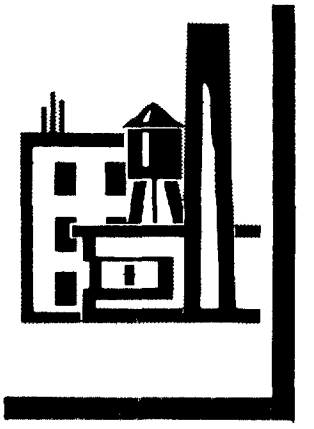
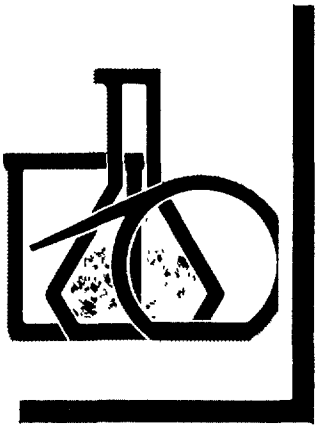
NIOSH

SPECIAL OCCUPATIONAL HAZARD REVIEW





ALDRIN/DIELDRIN

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

SPECIAL OCCUPATIONAL HAZARD REVIEW

FOR

ALDRIN/DIELDRIN

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
Division of Criteria Documentation and Standards Development
Rockville, Maryland

September 1978

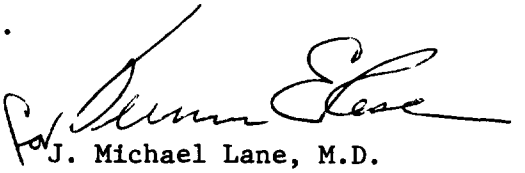
DISCLAIMER

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

DHEW (NIOSH) Publication No. 78-201

Preface

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards in their workplace. Pursuant to the fulfillment of this need, the National Institute for Occupational Safety and Health (NIOSH) has developed a strategy of disseminating information about adverse health effects of chemical or physical agents encountered by workers. This approach is intended to assist employers in providing protection for employees from exposure to these hazards. The Special Hazard Review serves to support and complement the other major standards development or hazards documentation activities of the Institute. The purpose of Special Hazard Reviews is to analyze and document, from a health standpoint, the problems associated with a given industrial chemical, process, or physical agent considered to have a special effect or hazard including a potential for producing carcinogenic, mutagenic, or teratogenic effects, and to recommend the implementation of engineering controls and work practices to alleviate these problems. While the Special Hazard Review is not intended to supplant the more comprehensive NIOSH Criteria Document, nor the brief NIOSH Current Intelligence Bulletin, it is nevertheless prepared in such a way as to assist in the formulation of regulations.



J. Michael Lane, M.D.
Acting Director, National Institute
for Occupational Safety and Health

ACKNOWLEDGMENTS

Jimmy L. Perkins, M.S. of the Division of Criteria Documentation and Standards Development, Priorities and Research Analysis Branch, had program responsibility for this document and served as project officer. Clement Associates, Inc. under sub-contract to JRB Associates, Inc. developed the basic information for consideration by NIOSH staff and consultants under Contract 210-77-0006.

The Division review staff for this document consisted of Jon R. May, Ph.D. (Chairman), J. Henry Wills, Ph.D., and Charles C. Hassett, Ph.D., consultant.

SUMMARY AND RECOMMENDATIONS

NIOSH, as a World Health Organization (WHO) Collaborating Center for Occupational Health, is participating in a continuing WHO program which involves the establishment of international recommendations for occupational health standards for toxic substances. It is anticipated that one group of substances to be considered will be pesticides. At the present time, the most economically important pesticides are insecticides belonging to the organochlorine, organophosphorus, and carbamate classes. NIOSH has previously documented the criteria for and recommended to the U.S. Department of Labor a series of occupational standards dealing with the widely used insecticides parathion, methyl parathion, malathion, and carbaryl. This document on Aldrin/Dieldrin and a companion document prepared for DDT serve as comprehensive reports on three of the most representative compounds of the organochlorine class of insecticides. Together with the NIOSH criteria documents on the four insecticides previously mentioned, the Aldrin/Dieldrin and DDT reports will form the basis for NIOSH recommendations for international occupational health standards.

Although aldrin and dieldrin are no longer produced in the U.S., they may still be utilized for certain restricted uses, including subsurface ground insertion for termite control, dipping of non-food roots and tops, and mothproofing by using closed-system manufacturing processes (39 Federal Register 37246, October 18, 1974). Though the use of aldrin and dieldrin is banned in many foreign countries, these

insecticides are still manufactured in a number of European countries and are used throughout the world for public health purposes.

Although aldrin and dieldrin are more acutely toxic to humans than DDT, their acute oral toxicity is nevertheless quite low. The estimated human oral LD50 for the two insecticides is approximately 65 mg/kg. Like DDT, documented chronic toxicity in humans, clearly related to aldrin or dieldrin, is non-existent. Results of animal experiments, however, do indicate that aldrin and dieldrin have considerable potential for carcinogenic effects in humans. Aldrin and dieldrin were carcinogenic in mice in 20 experiments, having produced increased incidences of tumors, usually in males and females independently. Dieldrin, at dietary doses as low as 0.1 and 1 ppm, caused significant increases in both lung and liver tumors in mice. In 6 of 8 experiments with rats, aldrin and dieldrin induced the development of significantly more tumors than appeared in control rats though the sites of the tumors were inconsistent among the experiments.

Based on the demonstrated potentials for induction of tumors in both rats and mice by aldrin and dieldrin, NIOSH recommends that these two pesticides be controlled and handled in the workplace as suspected occupational carcinogens and that exposure be minimized to the greatest extent possible. With regard to airborne exposure, NIOSH recommends that workplace environmental limits no higher than 0.15 mg/cu m be established for both compounds. The recommended exposure limit is the lowest concentration detectable by the current NIOSH validated sampling and analytical methods (NIOSH methods S275 and S283). Workers should also avoid skin contact with aldrin and dieldrin, as these pesticides

can be absorbed through the skin. Percutaneous absorption is substantially increased when aldrin and dieldrin are dissolved in organic solvents.

CONTENTS

1. Extent of Exposure

1.1 Identity and Nomenclature

"Aldrin" is the common name approved by the International Standards Organization for a product containing not less than 95% of 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-exo-1,4-endo-5,8-dimethanonaphthalene. In Canada, aldrin refers to the pure compound, which is known as HHDN in Great Britain (IARC 1974). Aldrin can be degraded environmentally and metabolically into dieldrin (Jager 1970, IARC 1974). In 1967, the composition of technical aldrin was reported to be: 90.5% HHDN, 3.5% isodrin, 0.5% chlordene, 0.2% hexachlorocyclopentadiene (HCCPD), 0.6% hexachlorobutadiene, 0.5% octachlorocyclopentene, less than 0.1% hexachloroethane, 0.1% HHDN diadduct, less than 0.1% bicycloheptadiene (BCH), 0.3% toluene, and 3.6% other compounds (primarily a complex mixture of compounds formed by polymerization of HCCPD and BCH) (IARC 1974).

"Dieldrin" is the common name approved by the International Standards Organization for a product containing not less than 85% of 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-exo-1,4-endo-5,8-dimethano-naphthalene. In Canada, the name dieldrin refers to the pure compound, which is known in Great Britain as HEOD (IARC 1974). Technical dieldrin contains some aldrin and endrin, but the precise constitution of technical dieldrin does not appear to have been published.

The von Baeyer/IUPAC names for aldrin, dieldrin, and some of their major metabolites, together with Chemical Abstracts Service numbers and structural formulae, are listed in Table 5.1. The physical and chemical properties of aldrin and dieldrin and some of their synonyms and trade names,

are listed in Tables 5.2 and 5.3, respectively.

In this document, the words aldrin and dieldrin are used for the pure compounds (HHDN and HEOD, respectively). Where necessary, the technical products will be referred to as such.

1.2 Discovery and Introduction

Aldrin and dieldrin were first synthesized in the laboratory in about 1948 (Whetstone 1964). Commercial production in the United States was first reported in 1950 (U.S. Tariff Commission 1951).

1.3 Changing Use and Production Patterns

Table 1.3.1 summarizes estimates of the quantities of aldrin and dieldrin used in the United States for some of their principal end uses from 1954 to 1971. The major use of aldrin in the early 1950's was in protecting cotton against boll weevils. In the mid-1950's the superior effectiveness of dieldrin on cotton became widely known. By the late 1950's, however, the boll weevil had become resistant to all chlorinated insecticides, so only minor quantities were sold for this purpose in the 1960's. Nevertheless, aldrin, along with toxaphene and DDT, accounted for over half of all insecticides used by U.S. farmers in 1966 (USDHEW 1969).

In 1971, the following use pattern was estimated for aldrin in the United States: corn soil usage, 80%; termite and pest control operators, 14%; rice seed treatments, 1%; and miscellaneous soil applications including on tobacco, vegetables, and strawberries, 1%. The percentages of dieldrin consumed for various uses in 1971 were: termite and pest control operators, 44%; fruit (foliage), 20%; seed treatment, 14%; vegetables, 13%; and

TABLE 1.3.1

ESTIMATED U.S. CONSUMPTION OF ALDRIN AND DIELDRIN
IN SOME PRINCIPAL END USES
(in thousands of pounds)

Aldrin	Year			
	1954	1964	1968	1971
Cotton (foliage)	934	19	-	-
Corn (soil)	804	10,191	12,089	9,410
Grasshoppers	476	20	-	-
Potatoes (soil)	289	-	-	-
Peanuts	81	-	-	-
Citrus (soil)	-	35	200	150
Sugar beets	-	60	-	-
Seed treatment (except rice)	6	80	150	130
Rice seed treatment	-	235	472	286
Japanese beetle	-	13	-	-
White-fringed beetle	10	-	-	-
Dieldrin				
Cotton (foliage)	757	20	1	-
Public health	62	-	-	-
Government programs	133	205	104	-
Fruit (foliage) (plum curculio)	202	408	217	120
Mothproofing	-	320	158	-
Small grains (foliage)	175	180	-	-
Small package (home and garden use)	-	227	34	2

Adapted from Train 1974

miscellaneous uses including application on tobacco, sweet potatoes, and similar crops, 9% (Train 1974).

U.S. domestic sales of aldrin and dieldrin from 1950 through July 1, 1974, including consumer specialty sales but excluding sales to the World Health Organization (WHO) and the Agency for International Development (AID) are outlined in Table 1.3.2 (Train 1974). Aldrin consumption increased in the United States until 1966, when about 19 million pounds were sold. In contrast, the overall use of dieldrin dropped from a peak of 3.6 million pounds in 1956 to an estimated 600 thousand pounds in 1973.

On June 26, 1972, the U.S. Environmental Protection Agency (EPA) proposed cancellation of registrations of all pesticide products containing aldrin or dieldrin. During public hearings on the cancellation order, in August 1974, EPA suspended most registrations of aldrin and dieldrin, prohibiting their production for use within the United States (Train 1974). Production for exempted uses was discontinued in 1975. In November 1976, EPA issued Toxic Pollutant Effluent Standards prohibiting direct discharge of aldrin and dieldrin into ambient waters (USEPA 1977).

Johnson (1972) estimated that 9.9 million pounds of aldrin and 1 million pounds of dieldrin were produced in the United States in 1971. During the 6 months prior to July 1, 1974, 9.7 million pounds of aldrin were reportedly consumed (Train 1974). About 3 million pounds of aldrin from existing stocks were used in 1975 (Aspelin 1975) and probably smaller quantities were in 1976. Imports for exempted uses (subterranean uses against termites) are still permitted, but no information was found that indicated dieldrin is now being imported into the United States.

TABLE 1.3.2

U.S. DOMESTIC SALES OF ALDRIN AND DIELDRIN, 1950-74
(in thousands of pounds)

1950	1,456	0
1951	3,288	185
1952	814	750
1953	1,234	1,135
1954	2,993	1,777
1955	4,372	2,585
1956	6,495	3,635
1957	2,431	2,673
1958	4,971	3,074
1959	5,566	3,008
1960	8,109	2,650
1961	9,926	2,764
1962	10,886	2,990
1963	12,152	2,685
1964	12,693	2,052
1965	14,278	1,814
1966	19,327	1,908
1967	18,092	1,473
1968	13,690	1,332
1969	9,902	1,206
1970	8,909	749
1971	11,615	705
1972	11,868	740
1973 (estimated)	(10,000)	(576)
1974 (to July 1)	9,700	-

Adapted from Train 1974

Little information is available on present-day patterns of production and use in overseas countries that would indicate the potential for exposure to manfactures, formulators, and users. Table 1.3.3 summarizes estimates made by the United Nations Food and Agriculture Organization (FAO 1977) of the consumption of "aldrin and similar insecticides" in reporting countries in 1973, 1974, and 1975. These estimates are of limited value in assessing consumption of aldrin and dieldrin, however,

TABLE 1.3.3

ESTIMATED CONSUMPTION OF ALDRIN AND SIMILAR INSECTICIDES IN REPORTING COUNTRIES, 1973-75
(in thousands of kg, ie, metric tons)

Country	Year		
	1973	1974	1975
Africa			
Burundi	5	1	-*
Chad	27	-	-
Congo	3	-	-
Egypt	274	1,002	-
Ivory Coast	8	10	-
Madagascar	2	-	-
Niger	8	12	1
Nigeria	9	-	-
Swaziland	16	-	-
North and Central America			
Canada	180	-	138
Mexico	170	92	-
USA	40,533	-	-
South America			
Argentina	243	-	-
Bolivia	2	-	-
Chile	-	-	166
Uruguay	26	-	-
Asia			
Burma	3	1	-
Cyprus	-	-	1
India	1,200	1,270	652
Iran	123	-	-
Israel	1	-	-
Japan	1	-	-
Korea, Republic of	1,245	1,536	-
Kuwait	1	1	-
Pakistan	-	131	-
Europe			
Austria	5	2	2
Czechoslovakia	-	-	7
Germany (FDR)	17	-	-
Italy	15,541	4,540	-
Portugal	14	15	-

*Dash indicates no report was available but does not necessarily mean that no aldrin was used.

Adapted from FAO 1977

because the category also includes chlordane, endrin, and other widely used cyclodiene insecticides.

The following European countries were reported to be producing aldrin or dieldrin in 1972 or 1973 (the number of producing companies is given in parentheses): Belgium (1), Federal Republic of Germany (2), France (2), Italy (2), the Netherlands (1), and the United Kingdom (1). In 1972, Japan was reported to have had eight suppliers of aldrin/dieldrin and their formulations, some of which may also have been producers. The reported amounts of aldrin and dieldrin imported into Japan in 1970 were 143 thousand kg and 42 thousand kg, respectively (IARC 1974). At this time aldrin and dieldrin are being produced in the Netherlands and Venezuela, but no data on quantities produced are available.

The use of aldrin and dieldrin has been banned or severely restricted in Japan and in a number of European countries, including Sweden, the Federal Republic of Germany, the United Kingdom, and Italy. Aldrin has been banned in Norway and the USSR, and dieldrin has been banned in Switzerland (IARC 1974).

1.4 Exposure

Exposure of workers in a manufacturing plant in the Netherlands has been extimated indirectly by measuring levels of dieldrin in the blood (Jager 1970). Dieldrin levels in the blood of aldrin/dieldrin workers during the period of exposure were in the range 0.022-0.078 µg/ml. Mean levels showed a progressive decrease from 0.069 µg/ml in 1964 to 0.025 µg/ml in 1969 as a result of improved safety precautions in the plant. According

to the empirical storage of Hunter et al (1969), these mean levels would correspond to oral intakes of 800 and 290 µg/man/day, respectively (Jager 1970). For comparison, mean intakes by the general population in the United Kingdom and the United States were estimated to be in the range 3-22 µg/day (Jager 1970). However, re-analysis of the data from Hunter et al suggested that these estimates of intake are too high by a factor of 1.2-1.9 (Moriarty 1974) (see section 1.5.4).

Dieldrin levels in the blood of workers in a manufacturing plant in the United States were in the range 0.0012-0.137 µg/ml; the more highly exposed workers had estimated intakes in the range 0.7-1.1 mg/man/day (Hayes and Curley 1968). Aldrin and dieldrin levels in the blood of six workers at a formulating plant were at least as high as this, with at least one individual close to the threshold for intoxication of 0.30 µg/ml dieldrin (Mick et al 1971). Dieldrin concentrations in the urine of men working in a factory where aldrin and dieldrin were made and formulated were determined to be in the range 0.0053-0.0514 µg/ml, compared to 0.0008 µg/ml in persons from the general population (Cueto and Biros 1967).

Estimates of the potential exposure of agricultural workers to dieldrin under various conditions are summarized in Table 1.4.1. These measurements indicate the potential for very high rates of dermal exposure unless protective clothing is worn. Fletcher et al (1959) estimated that men spraying dieldrin in a public health program in East Africa came into dermal contact with about 1.8 mg of dieldrin/day. Levels of dieldrin and its metabolites in the urine of these men were in the range 0.4-1.1 µg/ml

(Cueto and Hayes 1962). The highest of these figures is more than twice that measured in highly exposed factory workers (Cueto and Biros 1967).

Observations of occupationally exposed workers, summarized in Section 3.3, show that exposures leading to clinical intoxication are not infrequent in certain types of application. According to the storage formula of Hunter et al (1969) the threshold level for intoxication of 0.30 µg/ml in blood proposed by Jager (1970) corresponds to repeated intakes of about 3.5 mg/man/day or to intermittent intake of correspondingly higher quantities.

