicated that the high level exposures were significanlty low so as to not represent a toxicological hazard to the operator.

Examination of chlordane in air of homes treated for termite control showed essentially that no traces of chlordane from newly treated houses was evident (Malina et al., 1959). Of 12 houses studied, two showed positive levels of chlordane with a maximum level of 0.04 μg at 126 days after treatment. Concentrations of chlordane in the air of houses treated for insect control appear to be extremely low.

III.D. Effects on Flora and Fauna - As chlordane is primarily a soil insecticide, one of the most significant features of its effect on the environment should be considered to be its effect on the soil fauna.

Edwards (1969, 1970) evaluated the ecological role played by invertebrates in the soil and the effects of pesticides on these organisms. A primary role of the soil fauna is the disintegration and digestion of plant residues to their organic and inorganic constituents, and working of the products into the soil structure.

The most important of the animals involved in soil conditioning are the earthworms followed closely by related worms and other arthropods. In places where only a few of these animals are present the soil is usually of poor structure and contains distinct layers of undecomposed organic matter near the surface. If there were no invertebrate populations in soils the process of soil formation would be slow or would stop altogether with drastic effects on the soil's fertility. Although not all soil animals are beneficial, the vast majority are vital to the continued well-being of the environment.

The general relationship between the amount of insecticide applied to the soil and the number of soil animals killed is not directly proportional but is more nearly logarithmic: a dose 10 times greater may kill only twice as many animals. It is, however, the more persistent pesticide, rather than the more toxic ones, that have had the most dramatic affect on the numbers of soil animals.

The most valuable of all soil invertebrates to man is probably the earthworm; these animals break down much of the plant debris reaching the soil and turn over the soil and aerate it. Although earthworms are not susceptible to many insecticides, chlordane, heptachlor and certain selected organophosphate and carbamate insecticides seriously decrease populations of earthworms. This aspect of chlordane toxicity to earthworms is valuable only in its use as a turf insecticide, whereas on golf course greens the presence of earthworms is undersirable and control is effected by chlordane. Another aspect is that chlorinated hydrocarbons can concentrate in the fatty tissues of earthworms, and although these are not toxic in themselves they may serve as a lower link in a food chain and as a source of residues in higher animals.

Gish (1970), examining the chlordane residues in soils from agricultural lands, observed that only one of eight states examined had levels of chlordane present. On the other hand, there were levels of approximately 25 ppb in earthworms indicating that earthworms tended to concentrate chlordane in their bodies when γ-chlordane was present below the sensitivity of the methods used to detect it in the soil.

II.D.2. Microflora - Data on the effects of chlordane on various other non-target organisms within the environment are scant. Chlordane at 1 ppm was found to affect phytoplankton by inhibiting carbon fixation (Ware and Roan, 1970). All cyclodiene insecticides, except endrin, were effective in inhibiting phytoplankton carbon fixation.

Winely and San Clemente (1970) observed that chlordane inhibited the growth and nitrite oxidation of Nitrobacter agiles. This organism is vital for the oxidation of the ammonium ion to the nitrate ion in the soil. The physiological effect of the interaction of chlordane with other organisms affecting nitrate production is extremely important and has not been determined. These authors also indicated that chlordane inhibited cytochrome-C-oxidase activity in Nitrobacter.

An examination for the presence of chlordane in water, suspended water plants, algae, chubs, bass, and clams in water from an area of extensive agricultural use indicated that the presence of chlordane was minute and no substantial build-up was evident in any of the organisms or media examined (Godsil and

Johnson, 1968). The concentration factor was 1.91 for algae, 1.20 for chubs, 0.9 for clams, and 0.45 for vascular plants, indicating no magnification of chlordane residues.

III.D.3. Shellfish - Examination of 132 samples of oysters from the South Atlantic and Gulf of Mexico areas showed that 20 samples were positive for chlordane with 19 of the 20 indicating levels of less than 10 ppb and one sample showing a level of 10 ppb (Bugg et al., 1967). Almost no chlordane was found to be concentrated in the oyster samples although positive higher values were obtained for most other chlorinated pesticides. Casper (1967) observed that oyster samples taken from Galveston Bay in 1964 were free of chlordane residues which was at that time being used in extensive mosquito control programs.

III.D.4. Fish - Extensive surveys have been made for chlordane residues in fish during the past several years. Henderson, et al. (1969), examined 590 fish samples from 50 stations in the Great Lakes and major river basins. One hundred and twenty-eight samples had residues of chlordane. However, only two areas (one in New York's Hudson River and one in Alabama's Tombigbee River) had residues greater than 1 ppm. Of the 128 positive fish samples obtained, 61 had residues of both chlordane and heptachlor epoxide. In general, the values were well below 0.5 ppm in most positive samples, and apparently the residues of chlordane existing in fish are extremely low and scattered.

Henderson et al. (1971), in a continuation of this study reported that residues of chlordane were found in fish at 6 of the 50 stations examined in 1969. Positive values were found in 16 of the 147 samples examined ranging from 0.09 to 13.5 ppm. Duke and Wilson (1971) examined the livers of fish from the Pacific Ocean and found no chlordane present in the 34 species of fish examined. Other chlorinated pesticides and PCB's were evident. It appears reasonable to assume at the present time that there is no substantial build-up of chlordane in fresh water fish, salt-water fish and lower forms of marine life including the oyster which is well known for its tendency to concentrate organochlorine pesticides.

Fish sensitivity to chlordane varies with the species, with fathead minnow more sensitive than goldfish, guppy, channel catfish, and rainbow trout (Jones, 1964). Chlordane was found to be less toxic than aldrin, dieldrin and endrin to the minnow, goldfish and guppy but more toxic than heptachlor. Chlordane is the least toxic of the cyclodiene compounds to the rainbow trout. Chlordane was found to be less toxic than DDT, γ-BHC and toxaphene to fingerling bluegill and large mouth bass. Macek et al. (1969), confirmed that chlordane was less toxic than other chlorinated pesticides to the bluegill. The following compounds were observed in order of decreasing toxicity: endrin, toxaphene, aldrin, dieldrin, methoxychlor, lindane and chlordane. Temperature was shown to have a marked effect on the susceptibility of bluegills to chlordane. This may be explained by the increased rate of absorption or the increased metabolic conversion of chlordane to a more toxic metabolite at higher temperatures.

III.D.5. Birds - There is little available data on the toxicological hazard of chlordane to various species of wildlife. Tucker and Crabtree (1970) reported that the female mallard duck (4-5 months old) was relatively insensitive to the acute effects of chlordane with an acute LD_{50} of 1.2 g/kg. Wazeter (1968) studied the subacute toxicity of chlordane to the Cotunix quail (2 weeks old). Quail were fed diets containing chlordane at levels of 25-200 ppm for 28 days. Death occurred at 200 ppm dietary levels, preceded by signs of hypoacticity, ataxia and prostration. The same signs were seen at 100 ppm although no deaths occurred and the animals appeared to recover rapidly, appearing normal at 28 days. No toxic effects were noted at 25 ppm in this study.

Although chlordane has been found as a residue in soil and as a contaminant in water, the build-up in wildlife from environmental exposure does not appear to be significant. Benson and Gabica (1970) found no chlordane residue in starlings, although traces of heptachlor and heptachlor epoxide were found in their fat. These birds are not at the top of the food chain but contribute to the diets of raptorial birds.

No chlordane was found in eggs of several birds (pheasant, bluewinged teal, and coots) by Johnson et al. (1970). Substantial levels of heptachlor epoxide were found in all eggs at levels varying from 0-10 ppm in the coot, 7-79 ppm in the teal and 16-220 ppm in the pheasant. In addition to the high concentrations of heptachlor epoxide there was evidence of high concentrations of other pesticides in the eggs. However, there was no evidence of reproduction problems.

An examination was made of birds and insects found in association with cotton fields heavily treated with insecticides including chlordane. No chlordane was found in any of the bird samples and only a trace of chlordane was found in an adult mayfly (El Sayed et al., 1967).

CHAPTER III

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CHAPTER IV

Residues in Crops and Food Items

IV.A. Tolerances - During the year 1950, public hearings were held on tolerances for certain pesticides on raw agricultural commodities. At that time toxicity and residue data for chlordane were presented. Taking all the evidence into consideration, and on the basis of criteria for safety at that time, the Food and Drug Administration (FDA) deemed that the margin of safety was sufficient to justify a tolerance of 0.2 ppm for residues of chlordane in or on 46 raw agricultural commodities (Federal Register, March 11, 1955; 20 FR 1473).

In 1963, FDA reevaluated the toxicological data on chlordane and found the available data inadequate to support a conclusion regarding the safety of the tolerances for chlordane and proposed that these tolerances be repealed and a tolerance of zero be established for all listed crops (Federal Register, December 5, 1963, 28 FR 12938). The Velsicol Chemical Corporation challenged the decision by the FDA, and the National Academy of Sciences, National Research Council appointed an FDA Advisory Committee to review the situation. The Advisory Committee recommended that the tolerance level of chlordane remain at 0.3 ppm. The FDA, after consideration of the findings and with the recommendations of the Advisory Committee and other available data, concluded that a tolerance of 0.3 ppm chlordane containing not more than 1% of the intermediate compound hexachlorocyclopentadiene be established on various raw agricultural commodities (Federal Register, April 5, 1965, 65 FR 3563).

Tolerances for chlordane were reviewed by the Food and Agricultural Organization/World Health Organization (FAO/WHO) (1968), and the following levels were presented: United States, 0.3 ppm (on wide variety of foods, approximately 50 individual crops); Canada, 0.3 ppm (on a wide variety of foods); European Economic Community, 0.2 ppm (combined total of all cyclodiene residues on fruits and vegetables); Netherlands, Belgium, Luxembourg, 0.1 ppm.

IV.B. Acceptable Daily Intake - On the basis of results of two long-term feeding studies in the rat, a no-effect level was established at 20 ppm; or 1 mg/kg/day (FAO/WHO, 1968). On the basis of the results of a 2-yr. feeding study in the dog, a no-effect level for dog was established at 3 ppm or 0.07 mg/kg/day. The acceptable daily intake for man was estimated to be 0.001 mg/kg body weight (Food and Agricultural Organization/World Health Organization, 1968).

IV.B.1. Acceptable Daily Intake - Chlordane residues in crops and food items were evaluated by the 1967 FAO/WHO Joint meeting (FAO/WHO, 1968). In general, the data suggest that the highest residues consistent with good agricultural practice will result in residues in root crops and, under certain conditions, in the leafy and stalk vegetables. General information concerning residues resulting from uses constituting good agricultural practice are summarized in Table 1.

TABLE 1. Residues of Chlordane in Crops

Crop	Residue (ppm)
Alfalfa	0.01-0.16
Barley, grain	0-0.06
Barley, straw	0.98-2.65
Beans	<0.01
Beets	0.17
Beet tops	0.01-0.1
Bell Peppers	
Broccoli	
Cabbage	
Cantaloupe	0.01-0.1
Carrots	0.01-1.5
Collards	
Cucumbers	0.08
Eggplant	
Lettuce	0.04
Peaches	0.08
Peanuts	1.74
Pineapple	0.15
Potatoes	<0.01-0.23
Radishes	0.03
Rutabaga	0.08-0.5
Snap beans	<0.01
Strawberries	<0.01
Sweet potatoes	0.01-0.4
Sugar beets	0.04-0.37
Tomatoes	<0.01
Turnips	0.01-0.16
Turnip tops	0.01-0.1

IV.B.2. Residues in Meat, Milk, and Eggs - Chlordane is absorbed from the gastrointestinal tract and through the skin. It is stored in the meat and adipose tissue, accumulates in the milk, and will pass into eggs. Administration of chlordane either by a single dermal application (Kawar, *et al.*, 1968), in the feed (Carter *et al.*, 1953; Herrick *et al.*, 1969), or from being fed in pastures containing chlordane residues (Westlake *et al.*, 1963; Knipling and Westlake, 1966) has been shown to result in significant residues in milk, meat and eggs.

Westlake et al. (1963) observed that cows grazing on pastures to which levels of 0.5 lb/acre had been applied showed an average of 0.03 ppm chlordane in their milk. Lower treatment levels of chlordane produced no milk residues. Heptachlor epoxide was observed in the milk samples and may have risen from the presence of heptachlor (6.4%) in the chlordane formulation or might be an artifact related to the presence of oxychlordane.

Tuinstra (1971) examined human milk and reported the presence of 0.06 ppm heptachlor epoxide although no chlordane was observed. Saha (1969a) reviewed some early data showing residues in milk and fat from chlordane-treated crops and from chlordane-treated animals. He concluded that chlordane occurring as a residue in food crops will pass into milk.