1.5 Metabolism and Pharmacokinetics

1.5.1 Metabolism in Mammals

The metabolism of aldrin and dieldrin has been reviewed by FAO/WHO (1971), by Jager (1970), and in greater detail by Menzie (1969). The principal metabolic pathways in mammals are summarized in Figure 1.5.1. In addition to the metabolites shown in Figure 1.5.1, 9-hydroxydieldrin (see Table 5.1) has been identified as a major metabolite in mammals (Baldwin et al 1972, Mueller et al 1975a,b).

The conversion of aldrin to dieldrin has been demonstrated in a number of mammalian species. This reaction takes place in liver microsomes and requires the presence of NADPH (Nakatsugawa et al 1965, Wong and Terriere 1965). The enzyme involved is aldrin epoxidase, the activity of which appears to vary greatly depending upon the preparation and the temperature of storage (Chan and Terriere 1969). Microsomal epoxidation of aldrin to dieldrin is greatly accelerated by inducers of mixed function oxidase activity, such as DDT (Gillett et al 1966) and phenobarbital

TABLE 1.4.1

SUMMARY OF PUBLISHED STUDIES ON POTENTIAL EXPOSURE OF WORKERS DIRECTLY APPLYING DIELDRIN

Activity	Exposure			Reference
	Respiratory (mg/hr)	Dermal (mg/hr)	Total (% toxic dose/hr)	
Hand-spraying of dwellings for disease vector control		18.6*	>0.33*	Fletcher et al 1959
Spraying pear orchards	0.03**	14.2	0.24	Wolfe et al 1963
Operating power air blast machine spraying fruit orchards	0.03	15.5	0.25	Wolfe et al 1967
Power handgun spraying fruit orchards from portable machine	0.03	15.1	0.25	"

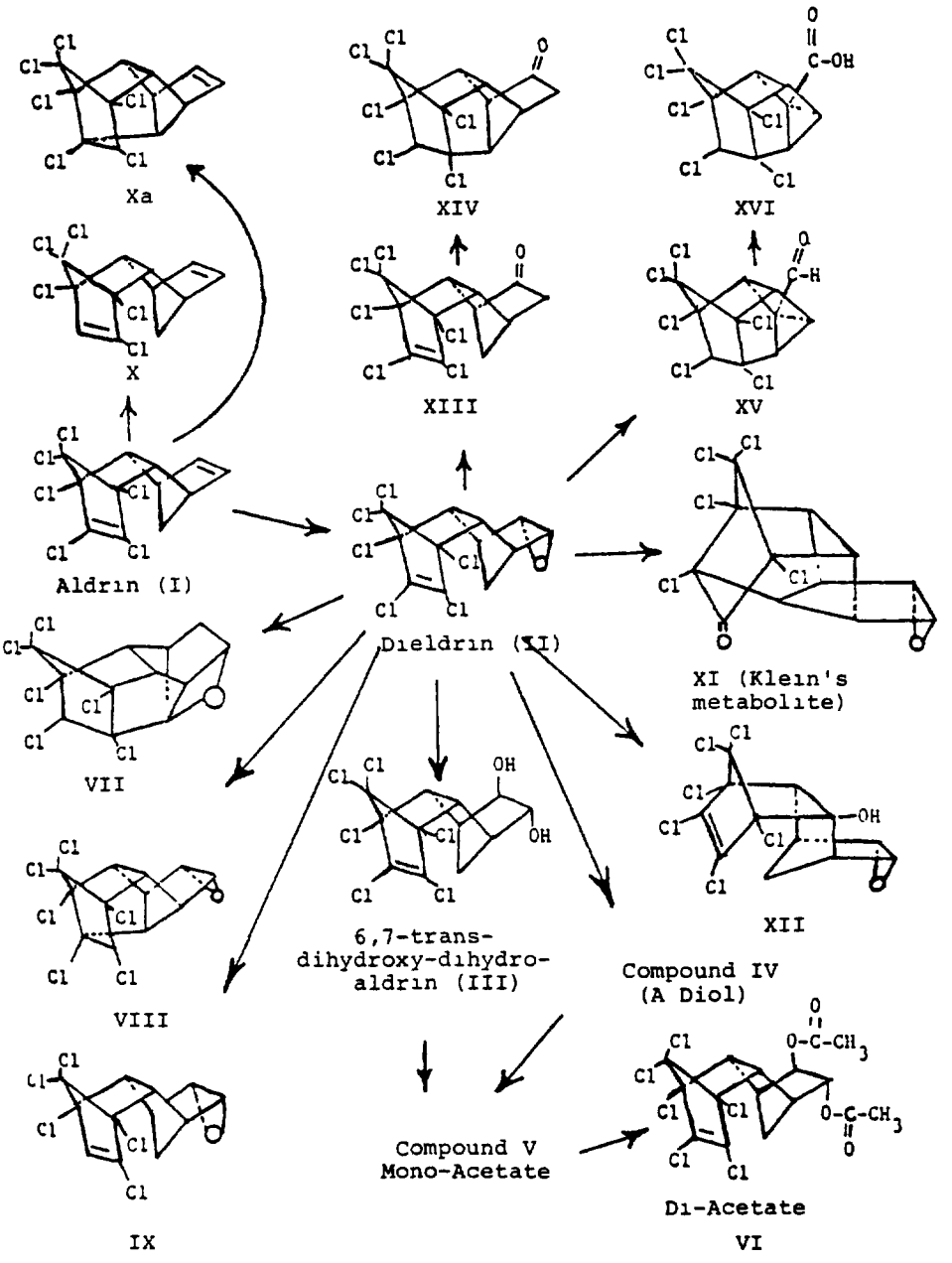
* Calculated by Wolfe et al 1967
**Original value (0.25 mg/hr) incorrectly derived

Adapted from Wolfe et al 1967

(Ghiasuddin and Menzer 1976). Aldrin is also converted to dieldrin in lung tissues of rabbits; dieldrin was detected within 3 minutes of initial exposure to aldrin (Mehendale et al 1974).

After rabbits were fed radiolabeled dieldrin, six different metabolites were identified in their urine. Of the total urinary excretion, 85%

Figure 1.5.1 (from Menzie 1969)
Metabolic Pathways of Aldrin and Dieldrin in Animals



consisted of one of the two enantiomorphic isomers of trans-6,7-dihydroxy-dihydroaldrin ("trans-aldrin-diol" or "trans-dihydro-aldrindiol"; compound III) (Jager 1970).

In a comparative study with mice and rats fed radiolabeled dieldrin, 10 times more radioactivity appeared in the feces than in the urine of both species. More unchanged dieldrin occurred in the urine of rats than in that of mice, and Klein's metabolite (XI) was identified only in rat urine, its proportion increasing from 3% to 67% during the 8 days after administration. Mice and rats excreted high levels of 9-hydroxydieldrin in feces (46% and 26%, respectively) and about one-third of the radioactivity was excreted as unidentified metabolites by the two species (Baldwin et al 1972). One of the fecal metabolites in the rat was identified as 6,7-trans-dihydroaldrindiol, and one of the urinary metabolites as hexachlorohexahydromethanoindene-1,3-dicarboxylic acid ("aldrindicarboxylic acid," see Table 5.1). Other major metabolites were listed by Menzie (1969) (see Figure 1.5.1).

In detailed studies of the metabolism of dieldrin by rat liver microsomes in vitro, the rate and pathways of metabolism were found to be influenced markedly by nutritional, hormonal, and environmental factors. One group of metabolites was produced in much higher yield by microsomes from males than by those from females (Oberholser et al 1977). Pretreatment of rats with phenobarbital, DDT, or dieldrin itself influenced not only the rate of metabolism of dieldrin but also the metabolic profile. Some metabolites increased the rates of their own metabolism, whereas the major

metabolite (probably 9-hydroxydieldrin) inhibited formation of all metabolites, including itself (Oberholser et al 1977).

Mueller et al (1975a) administered radiolabeled dieldrin to rhesus monkeys by the oral and intravenous routes. The main pathway of metabolism was direct oxidation resulting in 9-hydroxydieldrin. At high liver concentrations the epoxide ring was opened, leading to the production of trans-aldrindiol.

Hutson (1976) compared the metabolism of radiolabeled dieldrin in CFE rats and two strains of mice. The major metabolic pathways of dieldrin, leading to 9-hydroxydieldrin, 6,7-trans-dihydroaldrindiol, aldrindicarboxylic acid, and the pentachloroketone were found to be present in both species. The main differences between the species were a more rapid metabolism of dieldrin in rats, a much greater production of the pentachloroketone by rats, and the production of small amounts of polar urinary metabolites by mice. The two strains of mice were similar to one another in most but not all of the parameters measured.

Mueller et al (1975b) compared the metabolism of dieldrin in mice, rats, rabbits, rhesus monkeys, and chimpanzees. In all five species, 9-hydroxydieldrin and 6,7-trans-dihydroaldrindiol were the major metabolites.

The ratio of these two metabolites was similar in rats and rhesus monkeys. In the mouse and the rabbit, more of the dieldrin was metabolized to dihydrodiol (see Table 1.5.1). The rate of metabolism was highest in mice, with 33-34% excreted as metabolites within 10 days compared to 7-11% in rats, 11% in rhesus monkeys, and 3% in chimpanzees. The authors

TABLE 1.5.1

PERCENTAGE OF RADIOACTIVE MATERIAL EXCRETED WITHIN 10 DAYS AFTER SINGLE ORAL ADMINISTRATION OF ^{14}C-DIELDRIN

	Mice		Rats		Rabbits		Rhesus	Chimpanzee
	male	female	male	female	male	female	male	female
Dieldrin	5.5	3.2	0.8	2.8	0.3	0.5	9.0	3.2
12-OH-dieldrin	13.0	7.5	8.8	4.6	-	0.2	9.4	2.0
Aldrin-tr-diol	20.0	26.0	2.3	2.4	1.5	2.0	2.0	1.1
Total	38.5	36.9	11.9	9.8	1.8	2.7	20.4	6.3
Feces	36.6	35.0	11.3	9.3	0.3	0.5	16.0	5.0
Urine	1.9	1.9	0.6	0.5	1.5	2.2	4.4	1.3

Adapted from Mueller et al 1975b

suggested that the mouse liver would correspondingly be more highly exposed to the dihydrodiol. However, mice retained a higher percentage of administered dieldrin in their tissues than rats and almost as much as rhesus monkeys (see Table 1.5.5).

1.5.2 Metabolism in Humans

The limited data available on the metabolism of aldrin and dieldrin in humans have not shown qualitative differences between the metabolic pathways in humans and in other mammals. At least two unidentified polar metabolities of dieldrin have been isolated from human urine, fat, and bile (Cueto and Hayes 1962, Paschal et al 1974). One metabolite isolated

from the fat, bile, and gallstone of a pest control worker was tentatively identified as the aldehyde derivative, compound XV in Figure 1.5.1 (Paschal et al 1974). 9-Hydroxydieldrin has been identified in human feces (Richardson and Robinson 1971).

1.5.3 Pharmacokinetics in Experimental Animals

Data on the pharmacokinetics of aldrin/dieldrin in mammals were summarized by USDHEW (1969) and Jager (1970) and were critically reviewed by Moriarty (1974, 1975). A number of mathematical models have been proposed (Robinson et al 1969; USDHEW 1969; Garrettson and Curley 1969; Moriarty 1974, 1975; Lindstrom et al 1975, 1976).

When radiolabeled aldrin was fed to male rats, the radioactive material excreted in feces and urine consisted of aldrin, diedrin, and hydrophilic metabolites. Paper chromatography of extracts of feces and urine initially showed a high percentage of aldrin. The percentage of unchanged aldrin then decreased, while that of hydrophilic metabolites increased continuously for about 12 days. The distribution of excreted compounds then remained unchanged as long as aldrin was administered daily. After aldrin administration was discontinued, the percentage of aldrin decreased and that of dieldrin increased (Ludwig et al 1964). At a feeding rate of 4.3 μg/rat/day, a steady state level was reached after about 8 weeks; daily excretion of radioactive material thereafter approximated daily intake (Menzie 1969).

When rats were given radiolabeled dieldrin, intestinal absorption started almost immediately after oral administration, but the rate and

extent of the absorption varied with the vehicle used. The absorbed dieldrin was mainly transported by the portal vein blood, and only a small proportion via the lymph. Initially, dieldrin was distributed widely in the body, but redistribution took place rapidly in favor of fat. The storage level in the fat was related to the quantity ingested and varied according to species. Biliary excretion started shortly after absorption, mainly in the form of hydrophilic metabolites. A part of the excretion products was reabsorbed from the intestine and again transported to the liver. Thus, an enterohepatic circulation occurred. About 90% of the total dose was excreted as hydrophilic metabolites in the feces and about 10% in the urine (Heath and Vandekar 1964, Ludwig et al 1964).

Cole et al (1968) injected male rats, with and without bile fistulae, with 0.25 mg/kg dieldrin. The urine and feces were collected daily. The bile was collected 1, 3, 6, 12, and 24 hours after injection and subsequently at daily intervals. After 5-7 days, the animals were killed. Over 90% of the excreted dieldrin-derived materials was found in the feces from the intact rats or in the bile of the rats with a bile fistula. Fifty percent of the dieldrin administered was excreted within 3 days; 32% had been excreted in the bile after 6 hours.

Moss and Hathway (1964) found that the solubility of dieldrin in rabbit serum is 4,000 times greater than its solubility in water. In exposed rabbits and rats, dieldrin is primarily located in the erythrocytes and the blood plasma but not in the leucocytes, the platelets, or the erythrocyte stroma. The distribution between plasma and red cells

is roughly 2:1. In the red cells, dieldrin is largely associated with hemoglobin and an unknown constituent, while in the serum it is associated with albumin, alpha$_1$- and alpha$_2$-globulins, and another unidentified component. The erythrocyte membrane is freely permeable to dieldrin (Jager 1970).

After absorption, dieldrin is circulated through the body in the blood and is transferred in and out of other organs throughout the body. The rate of transport across membranes is believed to be highly tissue specific (Lindstrom et al 1976). Figure 1.5.2 shows a two-compartment model for the loss of dieldrin from the body after cessation of exposure. In this model, compartment 1 is identified with the blood, and the remainder of the body is considered together as compartment 2 (Moriarty 1975). Such a model has three rate constants, k_{01}, k_{12}, and k_{21}.

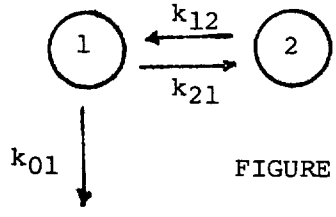


FIGURE 1.5.2 (Moriarty 1975)

If Q_1 is the amount of dieldrin in the blood and Q_2 the amount of dieldrin in the other body compartment, the model predicts:

$$Q_1 = X_1e^{-\lambda_1 t} + X_2e^{-\lambda_2 t}$$

$$Q_2 = X_3e^{-\lambda_1 t} + X_4e^{-\lambda_2 t}$$

where X_1, X_2, X_3, and X_4 are constants, and and are rate constants that depend in a complicated way on K_{01}, K_{12}, and K_{21} (Moriarty 1975). These equations provide a good description of data on uptake (Figure 1.5.3) and loss (Figure 1.5.4) of dieldrin from animals. Two-compartment models of this kind are usually needed to fit experimental data, although one-compartment models have been used where experimental data are limited (Richardson et al 1967, Moriarty 1975).

Tables 1.5.2 and 1.5.3 summarize data on the uptake and loss of dieldrin from experimental animals, as fitted to one- and two-compartment models (Moriarty 1975). Rats take up and excrete dieldrin considerably faster than larger mammals. In rats, dogs, and sheep, the three species for which data are available, rate constants ( ) for uptake are considerably larger than rate constants for loss (Moriarty 1975).

The compartmental models of Moriarty (1975) and others assume implicitly that the physiologic state of the animals remains constant for times much longer than $^{-1}$. Accordingly they predict an ultimate steady state concentration of dieldrin in the tissues of animals constantly exposed. However, actual data on experimental animals exposed for long periods at constant levels of exposure indicate that a true steady state is not reached (see Figure 1.5.3 for sheep, Figure 1.5.5 for rats). "Quasi-steady" states reached after long-term exposure are referred to in the literature, and the potential for storage after exposures of more than 1-2 years may be underestimated (Moriarty 1974, 1975).