Chlordane as a soil contaminant will migrate to certain crops. However, the probability is small that contamination of meat and milk will result from such residues.

Herrick et al. (1969) fed chickens levels of 0.08 ppm chlordane in feed for one week and detected no residues in the egg. They reported that a subsequent study at higher dosages resulted in residues in eggs which were reduced very slowly upon cessation of the feeding. The administration of 10 to 15 ppm chlordane to hens for five days resulted in residues of chlordane in fat (11 ppm) light meat (2.1 ppm) and dark meat (2.3 ppm). Hens, fed chlordane-containing diets for 5-1/2 months, were found to have residues of chlordane-containing materials in the fat and egg yolks. The residues in fat consisted primarily of O-chlordane, nonachlor, oxychlordane and compound E (probably a chlordene isomer). The total residues in fat were not substantially removed upon cessation (for periods of up to 30 days) of feeding.

Chlordane in commercial animal feed, as a source of residues in meat and milk, has been shown to be generally in the range of less than 0.05 ppm.

IV.C. Pesticide Monitoring

IV.C.1. Market-Basket Surveys - Surveys of foodstuff for the presence of chlordane have demonstrated that chlordane is infrequently present and only in low levels. Fifty percent of over 50,000 total samples taken during the period of 1964 to 1966 by the FDA contained pesticide residues. Approximately 0.1% of the samples contained residues of chlordane. Kraybill (1969), Duggan (1969) and Duggan et al. (1971), examining the market-basket surveys of the FDA, reported that chlordane was present above tolerance levels in only 17 of 25,000 samples examined. Chlordane is not among the top 10 chlorinated pesticides usually found as residues in food.

An examination of the chlordane residues in food in the United States from 1963 through 1969 indicated that there were traces of chlordane found on several domestic food crop items. The average value of these residues was between 1 and 5 ppb and was less than 1% of the samples tested. Occasional higher values were obtained which were always lower than 0.5 ppm. In the following products no residues of chlordane were observed: milk, dairy products, fruit, vegetables (leaf and stem), beans, meat (fat), eggs, fish, animal grains, infant and junior foods, nuts, and milk. Traces (0.001-0.005 ppm) were found on the following items: grains and cereals, vine and ear vegetables, root vegetables, poultry, shellfish, soybean products, corn, grain and oleomargarine. Finite residues were found on several cotton seed products: seed, 3 ppb; crude cotton seed oil, 14 ppb; cotton seed meal, 8 ppb; refined oil, 6 ppb; corn oil, 77 ppb.

IV.B.2. Other Residue Surveys - Field, wholesale and retail market sampling of agricultural commodities in Georgia indicate that levels of chlordane (some slightly higher than tolerance) were not widespread (Brown, 1969). In two of the three years during which the samples were taken, levels of chlordane above tolerance were reported.

Of 66 samples of a total diet in England and Wales taken in 1966-67, no chlordane (with a limit of sensitivity of 1 ppb) was observed (Abbott et al., 1969). Small quantities of Heptachlor epoxide were reported in meat, fat and cereals.

IV.C.3. Residues on Prepared Foods - Chlordane may become a contaminant of foods by several means in the household. The most obvious means of contamination is by direct treatment of cupboards (Wright and Jackson, 1971) by absorption from chlordane-treated shelf paper (Yeo and Bevenue, 1969a). Unpackaged wheat flour, polished rice and sugar were reasonbly effective in absorbing volatile components of chlordane. Chlordane will penetrate packaging materials and contaminate foods.

IV.D. Effect on Food Flavor - Although chlordane may be present in foods as a result of soil application, several studies have shown that its probable presence in food will result in no off-flavor or reduction of quality of the agricultural product. Studies have been reported for potatoes (Kirkpatrick, 1955; Greenwood and Tice, 1949), strawberries (Sweeney et al., 1968) and peanut butter (Gilpin et al., 1954). Although these studies did not measure the residue levels in the food it was assumed that a concentration of chlordane was present. However, Morgan et al. (1967) found residue levels greater than 1 ppm in peanuts following treatment at 2 lb/acre.

IV.E. Removal of Residues - When excessive pesticide residues occur in food and other media there are several common procedures for the removal of these contaminants. Street (1969) reviewed the common procedures for the removal of residues from food and from the environment including removal of residues from animals which might be contaminated. The problem of removing residues from soil and water takes on a significant dimension and removal is not only generally ineffectual but costly and prohibitive.

General methods including cultivation, planting absorbable crops, carbon absorption and leeching, all of which generally transfer the residue from one environmental factor to another. Many food processing operations, including washing, cooking, heating, etc., reduce the residues of most materials on food, depending primarily on the individual compounds. Cooking procedures which remove fat are generally helpful in removing chlordane residues from meat (Liska and Stadelman, 1969).

The International Union of Pure and Applied Chemistry Commission on Terminal Residues (Egan, 1969) considered the influence of cooking or processing operations on the nature and extent of residues of chlordane. Simple cooking had no significant effect on the level or composition of residues although processing operations for milk drastically reduced residues in certain products A reduction of almost 90% of the residue found directly after spraying alfalfa was obtained by standard handling and drying procedures normally used (Dahm, 1962). In the normal commercial production of vegetable oils, processes, including hydrogenation and carbon clarification, removed all traces of chlordane residues (Gooding, 1966).

Several recent studies have indicated that processing of milk into various products is effective in reducing chlordane residues (McCaskey and Liska, 1967; Li et al. 1970).

Approximately 90 to 100% of chlordane residue in potatoes was observed to be present in the peel and removal of the peel effectively reduced chlordane levels to zero (Saha et al., 1968). Boiling whole potatoes for 25 min removed only minute quantities of the residue while baking at 400°F for 1 hr. was effective in removing 80% of the residue. Washing and boiling rice contaminated with clordane was effective in removing 60 to 80% of the residue (Bevenue and Yeo, 1969). Cooking wheat flour was somewhat less effective but did remove an average of 53% of the residue. During the processing of chicken containing residues of chlordane, the pesticide content was dramatically reduced (Mc Caskey et al., 1968). Cooking chicken which contained from 2.1 to 2.3 ppm in meat, for 3 hr reduced the pesticide level to 0.8 ppm. When chicken was processed most pesticides associated with the fat were removed when the fat content was reduced by cooking. Apparently, with chlordane, washing and cooking are effective means of reducing residues in certain instances.