FIGURE 1.5.3 (Moriarty 1975)

INCREASE IN DIELDRIN CONCENTRATION (C) IN THE BLOOD OF SHEEP INGESTING 2 MG DIELDRIN/KG BODY WEIGHT

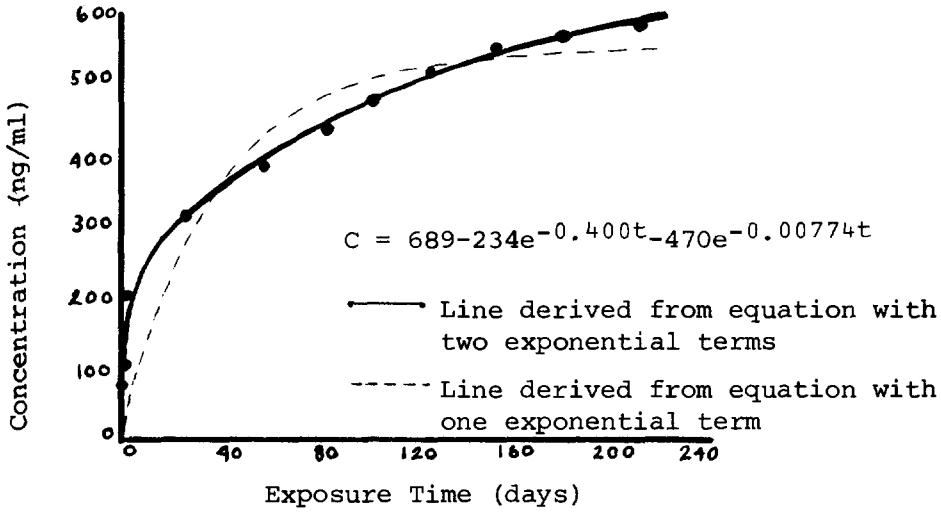


FIGURE 1.5.4 (Moriarty 1975)

DECREASE IN THE CONCENTRATION (C) OF DIELDRIN IN RAT BLOOD DURING THE FIRST 71 DAYS AFTER EXPOSURE

(Data fitted to an equation with two exponential terms)

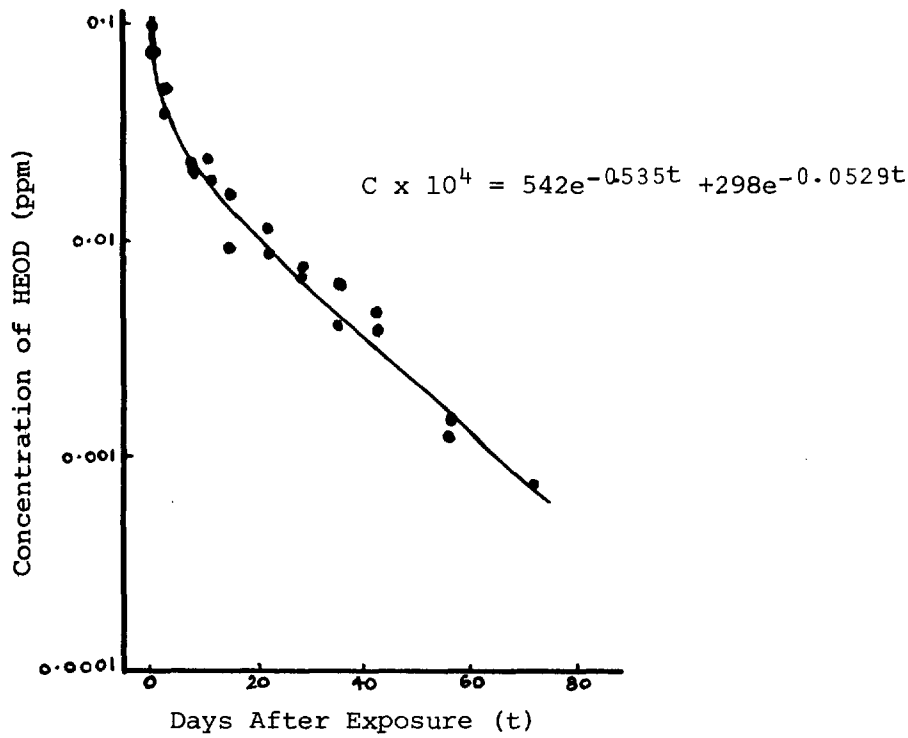


TABLE 1.5.2

INTAKE OF DIELDRIN BY VARIOUS MAMMALS

Species (and sex)	Tissue	Exposure Concentration	Duration of Experiment (days)	No. of Exponential Terms	λ (d^{-1})	C_∞* ppm
Rat (F)	Blood	50 ppm (diet)	183	1	0.25	0.25
Rat (F)	Liver	50 ppm (diet)	183	1	0.17	8.6
Rat (F)	Fat	50 ppm (diet)	183	1	0.12	184
Sheep	Blood	0.5 mg/kg/d	112	1	0.12	-*
Sheep	Blood	1.0 mg/kg/d	224	2	0.42, 0.029	0.21
Sheep	Blood	2.0 mg/kg/d	224	2	0.40, 0.077	0.69
Dog (M)	Blood	0.005 mg/kg/d	548	1	0.0088	0.011**
Dog (M)	Blood	0.05 mg/kg/d	548	1	0.017	0.047**
Dog (F)	Blood	0.005 mg/kg/d	548	1	0.031	0.0083**
Dog (F)	Blood	0.05 mg/kg/d	548	1	0.013	0.048**
Dog (F)	Fat	0.3 mg/kg/d, 5 d/wk	300	1	0.014	56

* Asymptotic concentration of dieldrin in tissues
**Steady state questionable (see text)

Adapted from Moriarty 1975

TABLE 1.5.3

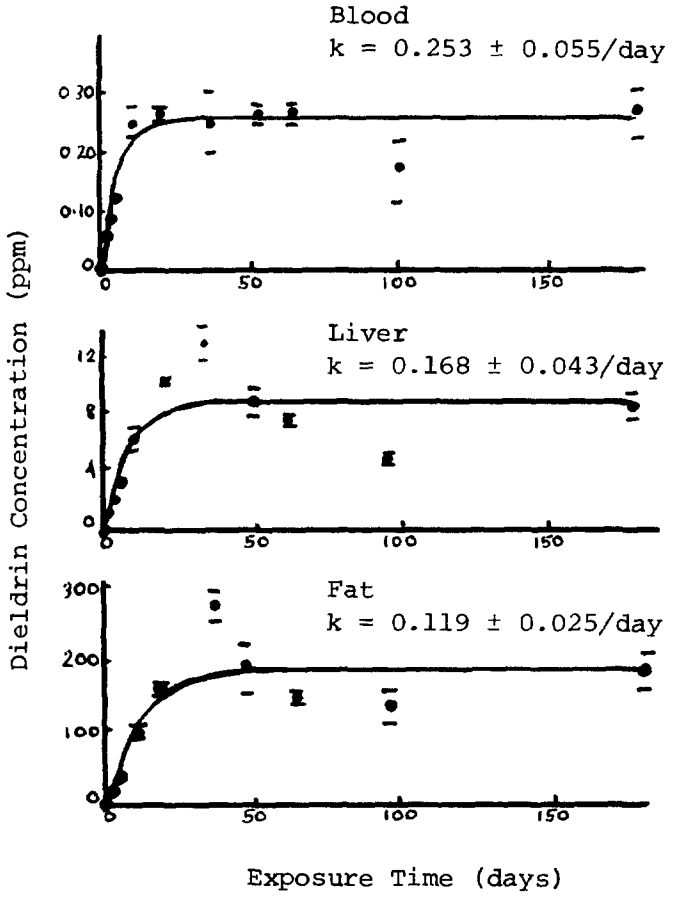
LOSS OF DIELDRIN RESIDUES FROM VARIOUS MAMMALS AFTER CESSATION OF EXPOSURE

Species (and sex)	Tissue	Initial Level (ppm)	Duration of Experiment (days)	No. of Exponential Terms	λ (d^{-1})	Half-life (days)
Rat (M)	Fat	47.6	19	1	0.13	5.2
Rat (M)	Fat	22.6	52	1	0.069	10.1
Rat (M)	Liver	3.5	52	1	0.091	7.6
Rat (M)	Brain	0.95	52	1	0.073	9.5
Rat (M)	Muscle	0.93	52	1	0.069	10.1
Rat (M)	Fat	15.9	84	2	0.43, 0.066	1.6, 10.5
Rat (M)	Blood	0.076	71	2	0.54, 0.053	1.3, 13.1
Rat (M)	Liver	0.85	59	2	0.54, 0.068	1.3, 10.2
Rat (F)	Fat	121	52	1	0.055	12.7
Rat (F)	Liver	5.0	52	1	0.052	13.4
Rat (F)	Brain	2.5	52	1	0.046	15.1
Rat (F)	Muscle	2.4	52	1	0.067	10.3
Dog	Fat	56	365	1	0.0055	127
Dog	Fat	80	330	1	0.0042	165
Cattle	Fat	78	224	1	0.0097	74
Sheep	Fat	79	252	1	0.0073	97

Adapted from Moriarty (1975)

FIGURE 1.5.5 (Moriarty 1974)

CHANGES IN THE CONCENTRATION OF DIELDRIN IN THE BLOOD, LIVER, AND FAT OF RATS FED A DIET CONTAINING DIELDRIN AT 500 PPM



(Data fitted to equations with one exponential term; horizontal bars indicate the standard error of the means)

TABLE 1.5.4

CONCENTRATION OF HEOD IN TISSUES OF ANIMALS AND HUMANS

Species	Sex	Dietary Exposure*		Mean (Geometric) Concentration of HEOD in Tissues (ppm)				Reference
		mg/kg diet (ppm)	mg/kg body weight	Blood	Fat	Liver	Brain	
Mouse	M	0	0	0.00091	0.39	0.020	-	Unpublished
		0.1	0.012	0.0039	1.55	0.176	-	work
		1.0	1.12	-	12.0	1.58	-	(Tunstall
		10.0	1.2	0.426	67.9	4.09	-	Laboratory)
	F	0	0	-	0.18	0.0175	-	
		0.1	0.016	0.0026	1.27	0.0774	-	
		1.0	0.16	0.044	10.9	1.05	-	
		10.0	1.6	0.52	62.8	5.44	-	
Rat	M	0	0	0.0009	0.060	0.0059	0.0020	Walker et
		0.1	0.00475	0.0021	0.259	0.0159	0.0069	al 1969
		1.0	0.0475	0.031	1.49	0.155	0.104	
		10.0	0.475	0.147	19.7	1.48	0.432	
	F	0	0	0.0015	0.31	0.011	0.0077	
		0.1	0.00582	0.0065	0.90	0.035	0.022	
		1.0	0.0582	0.086	13.9	0.43	0.29	
		10.0	0.582	0.395	57.8	2.97	1.13	
Dog	M	0	0	0.0045	1.09	0.165	0.038	Walker et
		0.15	0.005	0.0175	4.36	0.778	0.107	al 1969
		1.5	0.05	0.093	18.2	4.9	0.498	
	F	0	0	0.0040	0.794	0.129	0.062	
		0.15	0.005	0.0174	4.9	0.804	0.150	
		1.5	0.05	0.095	18.6	4.18	0.536	

TABLE 1.5.4 (Continued)

Species	Sex	Dietary Exposure*		Mean (Geometric) Concentration of HEOD in Tissues (ppm)				Reference
		mg/kg diet (ppm)	mg/kg body weight	Blood	Fat	Liver	Brain	
Rhesus monkey	-	0	0	0.0028	0.157	0.147	0.0235	Unpublished work (Tunstall Laboratory)
		0.01	0.00026	0.0038	0.386	1.18	0.0245	
		0.1	0.0033	0.0075	1.01	1.20	0.0344	
		0.5	0.013	0.022	4.98	3.96	0.142	
		1.0	0.028	0.033	8.29	5.24	0.171	
		1.75	0.041	0.075	19.1	7.55	0.465	
Human		0.006	0.00013	(0.0011)**	0.17	0.03	0.0053	de Vlieger et al 1968
Workmen, Pernis*** 1964		0.535	0.01146	0.069	(10.9)	(1.81)	(0.34)	
Formulators pre-1960		0.791	0.01694	0.102	(16.1)	(2.68)	(0.50)	
		(1.55)	(0.03323)	(0.2)	(31.6)	(5.26)	(0.99)	

*The concentrations (mg HEOD/kg diet) are the nominal added concentrations of HEOD, except for the rhesus monkey, which received dieldrin incorporated into the solid diet. The equivalent intakes per kg body weight were calculated for the mouse, rat, and dog from observations made at Tunstall Laboratory; for the rhesus monkey from data supplied by Kettering Laboratory; and for humans from the mean concentration in body fat according to the formula:

$$\text{daily intake} = \frac{\text{concentration of HEOD in body fat}}{0.0185}$$

and assuming 70 kg as body weight. (The concentration in the human diet is based on a solid food intake of 1.5 kg/day.)

**Estimated from concentration in body fat according to the ratio of 158 for concentration in body fat to that in blood

***Concentrations in tissue (in parentheses) derived from the mean concentration in blood; pre-1960 values estimated, based on clinical observations of the workmen at Pernis

Adapted from USEPA 1974

Data for a number of species, such as that presented in Table 1.5.4 suggest that residues in tissues after long-term exposure are proportional to the rates of intake (USEPA 1974, USDHEW 1969, Moriarty 1975). Table 1.5.5 summarizes the "storage factors" for dieldrin in blood and fat of various species after low-level exposure. The storage factor is defined as the concentration of dieldrin in the tissue at "quasi-steady" state divided by the concentration in the diet.

The storage of dieldrin in mammals is affected by interactions with other chemicals, especially enzyme inducers. Storage of dieldrin in the fat of female rats was markedly reduced and the excretion of polar dieldrin metabolites was markedly increased when DDT was fed simultaneously (Street 1964, Street and Chadwick 1967). A similar reduction in storage of dieldrin was produced by treatment with phenobarbital (Cueto and Hayes 1965), aminopyrine, tolbutamide, phenylbutazone, and heptabarbital (Street et al 1966).

Dieldrin has been shown to cross the placenta in a number of experimental animals, including rabbits, rats, pigs, and cows (IARC 1974). Dieldrin is excreted in the milk of rabbits, cows, and rats (Jager 1970, Harr et al 1970a).

TABLE 1.5.5

STORAGE FACTORS FOR DIELDRIN IN BLOOD AND FAT OF ANIMALS EXPOSED FOR LONG PERIODS TO DIELDRIN AT DIETARY LEVELS OF 0.1-0.15 PPM

Species	Sex	Storage Factor*	
		In Blood	In Fat
Mouse	M	0.039	15.5
Mouse	F	0.026	12.7
Rat	M	0.021	2.6
Rat	F	0.065	9.0
Dog	M	0.117	29.1
Dog	F	0.116	32.7
		0.075	10.0

*The concentration of dieldrin in the tissue at "quasi-steady" state divided by the concentration in the diet; calculated from data in Table 1.5.4

1.5.4 Pharmacokinetics in Humans

Dieldrin is absorbed into the human body after ingestion (Hunter et al 1967, 1969), percutaneous absorption (Feldman and Maibach 1974), and presumably after inhalation. When small doses (4 $\mu g/cm^2$) of radiolabeled aldrin and dieldrin in acetone solution were applied to the skin of male volunteers, 7.8% and 7.7%, respectively, of the radioactivity were excreted in urine within 120 hours. By contrast, when aldrin and dieldrin were injected intravenously, only 3.6% and 3.3%, respectively, were excreted in the urine (Feldman and Maibach 1974).

After ingestion, aldrin and dieldrin are circulated throughout the body in the blood, mainly in the plasma but to a lesser degree in the erythrocytes (Mick et al 1971, Morgan et al 1972). Most of the dieldrin in the plasma is bound to serum protein, and extremely little is partitioned into the cerebrospinal fluid (Garrettson and Curley 1969). Dieldrin is found in a wide variety of organs, its distribution generally paralleling that of the fat in the tissues (Table 1.5.6).

Dieldrin is excreted slowly in the bile. Samples taken from a pest-control operator during surgery contained dieldrin at concentrations of 24.6 ppm in adipose lipid, 165 ppb in blood serum, and 159 ppb in bile. Two hydrophilic metabolites were also identified in bile (Paschal et al 1974).

Data on the uptake and loss of dieldrin in the human body have been fitted to one-compartment models. In a study in which male volunteers ingested 50 or 211 µg of dieldrin daily for 2 years, the rate constants for uptake were estimated by the original authors to be about 0.007, corresponding to a half-time of about 100 days (Hunter et al 1967, 1969).

TABLE 1.5.6

AVERAGE CONCENTRATIONS OF DIELDRIN IN VARIOUS TISSUES FROM AUTOPSIES OF 44 PEOPLE IN THE GENERAL POPULATION

Tissue	No. of Samples	Lipid Content (%)	Dieldrin (ppm)
Perirenal fat	30	55.7	0.0300
Mesenteric fat	29	54.2	0.0630
Panniculus fat	30	60.6	0.0270
Bone marrow	19	20.6	0.0620
Lymph node	11	8.6	0.0190
Adrenal	18	10.5	0.0060
Kidney	38	3.2	0.0056
Liver	42	2.1	0.0037
Brain	32	7.9	0.0031
Gonad	36	1.3	0.0021
Lung	25	0.7	0.0022
Spleen	27	0.6	0.0021

Adapted from Casarett et al 1968

However, analysis by Moriarty (1975) has shown that the rate constants were actually considerably lower, corresponding to half-times of 150-200 days. Estimates for the half-life of dieldrin in the human body after exposure ends are 266 days (based on exposed workers: Jager 1970, Moriarty 1975), 50-167 days (based on exposed workers: Kazantzis et al 1964, Brown et al 1964), and 50 days (based on a poisoned child: Garrettson and Curley 1969). The shorter half-lives are based on poisoning victims therapeutically treated with drugs such as phenobarbital and diphenylhydantoin.

Hunter et al (1967, 1969) suggested that "steady state" concentrations were reached in their experimental subjects after 9-12 months of constant exposure. However, Moriarty (1975) has shown that this apparent steady

state was an artifact of their mathematical procedure. In fact, dieldrin concentrations in fat and blood were still rising at the end of the 2-year study, and it is not completely clear that a steady state would ever have been reached. However, Moriarty was able to fit a one-compartment model to data for five of the six men, predicting asymptotic levels in blood 1.2-1.9 times higher than those reported by Hunter et al (Table 1.5.7). Accordingly the equations proposed by Hunter et al to describe the "steady state" in middle-aged men should be modified to the following:

Concentration of HEOD in blood (ppm) = $1.3\ 10^{-4}$ amount ingested (µg/day)

Concentration of HEOD in fat (ppm) = $2.8\ 10^{-2}$ amount ingested (µg/day)

The corresponding storage factors (assuming 1.5 kg/day intake of food) are 0.2 for blood and 42 for fat. These are higher than those reported for other experimental mammals and 3-10 times greater than those reported in mice and rats (Table 1.5.5).