CHAPTER IV

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CHAPTER V

Toxicology and Epidemiology of Chlordane

V.A. Toxicity to Laboratory Animals - No exact standards of identity exist for technical chlordane except the percent of chlordane (68-69%) in the product. Thus, the pharmacological and toxicological properties may vary from experiment to experiment bacause of possible variation in the composition of chlordane. However, Ingle (1952) contends that chlordane is not as toxic "as reported several years ago," due to elimination of the highly toxic intermediate, hexachlorocyclopentadiene which is now present in amounts of less than 1% in technical chlordane. The U.S. specifications of chlordane call for not more than 1% hexachlorocyclopentadiene.

Technical chlordane, on which the majority of the toxicity studies have been carried out, is a mixture of substances, including alpha-chlordane, beta-chlordane, chlordene, hexachlor, heptachlor, nonachlor, and several minor components including hexachlorocyclopentadiene. The technical grade is a mixture containing 36-46% chlordane isomers and closely related chlorinated bicyclic analogs.

Chlordane is absorbed from the gastrointestinal tract, the respiratory tract, and through the skin (Ambrose et al., 1953). It is stored in the adipose tissue of rats, sheep, goats, and cows and is transmitted to the milk.

Chlordane acts on the central nervous system, but the exact mechanism of this action has not been elucidated. Large doses induce nausea and/or vomiting. On repeated dosage, chlordane produces microscopic changes in the liver and kidneys of some experimental animals. Somewhat different lesions may be produced by a single fatal dose.

Chlordane stimulates liver microsomal activity. Single doses or multiple doses at relatively low levels have been shown to increase microsomal activity in the rat. It has been demonstrated that the acute administration of chlordane affects steroid action in mammals.

V.A.1. Acute and Subacute Toxicity Studies -- Chlordane is a central nervous system stimulant and toxic doses produce hyperexcitability, lack of coordination, tremors, and convulsions. Barbiturates are effective against convulsions induced experimentally from all central locations. It, therefore, appears that the symptoms of chlordane poisoning have their origin in the central nervous system (Stohlman and Smith, 1950).

V.A.1.a. Acute and Subacute Oral Toxicity - Radeleff(1948), Choudhury and Robinson (1950), and Choudhury (1953) described the typical chlorinated hydrocarbon insecticide signs and symptoms which include motor ataxia, convulsions and cyanosis followed by death. The pathological signs include hemorrhage of the gastrointestinal tract, kidneys, lung, and heart. Pulmonary congestion and edema, and degeneration of the central nervous system are also observed.

When a diet containing 1000 ppm of chlordane was fed to 12 male rats, all of them died within 10 days. When 12 rats were fed 500 ppm, all died within 70 days; Nine of 12 rats fed 300 ppm were alive after 100 days (Stohlman et al., 1950).

Daily oral doses of 6.25 to 25 mg/kg of chlordane given to 5 rats for 15 days produced no tremors or convulsions, but daily doses of 50 mg/kg produced toxic symptoms and two of the animals died. When chlordane was fed at levels of 100 mg/kg, all of the animals died. Intracytoplasmic bodies in the liver cells were found at all levels and their number as in proportion to the dose used (Ambrose et al., 1953).

Groups of 6 females and 6 males were fed 2.5 ppm or 25 ppm of a sample of technical chlordane containing 60 to 75% chlordane and 25 to 40% unrelated products for up to nine months. Centrolobular cell hypertrophy, peripheral migration of cytoplasmic granules and the presence of cytoplasmic bodies were observed in 1 male at 2.5 ppm and in 5 males at 12.5 ppm (Ortega et al., 1957).

Chlordane was given in varying oral doses to dogs for 7 days; convulsions were seen in one dog at 200 mg/kg (lowest dose) but 700 mg/kg (highest dose) did not produce any effect (Batte and Turk, 1948).

Four groups of 2 to 4 dogs were given chlordane orally in doses of 5 to 200 mg/kg body-weight. All of the dogs died within periods of 25 days to 93 weeks (Lehman, 1952).

V.A.1.b. Dermal Toxicity - Ingle (1965) observed that hexachlorocyclopentadiene in small amounts was rapidly absorbed through the skin producing severe liver damage. He attributes much of the toxicity of early technical chlordane to its content of this intermediate. Ingle states that the dermal toxicity of the current technical chlordane is reduced due to its lower content of hexachlorocyclopentadiene.

V.A.1.c. Inhalation Toxicity - Ingle (1965) described deaths of pigeons at FDA and mice at Carworth Farms, Inc. which were placed in an animal room after it had been cleaned with solutions containing chlordane. Nickerson and Radeleff (1951a, 1951b) exposed pigeons (60 days) and young chicks (30 days) to high levels of chlordane (1g/sq ft) with no apparent adverse effects on either. Moore and Carter (1954) observed that spraying turkey cages with a mixture of 2% chlordane and 0.4 lindane caused subsequent high mortality of the turkeys. Findings by Ingle (1965) and others on a wide variety of animals indicate in early preparations that hexachlorocyclopentadiene, not chlordane, was probably the primary cause of the irritant and toxic properties of the preparation. Ingle (1965) observed that small amounts of the intermediate were rapidly absorbed through the skin to produce severe liver damage.

Table 1. Acute Toxicity of Chlordane in Animals

ANIMAL	ROUTE	LD_{50}	REFERENCES
Rat	Oral	200-590*	Ambrose et al. (1953) Ingle,(1955) Stohlman et al. (1950)
	Oral	335-430	Gaines (1960)
Mouse	Oral	430	FDA (1947)
Rabbit	Oral	100-300* 20-40	Stohlman et al. (1950) Ingle (1955)
Goat	Oral	180	Welch (1948)
Sheep	Oral	500-1000	Welch (1948)
Chicken	Oral	220-230	Turner and Eden (1952)

*The differences are explained by the use of different solvents and by the fact that the chlordane produced prior to 1950 contained a considerable amount of hexachlorocylopentadiene (Ingle, 1965; Lehman, 1952).

V.A.2. Chronic Toxicity Studies - All rats on 1,000 ppm dietary chlordane died within 10 days; all rats on 500 ppm died within 70 days; and, 3 of 12 rats on 300 ppm died within 100 days (Stohlman *et al.*, 1950).