TABLE 1.5.7

ESTIMATES OF ASYMPTOTIC LEVELS OF DIELDRIN IN BLOOD OF MEN EXPERIMENTALLY EXPOSED FOR 2 YEARS

Daily Intake	Estimate of Level (ppb)	
(µg HEOD)	By Hunter et al 1969	By Moriarty 1974
50	6.6 ± 0.3	8.0 ± 0.7
50	7.9 ± 1.3	14.3 ± 11.3
50	5.0 ± 0.3	6.4 ± 0.6
211	25.2 ± 3.9	-*
211	20.5 ± 1.5	26.0 ± 3.4
211	16.9 ± 1.8	25.6 ± 9.3

*Calculation impossible because data did not fit asymptotic model

In surveys of the general population of the United States, mean dieldrin levels in the adipose tissue lipids have been found to be about twice as high in adults (25 years and older) than in children (3-14 years), although children are believed to ingest more dieldrin because of their higher consumption of milk products (Train 1974). This suggests that storage factors increase with age, probably by a factor of 5 or more between childhood and middle age.

Storage of dieldrin may be modified by interaction with other chemicals, especially enzyme inducers. In a study by Davies et al (1971), volunteers given diphenylhydantoin at a rate of 300 mg/man/day for 9 months showed a reduction in dieldrin residues in fat by 73%.

Dieldrin crosses the placenta into the human fetus and is excreted into human milk (USDHEW 1969, Jager 1970). Polishuk et al (1977a) showed that dieldrin levels in lipids of the fetus were two to six times higher than those in maternal lipids. The same group showed that dieldrin levels in human milk lipids were lower than those in plasma lipids: mean 0.58 versus 2.0 ppm (Polishuk et al 1977b). Data from an EPA Human Monitoring Survey showed that, in the United States, mean levels of dieldrin in human adipose tissue lipids are about 0.19 ppm and those in human milk lipids are about 0.12 ppm (Train 1974). According to the data given above and if an excretion of about 25 g/day lipids in milk is assumed, the average lactating woman ingests about 7 µg/day and excretes about 4 µg/day in milk. The corresponding intakes per unit body weight are about 0.1 µg/kg/day in the mother and 0.8 µg/kg/day in the breast-fed infant.

2. Toxic Effects in Animals

2.1 General Toxicity

2.1.1 Acute Toxicity

Table 2.1.1 summarizes acute toxicity data for aldrin and dieldrin. The LD_{50}'s vary with the concentration (Barnes and Heath 1964) and the vehicle used (Heath and Vandekar 1964). Organic solvents and vegetable oils increase the toxicity by enhancing the rate of absorption of toxicant into the body (Jager 1970). The toxicity also varies between species, as shown in Table 2.1.2 for dieldrin and its photoisomerization product, photodieldrin.

The main signs of acute aldrin and dieldrin intoxication are increased irritability and tremor, followed by tonic-clonic convulsions, with the central nervous system as the principal site of action. Rats injected with nonlethal doses were found to recover fully and to show no delayed effects (Heath and Vandekar 1964).

2.1.2. Factors Modifying Toxicity

In addition to interspecific differences in susceptibility, the toxicities of aldrin and dieldrin vary according to the mode of administration: highest toxicity via the intravenous route, lower via the oral route, and lowest from dermal application. Studies by Treon and Cleveland (1955) and Heath and Vandekar (1964) indicated that aldrin and dieldrin are slightly more toxic to female than to male rats (see Table 2.1.1). Table 2.1.2 shows this also to be the case for dogs.

TABLE 2.1.1

ACUTE TOXICITY OF ALDRIN AND DIELDRIN IN EXPERIMENTAL ANIMALS

Species	Strain	Sex	Route	Formulation	LD_{50} (mg/kg)	
					Aldrin	Dieldrin
Rat	Wistar	F	Oral	Arachis oil	-	50.8
Rat	Wistar	M	Oral	Arachis oil	-	63.5
Rat	CFE*		Oral	Peanut oil	45.9	38.3
Rat	CFE		Oral	Arom. solv.	18.8	-
Rat	CFE		Oral	40% emulsifiable conc.	56.4	-
Rat	CFE		Oral	40% wettable powder	62.5	-
Rat	CFE		Oral	75% dust conc.	72.2	-
Rat	CFE		Oral	2.5% field strength dust	109.0	-
Rat	CFE		Oral	20% emulsifiable conc.	-	55.9
Rat	CFE		Oral	50% wettable powder	-	52.1
Mouse	-		Oral	-	95	75-100
Mouse	-		Oral	-	44	38
Guinea pig	-		Oral	-	33	49-59
Rabbit	-		Oral	-	50-80	45-50
Dog	-		Oral	-	65-95	56-80
Sheep	-		Oral	-	-	50-75
Rat	CFE		Dermal	40% emulsifiable conc.	194.0	-
Rat	CFE		Dermal	40% wettable powder	274.0	-
Rat	CFE		Dermal	75% dust conc.	269.0	-
Rat	CFE		Dermal	2.5% field dust strength	<100.0	-
Rat	CFE	M	Dermal	20% emulsifiable conc.	-	213.8
Rat	CFE	F	Dermal	20% emulsifiable conc.	-	119.9
Rat	CFE		Dermal	50% wettable powder	-	213.4
Rat	Wistar	F	ip	Glycerol	-	55.9
Rat	Wistar	F	iv	Glycerol	-	8.9
Mouse	-		iv	-	21.5	15.2

*Carworth Farm E strain

Adapted from Jager 1970

TABLE 2.1.2

THE LD_{50}'s OF PHOTODIELDRIN AND DIELDRIN

Species	Approximate LD_{50} (mg/kg)	
	Photodieldrin	Dieldrin
Rat	10	47
Mouse	7	77
Guinea pig	3	24
Dog (M)	140	120
Dog (F)	100	90
Chicken	80	48
Pigeon	90	250

Adapted from FAO/WHO 1971

Another factor modifying the toxicity of aldrin/dieldrin is diet. Heath and Vandekar (1964) found that rats underfed for a prolonged period before dosing were considerably more susceptible to toxic doses of aldrin and dieldrin than those fed normally, probably because of lower storage capacity in adipose tissue and consequently higher dieldrin levels in the blood and in the central nervous system.

2.1.3. Mode of Action

The exact mode of action of aldrin and dieldrin on the central nervous system is still not fully understood. Hathway and Mallinson (1964) re-

ported that the action of dieldrin leads to liberation of ammonia in the brain before convulsions begin and throughout their course. They suggested that dieldrin may inhibit glutamine synthesis in the brain.

Studies conducted on cockroaches suggest that a metabolite, probably trans-6,7-dihydroxydihydroaldrin, may be the active neurotoxic agent, because this metabolite caused an immediate reaction when applied to isolated nerve axons, whereas dieldrin elicited a weaker response which occurred only after a delay (Wang et al 1971).

2.1.4 Effects Observed in Long-Term Feeding Studies

In a study of slightly more than 15 months duration, dogs fed diets containing either aldrin or dieldrin at 1 and 3 ppm survived the entire test period. Increased liver weights were observed in the dogs fed the diets with dieldrin at 1 and 3 ppm and in those given aldrin at 3 ppm. Minor liver cell changes were seen in dogs fed aldrin at 3 ppm, but none were seen in dogs fed dieldrin (Treon and Cleveland 1955).

In a 2-year study conducted by Fitzhugh et al (1964) dogs were fed aldrin or dieldrin in the diet at dosages of 0.2, 0.5, 1.0, 2.0, 5.0, and 10.0 mg/kg. A "no-effect level" of 0.2 mg/kg (equivalent to about 6 ppm in the diet) was established for both compounds. Neither clinical nor histopathologic abnormalities were reported at this dose level. At 0.5 mg/kg, the dogs suffered from convulsions; 4/4 dogs fed aldrin and 1/4 dogs fed dieldrin died during the 2-year exposure period. At higher dose levels, all dogs died within 49 weeks. At autopsy they displayed fatty changes in their livers and renal tubules.

A male and a female dog were exposed to dietary dieldrin at a rate of 0.2 mg/kg/day for 5 years. The only effects observed were increased serum alkaline phosphatase activity in both animals and increased bromosulphthalein clearance in the male. The latter change was considered a sign of stimulation of miscrosomal enzyme activity (Jager 1970).

In a 2-year study, Walker et al (1969) daily gave groups of five male and five female beagles capsules containing 0.05 mg/kg doses of recrystallized dieldrin in olive oil. Control dogs received capsules containing olive oil only. General health, behavior, and body weight were unaffected in each group. Electroencephalographic recordings showed no difference between the control and the high dose group. The results of hematologic studies and urinalyses were similar in all groups. The serum alkaline phosphatase level in the dogs given 0.05 mg/kg was higher after the 18th week than in the controls. At autopsy the only significant finding was an increase in the liver-to-body weight ratio in the high dose group. This increase was not associated with any histologic anomaly.

Treon and Cleveland (1955) fed male and female rats diets containing either aldrin or dieldrin at 2.5, 12.5, and 25 ppm for up to 2 years. A slight increase in the ratio of liver weight to body weight was observed in both males and females, even at the lowest dose level. Liver lesions were recorded for animals in all of the experimental groups.

In a feeding study conducted by Fitzhugh et al (1964), male and female rats received diets containing aldrin or dieldrin at 0.5, 2, 10,

50, 100, and 150 ppm for 2 years. The rats exposed at 50 ppm and above suffered a dose-related reduction in lifespan and a high incidence of nephritis and microscopic liver lesions described as characteristic results of exposure to chlorinated hydrocarbons. Increased liver weight and "minimal" liver cell changes were observed even in the rats fed aldrin or dieldrin at 0.5 ppm. However, 0.5 ppm was considered a "minimal effect level" and was used as the basis for WHO's Acceptable Daily Intake (FAO/WHO 1971). For further evaluation of this experiment see Sections 2.2.1, 2.2.2, and 2.5.

Walker et al (1969) fed recrystallized dieldrin (99% purity) at dietary levels of 0.1, 1.0, or 10 ppm to groups of 25 male and 25 female rats for periods up to 2 years. Forty-five males and 45 females served as controls, but the control diet contained dieldrin at 0.026 ppm. Body weights and food intakes were unaffected by the added dieldrin, but at 10 ppm all the animals became irritable after 8-13 weeks; occasional convulsions occurred in this group during handling. No adverse effect on survival was observed. Liver weights were normal for the first 18 months, but after 2 years increased liver weights and liver-to-body weight ratios were observed in the groups fed 10 ppm. For further evaluation of this experiment see Section 2.5.

A series of long-term feeding studies with recrystallized dieldrin (99% pure) in CF1 mice was conducted at Tunstall Laboratory (Walker et al 1972; Thorpe and Walker 1973). The most striking effect was a dose-related increase of liver tumors in all experiments (for details

see Section 2.5). Survival was markedly reduced in mice receiving dieldrin at 10 and 5 ppm and in female mice at 2.5 ppm, but not in males at 2.5 ppm or in either sex at lower concentrations (Figure 2.1.1).

Murphy and Korschgen (1970) conducted 3-year feeding tests on white-tailed deer. Groups of 10 deer and their progeny were given dieldrin at 5 or 25 ppm. No signs of overt intoxication were observed, and 9 or 10 adult deer in each group survived the 3 years. Growth was slower and remained reduced in dieldrin-exposed females that were immature when the study began. Hematologic values and serum protein concentrations were not significantly related to treatment. Liver-to-body weight ratios were significantly larger in deer given dieldrin at 25 ppm, and pituitary glands were smaller and thyroids were larger in deer fed dieldrin.

Male rhesus monkeys were fed dieldrin at 0.1, 0.5, 1.0, 1.75, and 5.0 ppm (0.002-0.07 mg/kg/d) in the diet for about 6 years. No significant liver changes were observed at dietary levels below 1.0 ppm. A dose-related increase in microsomal P450 was found at the higher levels, and increased microsomal enzyme activity was observed at the 1.0 and 1.75 ppm levels, but no changes in subcellular structure were found (Wright 1974, Jager 1970).

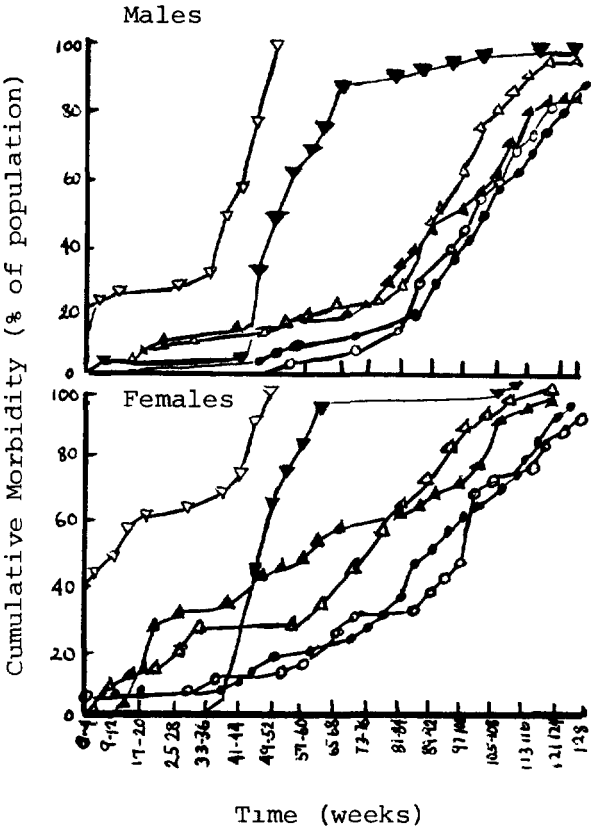
2.2 Organ-Specific Effects

2.2.1 Liver Effects

Histologic changes occur in the livers of rats given repeated doses of certain chlorinated hydrocarbon compounds. These changes have been studied in rats exposed to DDT or to dieldrin and appear to be similar

FIGURE 2.1.1 (Walker et al 1972)

CUMULATIVE MORBIDITY OF MICE FED DIELDRIN
AT LEVELS OF 0 (●), 1.25 (○), 2.5 (▲), 5 (△),
10 (▼), OR 20(▽) PPM



for each compound (USDHEW 1969). The histologic changes in the parenchymal cells of the liver consist of increased deposition of fat, margination of cytoplasmic granules, and hypertrophy of cells. The most characteristic change is the formation of complex lipoid cytoplasmic inclusion bodies termed "lipospheres." In rats fed dieldrin, structural changes in the liver included an increase in the amount of smooth endoplasmic reticulum (SER) associated with induction of microsomal enzymes (Wright 1974). Fitzhugh et al (1964) reported that the severity of these histopathologic changes increased progressively with dosage of both aldrin and dieldrin (see Table 2.2.1).

Kimbrough et al (1971) found morphologic changes, including an increase in SER and atypical mitochondria, in adult male rats fed technical grade dieldrin at 50 or 100 ppm for 8 weeks. Effects were more pronounced in rats fed DDT and dieldrin simultaneously.

In comparative studies, single doses of dieldrin caused a marked proliferation of SER in the livers of rats given 8 mg/kg and in dogs given 2 mg/kg but caused less marked effects in mice given 0.16-7.5 mg/kg. Increases in SER were accompanied by increased microsomal enzyme activity (see Section 2.2.2). In mice, an increase in liver DNA content indicated cell proliferation, whereas rats and dogs showed cellular hypertrophy (Jager 1970; Wright 1974).

Liver lesions induced in mice and rats by aldrin and dieldrin after long-term feeding (15-26 months) have been re-evaluated by Reuber (1974, 1975, 1976). He reported that the lesions spanned all stages of de-

TABLE 2.2.1

CHARACTERISTIC "CHLORINATED INSECTICIDE" CHANGES IN LIVERS OF RATS FED ALDRIN OR DIELDRIN

Dietary Concentration (ppm)	Degree of Liver Change*						Number of Livers Sectioned
	N	T	VS	S	S-M&M	>M	
Control							
None	16	1	0	0	0	0	17
Aldrin							
0.5	15	4	0	0	0	0	19
2	10	8	0	1	0	0	19
10	11	3	7	1	0	0	22
50	0	0	0	6	10	2	18
100	0	0	0	0	5	6	11
150	0	0	0	0	2	7	9
Dieldrin							
0.5	17	4	0	1	0	0	22
2	12	5	5	1	0	0	23
10	7	7	3	1	0	0	18
50	0	0	3	8	6	3	20
100	0	0	1	1	8	8	18
150	0	0	0	1	5	5	11

*N = none, T = trace or minimal, VS = very slight, S = slight, and M = moderate; figures based on microscopic sections

Adapted from Fitzhugh et al 1964

velopment from hypertrophy, through areas or foci of hyperplasia to hyperplastic nodules and well differentiated or moderately well differentiated hepatocellular carcinomas. Reuber (1976) described and illustrated stages in this progressive development. For further details see Section 2.5.

2.2.2 Liver Microsomal Enzymes

Many compounds, including phenobarbital and chlorianted hydrocarbon insecticides such as DDT and dieldrin, stimulate the drug-metabolizing enzyme system of the liver and are frequently associated with liver enlargement (Fouts 1963, Hard and Fouts 1963, Hart et al 1963, Gilbert and Goldberg 1967, Conney et al 1967, Remmer 1967, Kupfer 1967, Rubin et al 1968, Kimbrough et al 1968, Conney 1967, 1969). The increased activity of microsomal enzymes leads to enhanced rates of metabolism of steroid hormones (see Section 2.3.8) and other chemicals, including dieldrin itself (Oberholser et al 1977). Triolo and Coon (1966a,b) reported that a single dose of aldrin and dieldrin at 1 mg/kg body weight administered to rats caused a reduction in the toxicity of parathion, paraoxan, and several other organophosphates administered 4 days later. This effect was attributed to enhance metabolism of the organophosphates.

Rats fed 200 ppm of dieldrin in the diet showed cellular changes observable with electron microscopy within 24 hours. These changes were correlated with an increased activity of certain enzymes, such as those capable of hydroxylating aniline or catalyzing the o-dealkylation of chlorfenvinphos, but the activity of other enzymes such as acid phosphatase or glucose-6-phosphatase did not change (Jager 1970).

In dogs fed dieldrin at 0.05 mg/kg/day for 2 years, cellular changes observable by electron microscopy were similar to those found in rats (Jager 1970, Wright 1974). In the dog, however, unlike in the rat, increased activity of liver and serum alkaline phosphatases was observed at the highest dose level (Walker et al 1969). Street et al (1969) reported a dietary "threshold" level for hepatic enzyme induction by dieldrin of 1 ppm after 2 weeks oral administration to rats, compared with 5 ppm for DDT. Den Tonkelaar and van Esch (1974) found markedly stimulated aminopyrine demethylase activity in male rats fed dieldrin for 2 weeks at 2 ppm, the lowest dietary concentration tested.

2.2.3 Kidney Effects

Fitzhugh et al (1964) observed a marked increase in kidney lesions, diagnosed as slight or moderate nephritis, in rats given aldrin or dieldrin at 50-150 ppm for 2 years (Table 2.2.2). In examining kidney

TABLE 2.2.2

GROSS AND MICROSCOPIC PATHOLOGY IN THE KIDNEYS OF RATS EXPOSED TO ALDRIN OR DIELDRIN FOR 2 YEARS

Dietary Concentration (ppm)	% Survival		No. of Livers Sectioned	Nephritis	
	18 mo	24 mo		S or M	>M
Control					
None	75	50	17	6	1
Aldrin					
0.5	75	50	19	4	2
2	83	50	19	4	3
10	67	42	22	8	1
50	63	25	18	1	2
100	42	17	11	4	5
150	17	4	9	3	2
Dieldrin					
0.5	79	42	22	5	3
2	88	63	23	6	0
10	79	25	18	6	1
50	67	21	20	6	3
100	50	13	18	2	8
150	21	4	11	7	1

*S = slight and M = moderate; figures based on the microscopic sections, except for the inclusion of one markedly damaged kidney, based on gross appearance only, in the 100 ppm aldrin group

Adapted from Fitzhugh et al 1964

sections from this study, Reuber (1974) found that chronic nephritis occurred more commonly in males than females and was very common at high dose levels, particularly of dieldrin; he suggested that the figures in Table 2.2.2 were probably underestimates because of the high mortality after 1 year, when the nephritis was unsually seen. Hemorrhagic and distended urinary bladders were usually associated with severe nephritis and were only seen in males that died. Reuber also found several cases of acute renal necrosis, especially in females, hyperplasia of the renal tubules, and one hyperplastic nodule.

2.2.4 Central Nervous System and Peripheral Motor Effects

As discussed in Section 2.1.3, the effects of aldrin and dieldrin on the central nervous system are not completely understood. Experiments involving long-term dietary exposure have demonstrated a variety of effects, including nonspecific neural lesions, impairment of learning, increased chronaxy, and impairment of muscular performance.

Harr et al (1970b) administered purified dieldrin at concentrations between 0.08 and 40 ppm in the diet to Wistar rats for up to 2 years. They reported nonspecific neural lesions, cranial edema, dieldrin residues in the brain, and convulsions in most exposed rats. No functional effects were observed at dietary concertrations below 2.1 ppm dieldrin, although cranial edema was observed at 0.63 ppm, and cerebral, cerebellar, brain-stem, and vascular lesions were at all dietary levels down to 0.08 ppm. Dieldrin residue levels of 9-11 ppm in the brain were associated with convulsions.

Smith et al (1976) exposed two groups of seven squirrel monkeys to technical dieldrin at two oral dose levels, 0.1 and 0.01 mg/kg/day. Two zero-dose controls were included. After 55 days the higher dose group was shifted to zero exposure and the lower dose group was shifted to exposure at the high dose; controls continued at zero exposure. The new regimens were continued for 54 days. The monkeys were presented with a visual nonspatial successive discrimination reversal task. During the first 55 days, before the change in regimen, control and low-dose monkeys learned the task, whereas high-dose monkeys did not ($P<0.001$). During the subsequent 54 days, the performance of each group remained approximately at the level achieved before the change in regimen. It was concluded that the high dose disrupted learning without affecting retention of the learned task. The authors suggested that this effect could be attributed to disruption of hippocampal activity. The low dose had no effect on task acquisition or retention.

Al-Hachim (1971) reported apparent effects of prenatal exposure to aldrin on the central nervous system of mice. The 38-day-old offspring of mice given aldrin at 2 or 4 mg/kg/day orally for 7 days during the third stage of gestation showed a significant reduction in body weight and a significant increase in electroshock seizure threshold compared to controls.

London and Pallade (1964) exposed rats to aldrin at 3 mg/kg/day in the diet for 6 months and then at 4.5 mg/kg/day for 7 months. They measured chronaxy by applying an electric current to the tails of the

rats and measuring the duration of the voltage pulse required to elicit a withdrawal response. They found that chronaxy was longer in the rats exposed to aldrin than in controls.

Khairy (1960) studied the effects of dieldrin exposure on the muscular performance of rats given diets containing the substance at 25 or 50 ppm for 60 days. The criterion for muscular performance was the time taken to pull a weight along a 250-cm runway. He observed a progressive deterioration of performance related to the amount of dieldrin administered. Jager (1970) reported that the gastrocnemius muscle of rats receiving dieldrin at 50 ppm in the diet for 7 months failed to maintain a tetanus comparable to that of control rats.

Medved' et al (1964) reported that, in cats, feeding of aldrin at 1 mg/kg/day or inhalation of aldrin at 0.1 mg/m^3 for an unspecified period caused marked lowering of conditioned reflexes and of unconditioned orientation reflexes. These reflexes required as much as 6-8 days to return to normal after exposure.

2.2.5 Effects in Other Organs

In 39- to 140-day-old female Wistar rats fed dieldrin at 2.5-10.0 ppm in the diet, Harr et al (1970a) found proliferation of reticuloendothelial components and pancreatic ductal cells. Fibrinoid degeneration, arteritis, endothelial proliferation, and perivascular edema were seen in small to medium sized arteries.

Although no data were found on dieldrin's effects on the mammalian thyroid, Jefferies and French (1972) reported that dieldrin

at 1, 2, and 4 mg/kg/day produced hyperplastic goiters in the thyroids of pigeons. In a visual examination, they observed that the thyroids were significantly enlarged and had small follicles with decreased amounts of colloid, epithelial hyperplasia, and vascular congestion.

2.3 Effects on Reproduction

2.3.1 In Mice

Good and Ware (1969) studied the effects of technical dieldrin on reproduction in 101 pairs of CFW mice, with a similar number of controls. At a dietary level of 5 ppm, dieldrin did not affect maternal mortality, fertility (defined as the percentage of pairs producing young), or fecundity (defined as the number of young per producing pair) but significantly reduced the average size of litters.

Virgo and Bellward (1975 a,b) studied the effects of technical dieldrin at dietary levels of 0, 2.5, 5, 10, 15, 20, and 25 ppm in SWV mice. Virgin and diparous females were studied. Dietary levels of 20 and 25 ppm caused maternal mortality. At levels up to 15 ppm, dieldrin had no effect on the incidence of breeding in parous females, nor did it affect fetal survival, the duration of gestation, or parturition. Levels of 10-15 ppm reduced fertility by 18% and there was a dose-related reduction (maximum 17%) in litter size. The reductions in fertility and litter size resulted from a lesion or lesions preceding implantation. Dieldrin exposure resulted in preweaning losses of entire litters in 100% of litters from dams exposed to dieldrin at 10 ppm or higher, 80% of litters from dams exposed

at 5 ppm, and 47% at 2.5 ppm, versus 31% in controls. Maternal cannibalism and neglect of pups were responsible for deaths in litters of dams fed dieldrin at 15 ppm or more, although it was considered that most of these pups would have died from toxic effects of dieldrin anyway.

In a six-generation study using Swiss mice exposed either to aldrin (3, 5, 10, and 25 ppm) or to dieldrin (3, 10, and 25 ppm), the principal adverse effects were on lactation indices and the viability of pups. Dieldrin at 10 ppm did not affect fertility in the mice in the first mating but decreased it by 31% in the second mating. This dose did not reduce litter size, and reproduction was not substantially affected at 3 ppm. The authors suggested that the adverse effects may have been mediated through hormonal imbalance rather than direct toxicity (Deichmann and Keplinger 1966, Keplinger et al 1970, Deichmann and MacDonald 1971).

2.3.2 In Rats

Results of a three-generation reproduction study in Carworth rats have been reported in summary form only (Treon and Cleveland 1955, Cleveland 1966). Aldrin or dieldrin was fed to rats at dietary levels of 0, 2.5, 12.5, and 25 ppm, and two sets of offspring were obtained from each generation. There was no reported effect on the number of pups per litter nor on the weight of the young rats at weaning. "Initially aldrin in the diet at levels of 12.5 ppm or higher and dieldrin at 2.5 ppm or higher appeared to reduce the

number of pregnancies in these rats. However, this effect tended to diminish to the point of disappearance when the feeding of aldrin at 12.5 ppm or lower was maintained over several generations." Incorporation of aldrin or dieldrin into the diet of parent rats during the period of suckling increased mortality among the offspring, the effect being "slight to moderate" at 2.5 ppm but higher at 12.5 or 25 ppm.

In a factorially designed experiment, Wistar rats weaned at 28 days were placed on diets containing dieldrin at a concentration of 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, 20, or 40 ppm (Harr et al 1970a). Twenty males and 20 females were included in each of the 10 exposure groups and in a control group. The animals were killed at various intervals ranging up to 750 days. Values for dam survival, conception rate, pup survival, and weaned litter size were normal in rats fed dieldrin at 0.08 and 0.16 ppm. In rats fed 0.31-1.25 ppm, there was a slight reduction in the survival of litters and a marked reduction in conception rates (to 73% in the first mating and 33% in the second mating). At dietary levels of 2.5-10 ppm, females survived to breeding age, but nursing pups either died in convulsions or starved. The calculated maximum dietary concentration of dieldrin consistent with normal reproduction was 0.26 ppm in the first breeding and 0.09 ppm in the second breeding. Computed dietary levels of dieldrin associated with various effects are shown in Table 2.3.1.

TABLE 2.3.1

DIETARY LEVELS OF DIELDRIN ASSOCIATED WITH VARIOUS LEVELS OF REPRODUCTIVE PERFORMANCE IN RATS

Measure of Reproductive Performance	Calculated Dietary Levels (ppm)	
	1st Breeding (146-day-old rats)	2nd Breeding (336-day-old rats)
50% dam survival	27.0	16.0
80% dam survival	21.0	9.0
*100% dam survival	10.0	5.0
30% conception rate	13.75	2.88
70% conception rate	2.50	0.24
*90% conception rate	0.36	0.09
3 pups of litter weaned	6.36	2.34
7 pups of litter weaned	1.39	0.50
*9 pups of litter weaned	0.26	0.26

*Normal

Adapted from Harr et al (1970a)

2.3.3 In Dogs

Kitselman (1953) exposed 9 male and 11 female dogs to recrystallized aldrin or dieldrin in food at doses of 0.2, 0.6, and 2.0 mg/kg/day in the diet for up to 1 year. Of the 11 exposed females, 9 became pregnant and came to term, but only 7 pups survived (4/4 from a bitch given dieldrin at 0.2 mg/kg, 2/5 from a bitch given aldrin at 0.2 mg/kg, and 1/5 from a bitch given aldrin at 0.6 mg/kg). The other 32 pups were either stillborn or died within 3 days after birth.

Deichmann and MacDonald (1971) and Deichmann et al (1971) exposed beagle dogs by capsule to technical aldrin at 0.15 mg/kg (four females), aldrin at 0.3 mg/kg (four males and three females), or a mixture of aldrin at 0.15 mg/kg plus 6 mg/kg recrystallized p,p'-DDT at 6 mg/kg (four males and four females). Capsules were given 5 days/week for 14 months, and then the dogs were maintained for up to 9 months on uncontaminated diets. Reproduction was severely affected in all three treatment groups, as evidenced by reduced fertility, reduced mammary development, and impaired lactation in the females, and stillbirths and increased mortality of pups. Only 26 pups were raised to weaning in 17 breeding attempts, compared to 78 pups from 18 control females.

2.3.4 In Raccoons

Frederickson (1973) reported on a study of the effects of chronic exposure to dieldrin on reproduction in raccoons. At 2.2 ppm in the diet (wet weight, corresponding to 6 ppm dry weight) most of the females died "under the stress of breeding." At 0.73 ppm in the diet statistically significant adverse effects on the estrous cycle and on the incidence of pregnancy were reported. Fetal death, resorption of embryos, and reduced litter size were also reported. The exposed females produced only 20% of the number of young produced by unexposed females. Seven of 15 exposed females failed to respond normally to the sexual behavior of males. Adverse effects were also noted in males, on the production of sperm, the quality of sperm, and total fertility.

2.3.5 In Rabbits

Wild-trapped cottontail rabbits were confined in 1-acre pens and exposed to granular dieldrin applied at 0.5 or 2.0 lb/acre (Malecki et al 1974). No significant effects were recorded on testis weight, date of breeding, ovulation rates, preimplantation losses, resorption of embryos, or embryonic litter size. No adequate measures of post-natal mortality were obtained. Precise exposure levels were not determined, but food plants contained dieldrin at 0.07-0.25 ppm, and brain residues of dieldrin in the rabbits were in the range 0.11-0.66 ppm.

2.3.6 In Sheep

Thirty-six ewes were fed dieldrin at 0, 1, 5, or 25 ppm during 40 months, which included two gestation periods (FAO/WHO 1971). Reproductive success was apparently normal at exposure concentrations up to 5 ppm. However, at 25 ppm the lambs died shortly after birth.

2.3.7 In Deer

Murphy and Korschgen (1970) studied reproduction in white-tailed deer exposed to dieldrin at dietary levels of 0 (controls), 5, and 25 ppm for 3 years. Ten females (five yearlings, five fawns) were included in each exposure group. No effects on conception rates or on mortality in utero were reported. Fawns from does fed dieldrin at 25 ppm were smaller at birth, and the number of postpartum deaths was increased in the 5 and 25 ppm exposure groups. The fertility of male progeny was not affected. Weight gains of fawns born to does exposed to dieldrin were significantly reduced.

2.3.8 Effects on Steroid Hormones

In a number of experiments dieldrin induced hepatic microsomal enzymes that can enhance the metabolism of steroid hormones such as testosterone and progesterone. Such effects have been reported even at dietary levels as low as 2 ppm (Conney et al 1967, Thomas and Lloyd 1973). Schein and Thomas (1975) showed that administration of dieldrin in five daily doses of 2.5 mg/kg or in one dose of 10 mg/kg increased hepatic microsomal protein and cytochome P450 concentration, increased testosterone hydroxylase activity, and altered the metabolism of testosterone in the liver and prostate of mice. These effects were enhanced by simultaneous or subsequent exposure to parathion (Schein and Thomas 1976). Similar enhancement of dieldrin effects on the metabolism of testosterone by exposure to carbaryl was reported by Schein et al (1976).

Exposure to dieldrin reduced the ability of the prostate gland of rats to assimilate testosterone both in vivo and in vitro (Blend and Schmidt 1971, Thomas et al 1973, 1975). Wakeling et al (1972) reported that dieldrin interfered with the binding of dihydrotestosterone to male sex hormone receptors in the nuclear and cytosol fractions of the rat prostate. Further studies by Wakeling and Visek (1973) suggested that the dieldrin interferes with the in vitro binding of 5-alpha-dihydrotestosterone to its androphilic molecule by a mechanism involving noncompetitive inhibition. Schein and Thomas (1975) showed that dieldrin at 1.25, 2.5, or 5 mg/kg/day for 5 days significantly reduced the total

uptake and subsequent metabolism of androgens in the anterior prostate of the mouse. Dieldrin at concentrations as low as 4×10^{-7}M in vitro effectively decreased the formation of dehydrotestosterone in the mouse anterior prostate and of androstanediol in the rat ventral prostate.

In addition to the actions of dieldrin upon the prostate glands of rodents, it apparently produces changes in the levels of serum luteinizing hormone (LH) (Blend and Lehnert 1973). Levels of LH were not affected when the rats were fed dieldrin at 0.7 ppm. At 6.2 ppm, dieldrin produced significant elevations in serum LH. Even in castrated rats, dieldrin (6.2 ppm) caused an increase in the serum levels of this gonadotropin. Dieldrin also caused a slight decrease in the ratio of body weight to pituitary gland weight and a small increase in the ratio of body weight to prostate gland weight. Blend and Lehnert (1973) suggested that the smaller prostate glands observed in the treated (0.7 ppm) rats were possibly caused by an action of dieldrin on hepatic microsomal enzymes that effectively lowered the levels of circulating androgens. These lowered androgen levels in the blood might account for the observed decreases in accessory sex organ weights.