Daily oral administration of chlordane at levels up to 25 mg/kg to rats for 15 days produced no tremors or convulsions, but caused toxic symptoms and death of 2 of 5 rats (Ambrose *et al.*, 1953). Rats fed dietary chlordane for up to nine months showed cellular alteration of the liver in 1 of 3 males and none of 3 females on 2.5 ppm and 2 of 3 males and none of 3 females on 25 ppm. "Lipospheres" were observed in the liver cells of one animal at 2.5 ppm chlordane. Hepatic cell margination and/or hypertrophy were observed in the males at 25 ppm chlordane (Ortega *et al.*, 1957).

In experiments conducted by FDA, rats were given from 25 to 75 ppm chlordane in the diet for 2 yr. The two higher levels caused moderate to severe signs of intoxication. The lowest level caused histologically evident liver damage. Lehman (1965) reported that all rats fed chlordane at dosage levels of from 2.5 to 400 ppm in the diet for 2 yr showed specific, though minimal hepatic cell changes characteristic of chlorinated hydrocarbon insecticides. These changes were apparent at the lowest dose, though minimal, and progressively increased in severity with increasing feeding levels. Liver/body-weight ratios increased in males at 25 ppm and in females at 75 ppm and were proportionately greater at higher levels.

Rats were fed 5 to 300 ppm technical chlordane for 2 yr. The lowest level at which tremors and convulsions appeared (or could be induced) was 30 ppm; growth was affected at 150 ppm; and liver damage was detected histologically at 10 ppm (Ingle, 1952). Rats showed no symptoms of toxicity on a diet of 150 ppm chlordane for 80 weeks, followed by 4 weeks on a chlordane-free diet, and then starved in an attempt to induce rapid release of residual chlordane from body fat.

In reinvestigation of the above study, levels ranging from 2.5 to 300 ppm chlordane in the diet were fed (Ingle, 1965). Lowest levels to affect growth and mortality and to cause microscopically evident liver damage were 300 and 50 ppm, respectively. Ambrose et al. (1953) fed rats levels ranging from 10 to 1280 ppm chlordane in the diet for 407 days. Liver weight was increased at 320 ppm and above. Cytoplasmic vacuoles containing fat and clusters of granules at the periphery of the cytoplasm were seen in males at 40 ppm and above and in females at 80 ppm and above.

In dogs fed chlordane at levels ranging from 80 to 320 ppm for up to 90 weeks (Lehman, 1965) growth was adversely affected at all levels, and all animals died. In a histopathological examination of the dogs, fatty degeneration of the liver was found to be the principal lesion at the 200 ppm level.

V.A.3. Reproduction Studies - Rats in a 3-generation reproduction study received dietary chlordane at levels ranging from 0.3 to 60 ppm. Levels up to and including 30 ppm chlordane had no affect on fertility, numbers of young, numbers of litters, or weight, growth, or mortality of the young animals to weaning. Autopsies of animals, after weaning, showed no gross or microscopic differences between the goups. At 60 ppm there was a high mortality in the second F_3 generation during the latter part of the nursing period.

Those animals that died showed gross and microscopic pathology changes characteristic of chlordane intoxication.

Survivors of this generation, however, showed no tissue changes. A third set of F_3 litters at 60 ppm again showed high mortality during the nursing period with gross and microscopic tissue changes characteristic of chlordane intoxication. A third F_3 generation litter from females removed from the 60 ppm group and placed on a chlordane-free diet for 30 days prior to remating showed no differences in any respect from control litters. There was no evidence of teratogenicity or tumorigenicity observed during the study (Food and Agriculture Organization/World Health Organization, 1968).

In a review of the perinatal toxicity of chlordane, Khera and Clegg (1969) reported that control rat pups suckled by parents fed 150 ppm chlordane exhibited toxicity due to chlordane residues in the milk.

The normally low levels of drug-metabolizing enzymes in the new-born rabbit were enhanced by treating the rabbit pups or the mothers with chlordane (Fouts and Hart, 1965). Chlordane apparently was excreted in the milk and stimulated the rabbit's drug metabolizing enzymes.

Tuinstra (1971) observed that human mother's milk did not contain chlordane as such but did contain 0.6 ppm heptachlor epoxide. As mentioned in other sections this observation might well be a combination of materials including oxychlordane. It was indicated that there appeared to be no physiological effect on infants to the presence of the chlorinated pesticides in the milk. Keplinger et al. (1968) reported that 25 ppm chlordane in the diet of mice for three generations had no effect on reproduction, but 50 and 100 ppm caused significant effects.

Chlordane is a possible contaminant of milk in the form of heptachlor epoxide or oxychlordane. Traces of chlordane or its metabolites in milk have been shown to have an effect on offspring. Apparently this affect appears to be limited to increased metabolic rates in the liver.

Chlordane fed at 25 ppm in the diet for eight weeks produced levels of 18 and 12 ppm chlordane in the fat of calves and sheep, respectively. After feeding was halted, the former level declined to zero within 20 weeks and the latter level was reduced in four weeks (Claborn *et al.*, 1953).

V.A.4. Carcinogenic Studies - No carcinogenicity studies, per se, have been carried out on chlordane. However, chlordane was not shown to be tumorigenic in long-term studies in rats (Ingle, 1965) or dogs (Wazeter, 1967).

V.A.5. Mutagenic and Teratogenic Studies - No mutagenic or teratogenic studies have been carried out on chlordane. However, in long-term rat (Food and Agricultural Organization, 1968) and mouse (Keplinger *et al.*, 1968) reproduction studies no evidence of teratogenesis was apparent.

V.A.6. Metabolic Studies - The metabolic fate of chlordane in biological systems is complicated due to the complex of components in the technical product. A complete picture of it would have to account for biological fate o each component, modified by any interaction of those that might occur *in vivo*.

Recently, the synthesis of both ^{14}C radioactive isomers of chlordane was reported (Korte, 1966). Following administration of these to rodents, chiefly hydrophilic metabolites and unchanged parent compound were excreted. Following an intravenous dose of Q-chlordane to rats the principal excretion was via the feces with only minute amounts occurring in the urine (Poonawalla and Korte, 1964).

Oral administration of these radioactive compounds to rabbits caused excretion of hydrophilic metabolites primarily in the urine and to a lesser extent in the feces. (Ludwig, 1966). The most polar urinary metabolite was assigned the structure 1-hydroxy-2 chloro-dehydrochlordene, with the stereochemical configuration of the 1- and 2-substituents unspecified.