2.4 Teratogenesis

Ottolenghi et al (1974) administered aldrin and dieldrin at approximately one-half the lethal dose to pregnant Syrian golden hamsters and to pregnant CD1 mice. Hamsters given aldrin at 50 mg/kg or dieldrin at 30 mg/kg by oral intubation on day 7, 8, or 9 of gestation showed

a high incidence of fetal death, growth retardation, and congenital abnormalities. The most frequent abnormalities were open eyes, webbed feet, cleft palate, cleft lip, and fused ribs. Dieldrin also induced a smaller number of other defects including exencephaly, platycrania, micrognathia, and ectrodactyly. Hamster pups exposed on day 8 of intrauterine development showed a much higher incidence of abnormalities (22% for aldrin, 33% for dieldrin) than those exposed on day 7 or 9. The same type of defects were induced in mice given aldrin at 25 mg/kg or dieldrin at 15 mg/kg by oral intubation on day 9 of gestation. The percentages were 33% for aldrin and 17% for dieldrin, versus zero in controls.

Chernoff et al (1975) administered dieldrin at doses of 1.5, 3.0, and 6.0 mg/kg to pregnant CD1 mice and CD rats by gastric intubation on days 7-16 of gestation. The highest dose caused maternal death and weight loss in rats but did not cause fetal mortality or anomalies. In mice, all three doses induced an increase in the number of supernumerary ribs in one of two experiments; the increase was statistically significant at 3 and 6 mg/kg. The 6 mg/kg dose also induced a decrease in the number of caudal ossification centers. The authors did not regard these as teratogenic effects. Photodieldrin administered at 0.15, 0.30, and 0.60 mg/kg induced no fetal toxicity or anomalies in rats and mice.

Boucard et al (1970) reported that dieldrin was teratogenic in rats and mice, but the incidence of anomalies was low in all exposed

groups. When data from three dosage regimens (day 6, days 6-14, and days 1-14) are pooled, the incidences in rats were: control, 1/1,336; 2.5 µg/kg/day, 4/655; 3.4 mg/kg/day, 5/617. In mice, the incidences were: control, 2/1,123; 2.5 µg/kg/day, 4/475; 3.4 mg/kg/day, 4/510. These results suggest that dieldrin has a weak teratogenic effect, but the effect was not statistically significant in any one treatment group. The malformations observed in the exposed animals included hydrocephaly (5), hydronephrosis (2), cleft palate (2), and miscellaneous abnormalities (10).

2.5 Carcinogenesis

The carcinogenicity of dieldrin was the principal focus of public hearings held in 1973-74 before the U.S. Environmental Protection Agency (EPA) on the cancellation of registrations of aldrin/dieldrin, and a large volume of expert testimony and exhibits on this subject was introduced into the public record (USEPA 1973-74). The most extensive published review is by Epstein (1975), but it was limited to material introduced by witnesses for parties arguing for cancellation and subsequent to its preparation additional material, including new data, revised diagnoses, and extended statistical analysis, was introduced by witnesses called by Shell Chemical Company (Thorpe 1974, Stevenson 1974, Hunt 1974, Sternberg 1974; see also Stevenson et al 1976).

Epstein (1975) concluded that aldrin/dieldrin has been shown to be carcinogenic in the liver in at least five independent experiments

with mice and in other sites, as well as in the liver, in at least one experiment with rats. The reported positive findings in rats were disputed on both pathologic and statistical grounds (Thorpe 1974, Stevenson 1974, Hunt 1974, Sternberg 1974). Dieldrin was also reported to be carcinogenic in the lung and other sites in several experiments with mice (Gross 1974), but this also was disputed on statistical grounds (Stevenson 1974, Hunt 1974). On reviewing the record, the Administrator of EPA concluded that dieldrin has been shown to be carcinogenic in the liver and lung of mice in several experiments and that "there is a strong probability that aldrin/dieldrin is a carcinogen in rats as well as mice" (Train 1974). The following is a brief summary of the experiments and reported findings, including the results of experiments recently reported by the National Cancer Institute (NCI 1977, 1978a,b).

2.5.1 FDA Studies 2 and 3 in C3H Mice

Following an earlier inconclusive experiment, two long-term feeding studies in C3HeB/Fe strain mice were carried out at the U.S. Food and Drug Administration and were reported by Davis and Fitzhugh (1962) and Davis (1965). In Study 2, groups of 215-218 mice, with about equal numbers of males and females, were fed diets containing aldrin or dieldrin at 10 ppm. A similar group of 217 unexposed mice was a control group. Average survival times were 51.6 weeks in exposed mice and 59.8 weeks in the controls. Liver tumors, described as "extending from very benign lesions to borderline carcinomas," were

found in 38/151 (23%) aldrin-exposed, 38/148 (24%) dieldrin-exposed, and 9/134 (7%) control mice. Hepatic tumors developed in mice exposed to aldrin in an average of 80 weeks, in dieldrin-exposed mice in 77 weeks, and in control mice in 89 weeks (Davis and Fitzhugh 1962).

In Study 3, groups of 200 mice, with equal numbers of each sex, were fed diets containing aldrin at 10 ppm, dieldrin at 10 ppm, or no added material. Exposed mice survived less well than controls but showed a markedly increased incidence of liver tumors diagnosed as "benign hepatomas" (Davis 1965: see Table 2.5.1).

TABLE 2.5.1

RESULTS OF FDA STUDY 3 WITH C3H MICE

Dietary Exposure	No. of Survivors			No. of Mice with Lesions* When Killed			No. of Mice with Tumor	
	52 wk	78 wk	104 wk	Hy	H	HC	Benign	Malignant
Control (0)	188	150	64	48	27	4	30	21
Aldrin (10 ppm)	152	121	31	72	65	3	61	9
Dieldrin (10 ppm)	169	117	39	71	69	5	71	9

*Hy = hyperplasia, H = "benign hepatoma," HC = hepatic carcinoma

Adapted by Davis 1965

Histologic material from both studies (excluding dieldrin-exposed mice from Study 3) was examined by Reuber (1974), with the results shown in Table 2.5.2. There were marked and highly statistically significant increases in hepatocellular carinomas in all four treated groups. The carcinomas and other hepatic lesions have been fully described and illustrated by Reuber (1974, 1975, 1976). Carcinomas in controls were generally small and single, in contrast with those in treated animals, which were larger and sometimes multiple. Metastases to the lungs were found in 4% of the males exposed to aldrin and 5% of the females exposed to dieldrin, although no serial sections were made. Hepatic vein thrombosis, causing massive liver necrosis and death, was diagnosed in about 5% of the treated mice. Carcinomas from 7/8 control mice, 9/10 mice exposed to aldrin, and 8/9 dieldrin-exposed mice were successfully transplanted into isologous hosts. The behavior of the transplants correlated well with the degree of malignancy as diagnosed histologically, the more highly malignant tumors growing more rapidly than those judged to be less malignant (Reuber 1974, 1975, 1976; Epstein 1975).

2.5.2 Tunstall Experiment 1 in CF1 Mice

This is the largest-scale experiment on the carcinogenicity of dieldrin. Because of the unusually large numbers of mice involved, the data have been analyzed extensively (Walker et al 1972, Gross 1974, Epstein 1975, Stevenson 1974, Hunt 1974, Thorpe 1974, IARC 1974). In addition to positive controls, the experiment included a total of

1,500 mice segregated into groups containing the following numbers of mice of each sex: 0.01 ppm dieldrin ("control"), 300; 0.1 ppm, 125; 1 ppm, 125; 10 ppm, 200 (Table 2.5.3).

From the 9th month onwards, palpable abdominal masses were detected in mice fed 10 ppm. These mice were killed when the enlargement was considered to be detrimental to their health. Thus, 50% of the mice fed dieldrin at 10 ppm were dead at 15 months and 50% in the other groups were at 20 months (Walker et al 1972).

There was a statistically significant and dose-related increase in liver tumors in dieldrin-exposed mice, in both sexes independently. The increase was significant in female mice even at 0.1 ppm (Table 2.5.3). Liver tumors also appeared earlier in the mice fed dieldrin than in control mice (Gross 1974). The liver tumors were classified into two types, "a" and "b," on the basis of their morphology (Walker et at 1972, Thorpe 1974). Type a tumors were described as nodular growths of solid cords of parenchymal cells, whereas type b tumors were papilliform and adenoid growths with cells proliferating in confluent sheets with necrosis and increased mitoses. Reuber (1974, 1976) pointed out that this morphologic classification does not correspond to the morphologic and biologic behavior of lesions of the liver in mice and rats. Whereas type b tumors were clearly malignant on biologic and morphologic criteria, type a tumors ranged from histologically well-differentiated hepatocellular carcinomas to hyperplastic nodules (Reuber 1974, 1976; Epstein 1975). Lung metastases were observed from 12/138 type b tumors (Walker et al 1972). Successful

TABLE 2.5.2

LIVER TUMORS IN MICE IN FDA STUDIES 2 AND 3

Group (and sex)	No. Examined	Av. Survival (weeks)	% Incidence of Liver Lesions*					
			NH	H	N	SC	LC	TC
Control (M)	73	89	40	12	18	18	12	30
Control (F)	53	93	72	11	13	2	2	4
Aldrin (M)	91	86	1	3	13	21	62	82
Aldrin (F)	85	80	1	6	8	29	55	85
Dieldrin (M)	71	91	0	3	10	17	70	87
Dieldrin (F)	71	81	0	4	8	21	66	87

*NH = no hyperplasia, H = hyperplasia, N = nodules, SC = small carcinomas (less than 5 mm), LC = large carcinomas, TC = total carcinomas

Adapted from Reuber 1974, Epstein 1975

transplantation of tumor tissue to unrelated mice provided further confirmation of malignancy (Thorpe 1974).

In Tunstall experiment 1 the incidences of pulmonary adenomas and pulmonary carcinomas in males and females exposed to dieldrin at 0.1 and 1 ppm were increased above those in controls (Table 2.5.3). The differences were statistically significant in females (Gross 1974, Epstein 1975). Although Stevenson (1974) presented revised data listing more females without tumors, the increased incidence of lung tumors remained statistically significant in both sexes combined (Gross 1974). The increased incidence of lung tumors was also significant in the

TABLE 2.5.3

RESULTS OF TUNSTALL EXPERIMENT 1 IN CF1 MICE

Dose (ppm)	No. of Mice	% with Liver Tumors (Type a/Type b)		% with Lung Metastases	% with Lung Tumors*		% with Lymphoid Tumors	% with Other Tumors
					A	C		
Males								
0	288	20	(16/4)	0.7	33	8	35	6
0.1	124	26	(22/4)	0.8	38	11	21	3
1.0	111	31	(23/8)	0.4	38	12	20	5
10.0	176	94	(37/57)	0.6	18	1	24	2
Females								
0	297	13	(13/0)	0	16	6	40	7
0.1	90	27	(23/4)	0	26	13	50	9
1.0	87	37	(31/6)	1.1	34	14	54	17
10.0	148	92	(37/55)	4.5	10	0	5	1

*A = adenomas, C = carcinomas

Adapted from Walker et al 1972, Epstein 1975

subsample of mice without liver tumors (Gross 1974). These statistical comparisons omitted the mice fed the diet containing dieldrin at 10 ppm, because many died or were killed early in the experiment (Gross 1974). However, a "relative risk" analysis incorporating data on age at death showed a highly significant dose-related increase of lung tumors in both sexes independently (Table 2.5.4, Hunt 1974). There were also statistically significant increases in lymphoid tumors and in "other" tumors in females in the data as originally published (Gross 1974), but the differences were not significant according to the revised data (Hunt 1974).

2.5.3 Tunstall Experimental Series 2 in CF1 Mice

The Tunstall experimental series 2 (Walker et al 1972) comprised six independent tests, each with its own controls but involving smaller numbers of animals (10-33 mice per treated group) than experiment 1. Study 2.1 was a dose-response experiment in which mice were exposed to dieldrin at dietary concentrations of 1.25, 2.5, 5, 10, and 20 ppm. Study 2.2 involved three groups exposed to dieldrin at 10 ppm, two of which were fed diets sterilized with gamma rays or ethylene oxide. Study 2.3 compared tumor incidences in groups of mice fed DDT at 50 ppm, DDT at 100 ppm, and a mixture of dieldrin at 5 ppm and DDT at 50 ppm. Study 2.4 compared tumor incidences in mice exposed to dieldrin, beginning early in life, for 2, 4, 8, 16, 32, and 64 weeks.

The incidence of liver tumors was significantly increased in both males and females independently in each of the six experiments (Tables

TABLE 2.5.4

SUMMARY OF CHI-SQUARE VALUES FROM RELATIVE RISK ANALYSIS OF TUMOR INCIDENCE IN TUNSTALL EXPERIMENTS

Tumors	Experiment					
	1 (df=3)	2.1 (df=5)	2.2a (df=1)	2.2b (df=1)	2.2c (df=1)	4 (df=1)
Male Mice						
Liver, type a	210*	90.2*	18.4*	9.4*	9.0*	3.1*
Liver, type b	535*	93.5*	6.2*	6.0*	5.1*	29.7*
Liver, total	725*	143*	28.3*	19.5*	16.1*	37.3*
Lung, benign	31.8*	4.89	3.8*	0.1	0.7	0.1
Lung, malignant	6.83	-	--	-	-	0.0
Lung, total	30.2*	3.03	3.8*	0.1	0.8	0.0
Female Mice						
Liver, type a	261*	113*	11.0*	22.3*	18.2*	0.3
Liver, type b	547*	45.1*	9.8*	2.1	7.1*	66.0*
Liver, total	807*	165*	24.5*	26.9*	28.5*	56.5*
Lung, benign	27.5*	5.37	1.8	-	4.6*	1.7
Lung, malignant	2.82	-	-	-	-	0.0
Lung, total	21.2*	6.38	1.1	1.0	4.6*	0.9

*Statistically significant (P less than 0.05); df = degrees of freedom

Note: Data for experiment 3 not included, because the statistical analysis included data on other chemicals

Adapted from Hunt 1974

2.5.4 and 2.5.5, Walker et al 1972, Epstein 1975). In study 2.1, the increase was uniformly dose-related in both sexes when allowance was made for age at death (Hunt 1974). In study 2.3, there was evidence for synergistic action of dieldrin and DDT (Table 2.5.5). In study 2.4, liver tumor incidence was increased even in animals exposed for only 8, 4, or 2 weeks (Table 2.5.6). In addition, the age-adjusted incidence of

lung tumors was increased in 10 of 12 groups exposed to dieldrin, the increase being statistically significant in males in Study 2.2a and in females in Studies 2.2c and 3 (Table 2.5.4). The age-adjusted incidence of other tumors was statistically significantly increased in females in Study 2.4 (Hunt 1974).

TABLE 2.5.5

LIVER LESIONS* IN MICE IN TUNSTALL EXPERIMENT 2.3

Dietary Exposure	No. and Sex of Mice Examined	% Incidence of Liver Lesions**					
		NH	H	N	SC	LC	TC
Control	45 M	62	29	9	0	0	0
Control	32 F	47	44	9	0	0	0
DDT at 50 ppm	31 M	31	34	28	6	0	6
DDT at 50 ppm	31 F	32	16	35	13	3	16
DDT at 50 ppm and Dieldrin at 5 ppm	33 M	3	18	21	15	42	58
DDT at 50 ppm and Dieldrin at 5 ppm	31 F	0	0	6	29	65	94

* Diagnosed by Reuber (1974)

** NH = no hyperplasia, H = hyperplasia, N = nodules, SC = small carcinomas (less than 5 mm), LC = large carcinomas, TC = total carcinomas

Adapted from Epstein 1975

2.5.4 Tunstall Experiment 3 in CF1 Mice

In Tunstall experiment 3, CF1 mice were exposed, beginning at 4 weeks, to dieldrin in the diet at one concentration, 10 ppm. Relatively few mice were used. Mice were not killed when abdominal masses became large, but were if they became moribund. Mice surviving to 110 weeks were killed then (Thorpe and Walker 1973).

TABLE 2.5.6

INCIDENCE OF LIVER TUMORS IN MICE EXPOSED TO DIELDRIN FOR DURATIONS OF 2-64 WEEKS

Duration of Feeding (weeks)	No. of Mice		No. of Mice with Liver Tumors (Type a/Type b)	
	M	F	M	F
0	18	16	2/0	1/0
2	13	9	2/0	2/0
4	10	12	0/1	3/1
8	10	12	3/1	4/0
16	11	8	4/0	3/0
32	10	10	4/0	4/0
64	13	9	6/7	6/2

Adapted from Walker et al 1972, Epstein 1975

The incidence of liver tumors was increased significantly in treated mice of both sexes (Table 2.5.7), and the tumors occurred significantly earlier in treated mice than in controls (Thorpe and Walker 1973, Epstein 1975). The incidence of pulmonary metastases was much higher than in Studies 1 and 2 (Table 2.5.7), presumably because the animals were not killed prematurely (Epstein 1975). The age-adjusted incidence of lung tumors was increased in females, but not significantly (Hunt 1974).

2.5.5 Tunstall Experiment 4 in Three Strains of Mice

In Tunstall experiment 4, the effects of exposure to dieldrin at 10 ppm were compared in CF1 mice, in LACG mice, and in hybrids of the two strains (Stevenson 1974, Thorpe 1974, Hunt 1974). Forty mice of each sex were used in each treatment group, with groups of 60 controls.

The age-adjusted incidence of liver tumors was highly significantly increased in all six treated groups (Table 2.5.4, Hunt 1974). The incidence of lung tumors was also increased in all six treated groups, although not significantly so in any one considered alone (Hunt 1974). However, the incidence of other tumors was significantly increased in treated female CF1 mice (Hunt 1974).

TABLE 2.5.7

INCIDENCE OF LIVER TUMORS IN MICE IN TUNSTALL EXPERIMENT 3

Group	No. of Mice	% with Liver Tumors (Type a/Type b)		% with Lung Metastases
Males				
Control	45	24	(20/4)	0
10 ppm	30	100	(47/53)	3
Females				
Control	44	23	(23/0)	0
10 ppm	30	87	(40/47)	17

Adapted from Thorpe and Walker 1973

2.5.6 University of Miami Study with Swiss-Webster Mice

Four hundred Swiss-Webster mice were exposed to dieldrin at 3 or 10 ppm in the diet, with appropriate controls (MacDonald et al 1972). The death rate was high because of fighting and amyloidosis, and the mean lifespan of the males was only 12-13 months. There was a marked increase in liver lesions in the treated groups. The lesions were originally reported as "nodulation or restorative hyperplasia," but a

number of these diagnoses were later amended to hepatocellular carcinomas (MacDonald et al 1973 addendum). Diagnoses as carcinomas were confirmed on representative slides by Reuber (1974) and other pathologists, as reviewed by Epstein (1975).

2.5.7 NCI Study with B6C3F1 Mice

The National Cancer Institute recently reported the results of a bioassay of technical aldrin and technical dieldrin for carcinogenicity in B6C3F1 mice (NCI 1978a). Groups of 50 mice of each sex were fed diets containing aldrin or dieldrin for 80 weeks, then observed for 10-13 weeks. The time-weighted average dietary concentrations of aldrin were 4 and 8 ppm for males and 3 and 6 ppm for females; dieldrin was fed at 2.5 and 5 ppm. Untreated matched controls were groups of 20 untreated male and 10 female mice. Pooled control groups, used for statistical evaluation, consisted of the matched controls combined with 92 untreated male and 79 untreated female mice from similar bioassays of other chemicals. All surviving mice were killed at 90-93 weeks.

The mice fed aldrin or dieldrin and the control mice had similar mean body weights. Hyperexcitability was observed in all treated groups with increasing frequency during the 2nd year of the study. Female mice fed aldrin showed a dose-related increase in mortality.

There was a significant dose-related increase in the incidence of hepatocellular carcinomas in male mice fed either chemical (matched controls 3/20, pooled controls 17/92, low-dose aldrin 16/49, high-dose aldrin 25/45, low-dose dieldrin 12/50, high-dose dieldrin 16/45). The incidence of hepatocellular carcinomas in females was higher in

all the exposed groups than in controls, but the differences were not statistically significant. No other tumors appeared at a significantly higher frequency in the exposed groups than in the controls.

2.5.8 NCI Study of B6C3F1 Mice Exposed to Photodieldrin

The National Cancer Institute has also reported the results of a bioassay of photodieldrin (recrystallized and without detectable residual dieldrin) for carcinogenicity in B6C3F1 mice (NCI 1977). Groups of 50 mice of each sex were fed diets containing photodieldrin at concentrations of 0.32 and 0.64 ppm for 80 weeks, then observed for 10-13 weeks. Matched controls were 10 untreated mice of each sex at each dose; pooled controls groups consisted of 60 untreated mice of each sex.

Convulsions and hyperactivity were noted in exposed male mice, but body weights and mortality were unaffected by exposure to photodieldrin. Exposed mice and controls showed no statistically significant differences in tumor incidence.

2.5.9 FDA Experiment 1 and 2 with Osborne-Mendel Rats

In the FDA experiment 1, initiated at the U.S. Food and Drug Administration (FDA) in 1952 but not published until 1964, 12 groups of 12 male and 12 female Osborne-Mendel rats were fed diets containing aldrin or dieldrin at 6 concentrations, from 0.5 to 150 ppm (Fitzhugh et al 1964). Exposure began at 3 weeks and continued until mice surviving after 2 years were killed. Twelve rats of each sex were controls. Only 68% (227/336) of the animals, including only 17/24

controls, were examined histologically. The many small groups of animals makes the experiment difficult to analyze with statistical rigor.

The exposed rats could be classified into two groups (Table 2.5.8). Those exposed to aldrin or dieldrin at high dietary concentrations (50-150 ppm) showed a dose-related decrease in survival, acute renal necrosis, chronic nephritis, and a high incidence of liver lesions (Fitzhugh et al 1964, Reuber 1974, Epstein 1975). Rats exposed to aldrin or dieldrin at lower concentrations (0.5-10 ppm) survived well and had a low incidence of liver and kidney lesions but a higher incidence than controls of tumors in other organs, primarily the lymphatic system and mammary glands (Fitzhugh et al 1964, Reuber 1974, Epstein 1975, Thorpe 1974). The increase in tumor incidence in the rats exposed at low concentrations is statistically significant if groups are pooled (Gross 1974, Hunt 1974). The increase in liver lesions is also statistically significant (Gross 1974, Epstein 1975), but the pathologic diagnoses have been disputed vigorously. Reuber (1974) diagnosed 18 hepatocellular carcinomas in exposed animals, whereas other pathologists diagnosed most of the lesions as hyperplastic nodules or even milder lesions (Thorpe 1974, Sternberg 1974). In the terminology of the Liver Cancer Workshop (Squire and Levitt 1975) most of the lesions would be classified as neoplastic nodules.

In a second experiment conducted at FDA in 1963, 43 Osborne-Mendel rats were exposed to dieldrin at 1 ppm for 2 years. There were 39 controls. The results were similar to those for the groups at the lower concentrations

TABLE 2.5.8

GROSS AND MICROSCOPIC PATHOLOGY OF SOME RATS IN FDA EXPERIMENT 1

Dietary Exposure (ppm)	Number Sectioned	Nephritis*				Urinary Bladder**		No. of Rats with Tumors***						
		0	<S	M&S	>M	Dis	Hem	A	B	C	D	E	F	Total
Control (0)	17	5	5	6	1	0	0	1	1	0	0	0	1	3
Aldrin														
0.5	19	3	10	4	2	0	0	5	3	2	3	0	1	10
2	19	4	8	4	3	0	0	2	3	2	0	0	0	7
10	22	3	10	8	1	0	0	2	3	0	0	2	2	8
50	18	8	7	1	2	2	1	2	3	0	0	0	0	5
100	11	1	2	4	5	3	2	4	0	0	1	0	0	5
150	9	1	3	3	2	4	2	1	0	0	0	0	0	1
Dieldrin														
0.5	22	5	9	5	3	1	0	4	1	1	1	0	2	8
2	23	9	8	6	0	1	0	2	4	0	0	1	2	8
10	18	5	6	6	1	1	0	2	0	1	0	1	0	4
50	20	5	6	6	3	0	0	1	2	0	0	0	1	4
100	18	5	3	2	8	2	1	0	0	0	1	0	2	3
150	11	1	2	7	1	2	2	0	0	0	0	0	0	0

*S = slight, M = moderate; based on microscopic sections except one markedly damaged kidney based on gross appearance only in the 100 ppm aldrin group

**Dis = distended, Hem = hemorrhagic

***A = pulmonary lymphosarcoma, B = fibroadenoma of breast, C = carcinoma of breast, D = lymphoid except lung, E = fibrosarcoma, F = other

Adapted from Fitzhugh et al 1964

in experiment 1, in that there was a statistically significant increase in lung and other tumors in males and a small incidence of liver lesions of disputed significance (Reuber 1974, Epstein 1975, Thorpe 1974).

2.5.10 Tunstall Experiment with CFE Rats

Groups of 25 male and 25 female CFE strain rats were fed diets containing recrystallized dieldrin added at concentrations of 0.1, 1, and 10 ppm. Exposure began at 5 weeks of age and continued for 2 years. A control group of 45 animals of each sex was fed a diet containing dieldrin at 0.026 ppm. The results of the experiment as originally reported (Walker et al 1969) are summarized in Table 2.5.9. Subsequently, revised data have been reported (Stevenson et al 1976). There was an increase in tumor incidence, primarily in the thyroid and mammary glands, in the females exposed at 0.1 and 1 ppm. This increase was of marginal statistical significance in the pooled groups (Gross 1974, Epstein 1975). With the revised data the difference was statistically significant in a conventional analysis but not in an actuarial analysis (Stevenson et al 1975). There was no increase in tumor incidence in rats of either sex fed diets containing dieldrin at 10 ppm.

2.5.11 NCI Experiment with Aldrin and Dieldrin in Osborne-Mendel Rats

The National Cancer Institute recently reported the results of a bioassay of technical aldrin and technical dieldrin for carcinogenicity in Osborne-Mendel rats (NCI 1978a). Groups of 50 rats of each sex were fed diets containing aldrin or dieldrin at one of two concentrations for 59-80 weeks and were then observed for an additional 30-52 weeks. The dietary concentrations of aldrin were 30 and 60 ppm, and the time-

TABLE 2.5.9

TUMORS IN RATS FED DIELDRIN FOR 2 YEARS

Dietary Concentration (ppm)	No. of Rats	Tumors				No. of Rats with Tumors	% Tumor Incidence
		Thyroid	Pituitary	Mammary	Other		
Males							
0.026	43	3	2	1	6	12	28
0.1	23	2	2	-	2	6	26
1.0	23	2	1	-	3	5	22
10.0	23	4	2	-	2	8	35
Females							
0.026	43	3	2	13	3	19	44
0.1	23	6	1	11	2	15	65
1.0	23	4	1	10	4	14	61
10.0	23	3	2	8	-	12	52

Adapted from Walker et al 1969

weighted average dietary concentrations of dieldrin were 29 and 65 ppm. Matched control groups were 10 untreated rats of each sex; pooled controls, used for statistical evaluation, consisted of the matched-control groups combined with 58 untreated males and 60 untreated females from similar bioassays of other chemicals. All surviving rats were killed at 111-113 weeks.

Hyperexcitability was observed in all exposed groups with increasing frequency and severity during the 2nd year. Rats fed dieldrin had a higher death rate than controls during the first 90 weeks of the experiment. During the 2nd year, the mean body weights of rats fed either aldrin or dieldrin were lower than those of the controls. Rats fed aldrin had an increased incidence of thyroid tumors, including follicular-cell adenoma and carcinoma. In males, the incidences were 4/48 for pooled controls, 14/38 at the low dose, and 8/38 at the high dose; in females, they were 3/52 for pooled controls, 10/39 at the low dose, and 7/46 at the high dose. The increases were statistically significant in the males (P=0.001) and the females (P=0.009) at the low dose but not in either high dose group. There was also an increased incidence of adrenal cortical adenomas in exposed females (pooled controls 0/55, low dose 8/45, high dose 1/48), which was also statistically significant in the rats at the low dose (P=0.001) but not in those at the high dose. In the males, a significant increase in pancreatic islet tumors occurred at the low dose (P=0.043) but not at the high dose.

Female rats fed dieldrin had an increased incidence of adrenal cortical tumors (adenoma or carcinoma). The incidences were 0/55 in

pooled controls, 6/45 at the low dose, and 2/40 at the high dose. As in rats fed aldrin, this increase was statistically significant in the rats at the low dose (P=0.007) but not in those at the high dose. There was also a statistically significant (P=0.030) dose-related increase in incidence of thyroid tumors in females.

2.5.12 NCI Experiment with Dieldrin in Fischer Rats

The National Cancer Institute also reported the results of a bioassay of recrystallized dieldrin for carcinogenicity in Fisher 344 rats (NCI 1978b). Groups of 24 rats of each sex were fed diets containing dieldrin at concentrations of 2, 10, and 50 ppm for 104-105 weeks. Matched control groups consisted of 24 untreated rats of each sex. All surviving rats were killed at 104-105 weeks.

The body weights of the exposed rats were essentially unaffected, but hyperexcitability, tremors, and coma were observed beginning in the 76th week in males at the high dose and in the 80th week in females at the high dose. Survival was not adversely affected by exposure.

There was no statistically significant differences in the tumor incidences in exposed rats and the controls; however, the thyroid and adrenal glands of the exposed rats were not examined histopathologically in this study.

2.5.13 NCI Experiment with Osborne-Mendel Rats Exposed to Photodieldrin

The National Cancer Institute also reported the results of a bioassay of photodieldrin for carcinogenicity in Osborne-Mendel rats (NCI 1977). The photodieldrin was recrystallized and contained no detectable residual dieldrin. Groups of 50 rats of each sex were fed

diets containing photodieldrin for 80 weeks and then observed for an additional 31-32 weeks. Male rats received photodieldrin at 5 and 10 ppm; the time-weighted average dietary concentrations for females were 3.4 and 7.5 ppm. Matched control groups were 10 untreated rats of each sex; pooled control groups, used for statistical evaluation, consisted of the matched controls combined with 65 untreated rats of each sex from other similarly conducted bioassays.

Convulsions and hyperactivity were noted in exposed rats of both sexes, but mortality and body weights were unaffected. The incidence of tumors of several types (mammary tumors and thyroid tumors in females and multiple-site hemangiomas in males) was higher in exposed rats than in controls. However, these increases were only marginally statistically significant and were considered not clearly associated with exposure to photodieldrin (NCI 1977).

2.5.14 Other Experiments

Several other long-term feeding experiments in mammals have been reported but are of little value as carcinogenicity tests because of defects in methodology or reporting (Epstein 1975, IARC 1974). Song and Harville (1964) reported neoplastic effects in mice and rats exposed to aldrin and dieldrin at high doses for short periods, but did not provide details. Treon and Cleveland (1955) and Cleveland (1966) referred to tests with aldrin and dieldrin in rats, but the data published were somewhat conflicting and were insufficient for evaluation. Deichmann et al (1967) reported a study with aldrin in rats exposed at 5 ppm. Deichmann et al (1970) fed rats aldrin and

dieldrin at 20, 30, and 50 ppm in the diet and reported a significant reduction in tumor incidence, but the lifespan in the exposed groups was markedly reduced and the data given were insufficent for estimating relative risks. Epstein (1975) also reviewed three studies with dogs exposed to aldrin and dieldrin for up to 2 years and one study with rhesus monkeys exposed to dieldrin for up to 6 years, but these studies are too short in relation to the lifespan of the animals to be acceptable carcinogenicity tests (IARC 1974).

2.6 Mutagenesis and Related Cytotoxic Effects

Bidwell et al (1975) conducted a comprehensive evaluation of the mutagenic potential of dieldrin, but the results have been reported only in abstract form. They used direct bacterial tests with and without microsomal activation, a host-mediated assay, analyses of blood and urine for active metabolites, a micronuclei test, metaphase analysis, a dominant lethal assay, and a heritable translocation test. In most of the tests with mammals, dieldrin was administered by gavage on a "sub-acute basis" at 0.08, 0.8, and 8 mg/kg in corn oil. The authors' overall evaluation of the data from mice was that dieldrin was negative for mutagenicity in all tests. Dieldrin did not increase the number of mutants in five tests with Salmonella, including excision repair-deficient mutants and frame-shift and base-analogue detection strains.

Dean et al (1975) reported the results of three tests of the mutagenic potential of recrystallized dieldrin. In a dominant lethal assay with mice, dieldrin gave marginally positive results in one

experiment, in that the number of fetal implantations in female mice mated with males given dieldrin at 12.5 or 25 mg/kg was significantly reduced in the 1st-3rd weeks after dosing, although the number of early fetal deaths was not increased. These results were not duplicated in a second experiment, in which the number of fetal implantations was increased in all three treatment groups. The test system seems to have been insensitive, because a positive control substance (cyclophosphamide) produced small effects even at 100 mg/kg. Dieldrin at 30 or 60 mg/kg caused a nonsignificant decrease in polyploidy in bone marrow cells from Chinese hamsters and no increase in chromatid gaps. In a host-mediated assay, dieldrin induced no changes in the rate of mitotic gene conversion in Saccharomyces cerevisiae (strain D4) when it was administered to mice in single doses of 25 and 50 mg/kg or repeated doses of 0.2, 5, and 10 mg/kg/day. However, the positive control (ethyl methanesulfonate of 400 mg/kg) produced only a slight increase in the rate of gene conversion.

McCann et al (1975) and McCann and Ames (1976) reported that dieldrin gave negative results for mutagenicity in the reversion bioassay with Salmonella typhimurium strains TA 1535, TA 1536, TA 98, and TA 100, both with and without activation by rat liver microsomal preparations (S-9). Van Dijck and van de Voorde (1976) similarly reported that aldrin and dieldrin were negative in this bioassay with activation by mouse liver microsomes. Marshall et al (1976) reported that dieldrin was not mutagenic in the S typhimurium bioassay, with or without rat liver microsomal homogenates. They used four strains of

S typhimurium: TA 1535, TA 1536, TA 1537, and TA 1538. They did not use the more sensitive strains, TA 98 and TA 100. Shirasu et al (1976) also reported that aldrin and dieldrin were negative for mutagenicity in the four strains of S typhimurium used by Marshall et al and in two tryptophaneless strains of E coli, but they did not use microsomal activation. They also reported that aldrin and dieldrin were negative for mutagenicity in recombination assays with Bacillus subtilis strains H17 Rec^+ and M45 Rec^-.

Swenberg et al (1976) found negative results for dieldrin in an in vitro alkaline elution assay for DNA damage in Chinese hamster (V79) cell culture with rat liver microsomal activation. Both McCann and Ames (1976) and Swenberg et al (1976) interpreted the results with dieldrin as "false negatives," because the systems used in their experiments otherwise usually give positive results with carcinogens.