However, Brooks (1969) assumes that the 2-chlorine atom will be in the endo-position and the 1-hydroxy group would be exo, which would imply simple hydrolytic replacement of one chlorine atom without inversion. Its molecular weight was estimated to be 391 and its empirical formula, $C_{10}H_7Cl_7$. Its acute toxicity to mice was approximately three times less than that of the α-chlordane (>1800 mg/kg).

Male rats given an acute dose of α-chlordane intravenously and killed 60 hr later showed approximately 75% of radioactivity excreted in the feces in the form of hydrophilic metabolites. There were high concentrations of radioactivity in both the fat and the GI tract (Poonawalla and Korte, 1964). Male rabbits orally administered transchlordane for 10 weeks, eliminated 47% of the dose in urine and 23% in feces. The major hydrophilic metabolite was again assigned the structure 1-hydroxy-2-chloro-dihydrochlordene. However, in this metabolite derived from γ-chlordane, the 2-chlorine atom would probably be in the endoposition, and the hydroxy group would probably be in the endoposition, again indicating hydrolytic replacement of the chlorine atom or simple oxidative dechlorination (Poonawalla and Korte, 1971).

Recently, a previously unreported metabolite of chlordane was isolated from mammalian fat milk and cheese (Polen _et al._, 1970, Schwemmer _et al._, 1970; Lawrence _et al._, 1970). This metabolite, which often migrates on a GLC column concurrently with heptachlor epoxide, may have been mistaken for it in residue analyses of certain foods. The metabolite, oxychlordane, an epoxide derivative of chlordane is postulated to be 1-exo-2-endo-4,5,6,7,8,8-octachloro-2,3-epoxy-2,3,3a,4,7,7a,-hexahydro-4,7-metahnoindene. The compound is formed from both α- and γ-chlordanes although to a greater extent from the former. When cows were fed 0.3 ppm cis, trans, or a cis- trans- mixture of chlordane for 30 days, no oxychlordane was found in milk. Cows on 1 ppm excreted low levels of oxychlordane in milk. Oxychlordane was also found in adipose tissue.

Street and Blau (1971) recently identified a metabolite, 1-exo-2-endo-dichlorochlordene-2, as an intermediate in the formation of oxychlordane. They found oxychlordane is produced by oxidative metabolism in rat liver homogenates fortified with NADP. It is formed very slowly by normal rat liver homogenates but was readily induced by DDT, dieldrin, heptabarbital and γ-chlordane. Rabbit preparations apparently convert dichlorochlordene readily to oxychlordane but do not readily convert chlordane to dichlorochlordene unless induced by exogenous substrates _in vivo_.

V.A.7. Effect of Chlordane on Enzymes

V.A.7.a. Enzyme Induction - Studies during the past decade have shown that the duration and intensity of action of many drugs depends upon the activities of drug metabolizing enzymes located primarily in the smooth endoplasmic reticulum (SER) of the liver cells. These enzymes catalyze the metabolism of drugs by many pathways such as: hydroxylation, dealkylation, deamination, sulfur-oxidation, azo-link reduction, and glucuronide formation.

The acute or chronic administration of a chemical may alter the pharmacologic activity of another by increasing the amount of drug metabolizing enzymes in the liver. This may facilitate the inactivation of the drug on the one hand; on the other it may activate the drug if the compound is metabolized to compounds which possess enhanced physiological activity.

Drug metabolism has been shown to be stimulated in animals by many different types of drugs and chemicals in the environment, including chlordane. Over 200 drugs and other chemicals are now known that stimulate drug metabolism in laboratory animals. Several extensive reviews have been published since the mid-1960's on the inductive effects of chlordane and other chemicals on drug metabolizing enzymes in the liver (Kuntzman, 1969; Conney, 1969; Street, 1969; Conney et al., 1969; Kupfer, 1967).

Studies conducted in the last decade demonstrated that treatment of animals with drugs, polycyclic hydrocarbons, and chlorinated insecticides increase the activity of liver microsomal oxidative drug-metabolizing enzymes. In turn, such an increase in microsomal enzyme activity was found to lead to an accelerated transformation of drugs in vivo and cause an altered duration of drug activity. The most potent inducers of these enzymes are some of the chlorinated insecticides, including chlordane. Single or multiple doses are relatively low levels that significantly increase the microsomal enzyme activity in rats.

Chlordane has been compared with phenobarbital in its stimulatory action on hepatic microsomal drug metabolism in mammals. Both agents cause increases in liver weight, microsomal protein, microsomal NADPH-oxidase, and microsomal cytochrome CO-binding pigments. Both agents can affect stimulation on drug metabolism in adrenalectomized or hypophysectomized rats. Ethionine can block the enzyme stimulation by both agents in normal rats (Hart and Fouts, 1965). The stimulatory actions of chlordane on microsomal drug metabolism do not add to those of phenobarbital. The actions of both chlordane and phenobarbital seem to be associated with a proliferation of SER in the liver cell.

Whether this biochemical and morphological response to chlordane can be considered to be a hepatoxic effect of chlordane or is rather an adaptive response to the toxic actions of these chemicals has been under deliberation for a considerable time. Several workers consider this inductive effect on animals and the associated cellular changes in the liver to be physiological adaptive responses rather than toxic effects.

It has been well demonstrated that acute administration of chlordane and other nonspecific inducers of liver metabolizing systems affect steroid actions in mammals. Chlordane pretreatment increases metabolism of estradiol-17-B to polar metabolites (Conney et al., 1965); decreases the growth promoting action of testosterone on the seminal vesicles of young rats (Levin et al., 1969); inhibits the increase of uterine weight caused by estrone (reduces uterotropic action of estrone); and decreases the concentration of estrone in the uterus (Welch et al., 1971).

The metabolism of C_{12}-steroids (progesterone and deoxycorticosterone) and a subsequent decrease in their pharmacological action was stimulated in male rats by pretreatment with chlordane (Kupfer, 1969). In adult ovariectomized mice, treatment with chlordane (but not DDT) increases estradiol-17-B metabolism, reduces estradiol-17-B-or estrone-increases in uterine weight, and decreases the concentration of estrogen in the uterus (Welch et al., 1971).

Lage et al. (1967) administered chlordane to adult male squirrel monkeys and found that the metabolism of digoxin was stimulated (DDT was not active under the conditions employed).

Pretreatment of rats with chlordane also decreased the toxicity of warfarin in vivo and increased its metabolism in vitro (Ikeda et al., 1968). Dogs pre-treated with chlordane followed by dicumarol had a reduced plasma level of dicumarol and the anticoagulant effect was reduced through the increased meta-bolism of the drug (Welch and Harrison, 1966).

Rats administered chlordane followed by phenylbutazone did not develop gastric ulcers as did similar animals treated with phenylbutazone alone (Welch and Harrison, 1966). The stimulatory effects of chlordane on drug metabolism in dogs was observed to be prolonged for as long as 21 weeks after discontinuing chlordane treatment (Burns et al., 1965). Oral treatment three times per week (5 mg/kg) for 7 weeks resulted in this prolonged accelerated metabolism of phenylbutazone.

Hydroxylase activity was stimulated in vivo by chlordane while in vitro chlordane (10^{-4}M) inhibited this enzyme reaction (Welch et al., 1967).

There are apparently substantial differences in the selectivity of drug metabolizing enzymes and in the stimulation as observed with different inducers and in various animal strains. Cram and Fouts (1967) observed differences in two mouse strains when examining the affect of chlordane and DDT on the meta-bolism of various substrates. In these two mouse strains there are significant differences in the inductive effects of γ-chlordane and DDT. The two mouse strains not only show similar stimulatory effects of DDT and γ-chlordane but also show differences in their inductive capabilities. The inductive effect of DDT and chlordane in the squirrel monkey are qualitatively similar (Juchau et al., 1966; Cram et al., 1965).

Chlordane is more active than DDT in stimulating drug metabolizing enzymes in primates although the spectrum of activity in the primates is similar with the two inducers.

The newborn infant is more sensitive than the adult to many drugs and ocassionally drugs produce neonatal effects after administration to the mother. An explanation for the sensitivity of infants to drugs came from the observation that newborn animals generally lack microsomal enzyme systems for the metabolism of many compounds. The normally low levels of drug metabolism enzyme activity in newborn rabbits was enhanced by treating the pups or the mothers they nursed with chlordane (Fouts and Hart, 1965).

The inductive effect evident in animal studies will presumably be observed in man. Kolmodin et al. (1969) observed that the plasma half-life of antipyrine in men occupationally exposed to chlordane is shorter, indicating that the microsomal enzyme system in man is induced.

The enhanced metabolism of chlordane by these inductive mechanisms may lead to the further formation of oxychlordane, a potent metabolite formed and stored in mammals. The toxicological significance of this effect has been evaluated in the chronic studies done with chlordane where induction of oxidative enzymes through the normal feeding of chlordane in the diet would result in the occurence and storage of oxychlordane.

The inductive interaction involving chlordane and the metabolism of toxicants, drugs and other substrates in mammals has been demonstrated to be an increase in enzyme synthesis rather than a stimulation of activity. This increased enzyme synthesis has apparently manifested itself in production of enzymes which are not necessarily specific for oxidative mechanisms. For example, Crevier et al. (1954); Ball et al. (1954); Kay (1966); Triolo and Coon (1966); Triolo et al. (1970); Williams and Casterline (1970); Casterline and Williams (1969a, 1969b), reported on the increased activity of esterases following chlordane treatment. It was postulated that this increased activity was responsible for the protective effect of chlorinated hydrocarbons when administered prior to organophosphate and carbamate esters. Williams et al. (1967), assumed that the chlordane-induced increase in liver and serum aliesterase activity was not primarily responsible for the protective effect of chlordane against two carbamate insecticides. More recently, Chapman and Liebman (1971) have assumed that the protective effect of chlordane and other inducing compounds against the toxicity of parathion is primarily due to the oxidative production of diethylhydrogen phosphate. On the basis of their data it seems reasonable to assume that the nonspecific oxidative induction mechanism of chlordane rather than esterase interaction may be responsible for the protective effect of chlordane against the toxicity of certain organophosphate esters.

The interactions of chlordane with other pesticides has been examined (Williams and Casterline, 1970; Street et al., 1969). It was observed that chlordane was less active than DDT in stimulating EPN detoxication and in the removal of stored dieldrin from fat. Chlordane decreased the mortality of a carbamate, Banol(R), but the protective effect was reduced by pretreatment with piperonyl butoxide.

Several studies have been reported on the interactions of diet and/or essential dietary factors with chlordane (Casterline and Williams, 1969a, 1969b; Boyd, 1969; Boyd and Taylor, 1969; Wagstaff and Street, 1971). Animals maintained on a protein-deficient diet showed a significant increase in susceptibility to acute chlordane toxicity. In general, it may be concluded that malnutrition plays a significant role in increasing the toxic effects of chlordane. Apparently, ascorbic acid is necessary for induction. Reduced levels of ascorbic acid resulted in lower induction levels of chlorinated hydrocarbons. Although the report of Wagstaff and Street (1971) did not primarily deal with chlordane induction the interaction of ascorbic acid in the inductive effects of chlorinated hydrocarbons was reported. Presumably this would be the same for chlordane.

V.A.7.a. Miscellaneous Effects - Studies on the mode of action of chlordane in insects and mammals have been limited to studies of adenosinetriphophosphate (ATPase) activity (Koch, 1969; Koch et al., 1969; Chu and Cutkomp, 1971; Akera et al., 1971). This relationship has not been conclusively defined as the etiological cause of the central nervous system stimulation seen in acute toxic response.

Chlordane has been shown to affect oxidative metabolism in a yeast system (Nelson and Williams, 1971); nitrite oxidation by Nitrobacter agiles (Winely and San Clemente, 1970); and carbon fixation in aquatic plankton (Ware and Roan, 1970). Gabliks and Friedman (1969) reported chlordane to be more toxic than DDT to mouse and human cells in cell culture and indicated that chlordane-exposed cells were more susceptible to infection by polio virus.

Chlordane had no effect *in vitro* or *in vivo* on an enzyme which hydrolyzes 3, 4-dichloropropionanilide (Williams and Jacobson, 1966). Williams (1969) found that a single dose of chlordane to rats reduced serum (23%) and liver (28%) glucuronidase activity eight days after administration.

V.B. Human Toxicity and Epidemiology - Fatality in humans has followed exposure to chlordane by both the oral and dermal routes. Acute poisoning may also follow inhalation exposure to chlordane. Low concentrations, estimated by Lensky and Evans (1952) to be about 10 mg/kg, result in classic signs of poisoning, including ataxia and convulsions. The fatal oral dose of chlordane for man is estimated to be between 6 and 600 g, although death of a patient with chronic liver disease has followed the exposure to an oral dose estimated to be between 2 and 4 g. The dermal exposure to 30 g of a 25% solution of chlordane has resulted in death (Hayes, 1963).

V.B.1. Signs and Symptoms of Poisoning - The signs and symptoms of acute chlordane intoxication in humans are similar to those observed in poisoning by other chlorinated hydrocarbons. Irritability, salivation, labored respiration, muscle tremors, convulsions, and death, with or without an immediately preceding period of deep depression, is a classical pattern of poisoning in experimental animals. These symptoms, which are referrable to the central nervous system, have all been observed in humans. In addition, nausea, vomiting, diarrhea, and abdominal pain have been reported to follow the ingestion of toxic doses of chlordane. Blurred vision, cough, ataxia, confusion, delirium, and mania are further symptoms noted after inhalation and skin absorption of toxic amounts of chlordane. Acute signs of poisoning usually appear within 45 minutes after ingestion. Death may occur within 24 hr, but it may be delayed many days following a toxic dose (Hayes, 1963; Stormont and Conley, 1955).

V.B.2. Laboratory Findings - Laboratory findings are usually negative and always nonspecific except that chlordane or related compounds may be demonstrated in stomach contents, urine, or tissues, especially fat (Hayes, 1963).

V.B.3. Treatment - Depending upon the condition of the patient, chlordane should be removed from the stomach either by an emetic or gastric lavage, followed by a saline laxative. Convulsions may be controlled by the use of barbiturates alone or in conjunction with calcium gluconate (Hayes, 1953; Stormont and Conley, 1955).

V.B.4. Human Poisonings - Several deaths have occurred after exposure to relatively high concentrations of chlordane. In some instances, the poisoning resulted from the exposure to chlordane in combination with other agricultural chemicals (Dinman, 1964; DePalma et al., 1970); in other instances the exposure was to chlordane alone (Derbes et al., 1955; Stormont and Conley, 1955; Lensky and Evans, 1952; Barnes, 1967; Aldrich and Holmes, 1969; and Curley and Garrettson, 1969). The high susceptibility of children to chlordane has been pointed out by several of the above authors.

Convulsions followed by recovery occurred in an infant following a dosage of about 10 mg/kg and in an adult following 32 mg/kg (Lensky and Evans, 1952).

One person receiving an accidental skin application of a 25% solution amounting to something over 30 g of technical chlordane developed symptoms within 40 min and died before medical attention was obtained (Dadley and Kammer, 1953).

In one patient, known to be an alcoholic, death followed exposure to a low oral dosage of chlordane (2-4 gm). Microscopic examination of the tissues revealed severe chronic fatty degeneration of the liver, characteristic of chronic alcoholism. Although this fatality cannot be attributed exclusively to chlordane, it is consistent with previous observations that the toxicity of some chlorinated hydrocarbons is much more enhanced in the presence of chronic liver damage (Hayes, 1963).

A woman with suicidal intent who ingested 6 g (104 mg/kg) of chlordane in talc suffered chemical burns of the mouth, severe gastritis, enteritis, diffuse pneumonia, lower nephron syndrom, and central nervous system excitation with terminal mania and convulsions. Death occurred after 9.5 days. The most important autopsy findings were those of severe necrotizing bronchopneumonia, and desquamation and degeneration of the renal tubular epithelium (Derbes et al., 1955).

An 18-yr old female showed convulsions but recovered after a dose of approximately 30 mg/kg. The amount retained after vomiting was estimated to be 10 mg/kg. Two infants, 15 months and 3 years of age, who ingested chlordane at 10 and 40 mg/kg, respectively, showed signs of severe poisoning (Stormont and Conley, 1955).

Chlordane ingestion by a 4-yr-old girl weighing 11 kg., resulted in intermittent clonic convulsions, coordination loss, and increased excitability. The use of gastric lavage and parenteral phenobarbital was followed by disappearance of these neurological signs and restoration of health. Initially, urine concentrations of chlordane were high, but fell rapidly to 0.05 ppm on the third day, although a sample of urine obtained on the 40th postingestion day revealed a rise to 0.13 ppm. Serum half-life of chlordane in this patient was found to be approximately 88 days (Aldrich and Holmes, 1969).

V.B.5. Epidemiological Studies - Workers engaged in the manufacture and formulation of chlordane for periods up to 15 yr have exhibited no evidence of harmful effects attributable to this insecticide. Air concentrations of 1.7 to 5 mg/m^3 have been reported for industrial manufacturing operations with exposure of personnel to this level producing no known adverse effects (Alvarez and Hyman, 1953; Fishbein et al., 1964). In a survey of more than 1105 persons who had been engaged in pest control operations for 1 to 30 yr (318 for 5 to 19 yr), three cases of toxicity due to chlordane were reported, the only symtoms specified being dizziness and headache (Stein and Hayes, 1964). An examination of persons occupationally exposed to chlordane showed that there were no apparent effects on renal function (Morgan and Roan, 1969).

Based on direct or circumstantial evidence, chlordane has been associated with several blood dyscrasias, including anemia, leukopenia, thrombocytopenia, and pancytopenia (American Medical Association Council on Drugs, 1962).

The role played by exogenous agents suspected of having an etiologic relationship to bone marrow failure is difficult to assess. The number of affected individuals usually is small in proportion to the population exposed. In addition, many of the suspected agents fail to reproduce marrow depression in the experimental animal. Since demonstration of a cause-and-effect relationship between a given agent and bone marrow failure can be established only by re-exposure of the affected individual, following recovery, such proof can rarely be established in human beings. Although the evidence implicating many chemicals, therefore, is entirely circumstantial, observations have been made with reference to certain agents and sufficient frequency to make a reasonable supposition as to the etiolgic relationship. That some persons are frequently exposed to prolonged contact with these agents and suffer no obvious effects cannot be denied, but the occurrence of bone marrow failure under such conditions is great enough to demand caution in occupational exposure to these agents (Loeb, 1967).

Hoffman et al. (1964; 1967) and Hayes et al. (1965) state that there is no evidence of the build-up of chlordane in adipose tissues of humans. However, in a recent unpublished study, Biros and Enos (1972) report finding a mean of 0.14 $\pm$ 0.09 (range from 0.03-0.40 ppm) random samples of human adipose tissue analyzed. Presumably this residue of oxychlordane in human fat has occurred as a result of exposure to chlordane. The source of exposure to yield these levels is a point of extreme interest and while it does not appear to result in any way defined toxicological response, the source of this contamination should be identified.

CHAPTER V

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