In contrast to the negative results summarized above, a number of investigators have reported positive results for aldrin and dieldrin in other bioassay systems. Majumdar et al (1976) reported that recrystallized dieldrin caused chromosome damage in bone marrow cells of mice in vivo and in human embryonic lung cells in vitro. Single intraperitoneal injections of dieldrin at 1, 30, and 50 mg/kg into STS mice caused pronounced mitotic inhibition and produced twofold to sixfold increases in chromosome abnormalities, primarily breaks and fragments, in bone marrow cells; these changes were statistically significant even at the lowest dose. At 1, 10, and 30 µg/ml, dieldrin caused similar effects in human lung cell cultures (WI-38) in vitro. The chemical also produced chromosomal interchanges

and rings. Cytotoxic studies using the WI-38 cell line revealed dose-response and time-response reactions to dieldrin.

Ahmed (1975) and Ahmed et al (1977) reported that aldrin and dieldrin, with rat liver microsomal activation, induced unscheduled DNA repair in human fibroblasts (VA-4) transformed by the SV-40 virus. The kinetics of dieldrin-induced damage and repair were studied through incorporation of bromodeoxyuridine into the damaged regions. Dieldrin also increased the mutation frequency in vitro of spontaneously transformed Chinese hamster cells (V79) to ouabain-resistant mutants.

Georgian (1975) found that aldrin induced chromosome aberrations in human lymphocyte cultures in vitro and in bone marrow cells of rats and mice exposed in vivo. Dose-response relationships were observed in both bioassays. In the lymphocyte bioassay, aldrin showed a narrow range of doses causing chromosomal changes, between 19 and 38 µg/ml, close to the cytotoxic concentrations. In the in vivo rodent bioassays the minimal dose inducing chromosomal aberrations was 19 mg/kg (single dose ip). No effects were observed at 9.6 mg/kg.

Markaryan (1966) reported that dieldrin administered to mice caused mitotic inhibition and a variety of chromosomal aberrations, including significant increases in the incidence of breaks, fragments, chromosome and chromatid bridges, and stickiness, but not of translocations or dicentrics. Guerzoni et al (1976) detected mutagenic activity on S cerevisiae by aldrin at 5 and 50 ppm.

Bunch and Low (1973) fed technical dieldrin at dietary concentrations of 4, 10, and 30 ppm to mallard ducks for 60 days and examined

bone marrow cell cultures from the ducks' offspring. No significant increase in chromosomal aberrations was observed, but dieldrin at 30 ppm caused a significant reduction in the rate of mitosis. Duck lymphocyte cultures exposed to dieldrin at 100 ppm showed a significant increase in the incidence of chromosomal aberrations, including gaps and breaks. Mitotic indices were significantly reduced at all dieldrin concentrations down to 0.1 ppm.

Walker et al (1977) reported that recrystallized dieldrin markedly inhibited incorporation of amino acid precursors of DNA, RNA, and protein into Ehrlich ascites tumor cells in vitro. Effects on incorporation of thymidine and uridine were marked at concentrations as low as 10^{-6}M (0.4 ppm). Daily injections of dieldrin at 1.5 mg/kg for 5 days into mice inhibited the growth of Ehrlich ascites tumor cells in vivo. Chung et al (1967) had earlier reported inconsistent effects of dieldrin on the synthesis of DNA, RNA, and protein in HeLa cells. Sheinman and Yannai (1974) reported that dieldrin, at concentrations as low as 25 µg/ml, was toxic to rat fetal liver primary culture cells and human kidney cell line B in vitro. Observed morphologic changes included granulation and shrinkage of the cytoplasm, formation of long and narrow cytoplasmic projections, and the appearance of giant cells.

3. Human Effects

3.1 Clinical and Case Reports

Aldrin and dieldrin, particularly in oil solution, are readily absorbed through the skin, the respiratory mucosa, and the gastrointestinal tract (Hayes 1963). Untoward symptoms in humans are known to result from oral doses as small as 10 mg/kg (Committee on Toxicology 1960, Hayes 1963, Jager 1970). The acute median lethal dose by the oral route lies between 20 and 95 mg/kg in various mammals (Table 2.1.1) and presumably lies in the same range in humans (Committee on Toxicology 1960, Hodge et al 1967). Several human deaths have been ascribed to ingestion of dieldrin, but no reliable information about doses is available (Committee on Toxicology 1960, Hayes 1963, Pribilla 1963, Weinig et al 1966, Preda et al 1963, Jager 1970, Symanski 1970, Gupta 1975). When a toxic dose of aldrin or dieldrin has been ingested or has contaminated the skin, a more or less typical syndrome appeared from 20 minutes to 24 hours afterwards. In all cases the principal site of action was the central nervous system, and the principal sign was a series of convulsions. The convulsions were self-remitting but recurred with increasing severity, characteristically alternating with periods of severe depression (Princi 1957; Hayes 1957, 1963; Bell 1960; Hoogendam et al 1962, 1965; Kazantzis et al 1964; Jager 1970).

Convulsions induced by the cyclodiene insecticides may be preceded by subjective complaints, but frequently they occurred with no forewarning or prodromal signs or symptoms (Hoogendam et al 1962). Abnormalities of the EEG, such as bilateral synchronous theta wave activity and occasional

bilateral synchronous spike and wave complexes, have been seen in patients without clinical illness both before and after convulsion (Kazantzis et at 1964). Myoclonia indicates that a convulsive episode is imminent. Prodromal signs that have been reported include headache, visual disturbances, dizziness, sweating, insomnia, nausea, and malaise. Convulsions are accompanied by loss of consciousness and "frothing at the mouth" but not incontinence (Hayes 1957, Patel and Rao 1958). Death may result from anoxemia (Princi 1957; Hayes 1963; Hoogendam et al 1962, 1965). The interval between oral intake or skin contact and the onset of symptoms, as well as the clinical picture, depend on the dose absorbed.

Many cases of aldrin and dieldrin poisoning have been described in the medical literature. In 1951, Spiotta described a case of acute convulsive aldrin poisoning in a 23-year-old man who ingested an aldrin emulsifiable concentrate in an attempted suicide. The man had convulsions accompanied by typical EEG changes but completely recovered.

Other investigators also reported epileptiform convulsions and EEG abnormalities. Drowsiness, lack of appetite, headache, and "prickly sensation of the skin" were reported in a man who had been previously exposed to dieldrin and became ill when his reducing diet resulted in mobilization of fat and release of the pesticide into the blood (Paul 1959). Disturbed sleep rhythm and manic and irrational behavior have been reported as sequelae (Fry 1964). Other autonomic manifestations have also been described (Gowdey and Stavraky 1955).

Garrettson and Curley (1969) reported that in a 4-year-old child accidentally poisoned via oral ingestion EEG abnormalities declined gradually over a 6-month period, paralleling the decline of dieldrin concentrations in serum. However, dieldrin residues in fat remained high for at least 8 months despite treatment with anticonvulsants.

In contrast to the phenomena observed after acute poisonings, after repeated exposures several spraymen developed a syndrome indistinguishable from idiopathic epilepsy, except that it ceased when the exposure was terminated (Hayes 1957). Myoclonic jerks and major motor seizures were reported in humans and animals exposed for 6-12 months to aldrin and BHC in contaminated flour; two persons died (Gupta 1975). A motor polyneuropathy resembling the Guillain-Barré syndrome is a rare complication of exposure (Jenkins and Toole 1964). In the usual acute intoxication, recovery is complete or well advanced within 24 hours, but animal experiments and clinical experience (Hayes 1957, Patel and Rao 1958) indicate the possibility of seizures for many days after a single dose or repeated doses. EEG anomalies may persist for days after apparent clinical recovery (Hoogendam et al 1962).

Transient kidney damage has been reported in some acute poisoning cases (Spiotta 1951, Jacobs and Lurie 1967, Nelson 1953, Committee on Toxicology 1960). Liver damage has also been reported, in one case persisting for more than 1 year (Committee on Toxicology 1960, Garrettson and Curley 1969).

In animals the percutaneous toxicity of dieldrin is almost as high as its oral toxicity (see Section 2.1.2). Dermal exposure usually results in systemic poisoning, without skin irritation or local sensitization except secondary to the solvent or vehicle, which is usually kerosene or xylene (Bundren et al 1952). However, Ross (1964) reported an incident of nonspecific dermatitis occurring on the legs of 288 police officers who wore wool socks impregnated with dieldrin as a mothproofing agent. Nelson (1953) and D'Eramo and Croce (1960) also reported contact dermatitis caused by aldrin. In addition, skin diseases such as scleroderma may facilitate cutaneous absorption of dieldrin, resulting in systemic poisoning (Starr and Clifford 1971).

One case of suicide by intravenous injection has been reported (Schwar 1965).

3.2 Studies in Volunteers

A 2-year study of volunteers with measured exposure to dieldrin was conducted with the primary purpose of studying the pharmacokinetics of dieldrin in men (Hunter et al 1967, 1969). The subjects were 13 healthy men, aged 21-52 years, with no history of recent occupational exposure to pesticides. Four groups of three or four men were given recrystallized dieldrin (99% HEOD) in gelatin capsules daily for 2 years at doses of 0, 10, 50 and 211 µg dieldrin/day. Added to the normal dietary intake from background contamination, this increased the daily intakes to approximately 14, 24, 64, and 225 µg/day, respectively. In addition to measurements of dieldrin concentrations in blood and fat, which were summarized in Section 1.5.4, urinalysis,

EEG studies, polygraphic recording of cardiorespiratory function, electromyographic studies, and blood chemistry, including estimation of blood plasma protein and urea, activity of plasma alkaline phosphatase, SGPT, and SGOT, and cholinesterase activities in erythrocytes and plasma, were performed. Full clinical examinations were made after 3, 9, 15, 18, and 24 months of exposure. The subjects were observed for 8 months after exposure was discontinued.

No changes were observed in any of the measured parameters, and no clinical or subjective symptoms attributable to exposure were recorded (Hunter et al 1967, 1969). A preliminary examination of the concentrations of p,p'-DDE in the blood of the volunteers (resulting from general environmental exposure) did not show any significant decrease relative to that of the control group (Jager 1970); such a decrease might have occurred if the exposure to dieldrin had significantly increased microsomal enzyme activity.

3.3 Studies of Occupationally Exposed Workers

The most extensive studies of occupationally exposed workers are those conducted at a manufacturing plant in the Netherlands and summarized by Jager (1970). Some followup studies of more highly exposed workers were reported by Versteeg and Jager (1973). A total of 826 men worked full-time in the plant for various periods between 1955 and 1968. Maintenance workers, plant cleaners, and formulators were included in this count, as well as operators. The workers were divided as follows:

Group A: 277 workers with exposure shorter than 1 year;

Group B: 316 workers with exposures of 1-4 years;

Group C: 223 workers with exposures of 4-13.25 years.

Group C was subdivided as follows:

Group C-1: 52 workers who left the company and could not be contacted for followup;

Group C-2: 75 workers transferred to other plants but still under medical surveillance;

Group C-3: 106 workers still working in the insecticide plant and having periodic medical examinations.

Within groups C-2 and C-3 three "extreme exposure" groups were identified:

Group C-2a: 17 workers transferred because insecticide levels in their blood exceeded intoxication thresholds;

Group C-2b: 9 workers who had had an episode of insecticide intoxication;

Group C-3a: 35 operators with an insecticide exposure of more than 10 years (through January 1, 1968). Their average length of exposure at that time was 11.1 years.

A number of workers with pre-existing medical disorders, primarily EEG changes, skin diseases, mental disturbances, or neurologic diseases, were rejected or preventively transferred from insecticide work (Jager 1970).

Although most or all of the workers in the extreme exposure group were exposed to aldrin and dieldrin, most were also exposed at times to endrin, Telodrin, or to organophosphate insecticides. The

mean dieldrin level in the blood of the "extreme exposure" group was 0.039 µg/ml. Those in aldrin/dieldrin workers at the time of exposure were in the range 0.022-0.078 µg/ml (Jager 1970).

Of 54 episodes of intoxication in the plant, 23 were attributed to aldrin or dieldrin, 15 of which involved convulsive seizures. Only a few of these episodes involved Group C workers (Jager 1970). With one exception, aldrin/dieldrin intoxications were not peracute but were preceded by prodromi or, in some cases, by a gradual increase of dieldrin levels in the blood. The threshold level of dieldrin in the blood for overt intoxication was determined to be 0.15-0.20 µg/ml, and that for induction of convulsions was about 0.30 µg/ml (Jager 1970).

Except for signs and symptoms of intercurrent diseases not related to insecticides and the clear specific signs and symptoms, in some cases, of overt poisoning, no abnormalities were observed in the long-term exposure groups (Jager 1970). Specifically, no increases in liver size or enzyme activity (alkaline phosphatase, SGOT, SGPT, LDH) were recorded in the extreme exposure groups. EEG patterns generally returned to normal after intoxication episodes. Absenteeism due to sickness or accident was higher in insecticide workers than in other workers in the same plant, but no single type of disease or accident was associated with exposure. Through 1973, when a few workers had worked in the plant for up to 18 years, two cases of cancer and one death had been reported in groups C-2 and C-3 (Jager 1970, Versteeg and Jager 1973); this compares with an expected number of three or

four in a group from the general population with the same age distribution (Seidman 1974).

In a statistical study, serum alkaline phosphatase and SGOT levels were found to increase with insecticide levels in the blood. This was attributed to "adaptation" of the liver to the chemicals. However, it was not established whether the correlation was with levels of dieldrin, Telodrin, or both (Jager 1970).

Workers exposed to endrin exhibited a marked increase in excretion of 6-beta-hydroxycortisol and a marked decrease in tissue storage levels of p,p'-DDE resulting from general environmental exposure. Both of these changes are indicative of stimulation of liver microsomal enzymes. However, workers exposed to aldrin/dieldrin showed no significant changes (Jager 1970). In a subsequent study, 14 aldrin/dieldrin workers showed a statistically significant increase over controls in urinary excretion of D-glutaric acid (another indirect measure of microsomal enzyme activity); endrin workers showed a larger increase (Hunter et al 1972). Dieldrin levels in the blood of the workers involved averaged 0.026 µg/ml but were not significantly correlated with D-glutaric acid excretion.

Other studies of workers occupationally exposed to aldrin/dieldrin have been considerably less detailed. Fletcher et al (1959) observed no clinical poisoning symptoms in spraymen in East Africa dermally exposed to dieldrin at 1.8 mg/kg/day. A 2-year study of 256 spraymen in Arakan, Burma, (dosage not reported) also failed to reveal any symptoms of toxicity in workers or household animals exposed

to the spray (U Than Pe and Venkat Rao 1960). Six workers at a pesticide formulating and packaging plant had aldrin and dieldrin in their blood at levels of 10-125 ppb and 100-312 ppb, respectively (Mick et at 1971). Although these levels exceed the threshold for intoxication identified by Jager (1970), the workers reported no complaints or health problems to the company physician. Hayes and Curley (1968) studied workers in a manufacturing plant whose exposure (estimated from levels in plasma and fat) was estimated to be in the range 0.72 mg/man/day. They were unable to find a relationship between dieldrin exposure and use of sick leave.

According to the AMA's Committee on Toxicology (1960), the proportion of workers poisoned in public health spraying programs involving the use of dieldrin around the world varied from 2 to 40 percent, with the proportion of cases involving convulsions ranging from 47 to 100 percent. Patel and Rao (1958) reported 20 cases of intoxication in 297 workers spraying dieldrin in India. Blázquez and Bianchini (1956) reported 22 cases in workers spraying dieldrin in Venezuela. Subsequently 51 cases of poisoning were reported in 285 workers spraying dieldrin in Venezuela (Committee on Toxicology 1960, Hayes 1957; Table 3.3.1). Hayes (1957) listed 13 cases of intoxication, including 1 fatality, in 92 spraymen in Ecuador, and 8 cases in 40 spraymen in Nigeria. Zavon and Hamman (1961) stated that nine countries had reported cases of dieldrin intoxication in spraymen, due predominantly to gross and continued exposure over a prolonged time period. Incidents usually occurred 3-8 months after a sprayman had

TABLE 3.3.1

POISONING IN SPRAYMEN EXPOSED TO DIELDRIN*

Duration of Exposure (months)	Spraymen Exposed for the Specified Duration		Total No. of Spraymen Exposed for the Specified Duration or Longer	Percentage of Poisoning in Total No. Exposed
	No.	Cases of Poisoning		
0- 3.9	69	0	285	0
4- 7.9	38	5	216	2
8-11.9	26	9	178	5
12-15.9	54	14	152	9
16-19.9	41	13	98	13
20-23.9	45	4	57	7
21-27.9	7	6	12	50
28-31.9	1	0	5	0
32-35.9	0	0	4	0
36-39.9	4	0	4	0
0-39.9	285	51	285	18

*Under practical working conditions in Venezuela

Adapted from Hayes 1957

started regular use of the pesticide. The spray programs involved applications of solutions of 0.68-2.5 percent dieldrin to surfaces at rates of 0.27-1.0 g/m^2 (Hayes 1957). Symptoms reported in studies of workmen exposed to dieldrin and aldrin for prolonged periods include dizziness, insomnia, muscle twitching, increased blood pressure, and electroencephalography (EEG) abnormalities consisting of bilateral synchronous theta-wave activity and occasional bilateral synchronous spike and wave complexes (Hayes 1957, Zavon and Hamman 1961, Committee on Toxicology 1960, Blázquez and Bianchini 1956). Removal from exposure was followed by reduction or complete loss of EEG abnormalities and convulsions, generally within a few months (Hoogendam et al 1962, 1965; Kazantzis et al 1964; Avar and Czégledi-Jankó 1970). Hayes (1957) also listed the following signs and symptoms in spraymen exposed for 30 or more weeks: blurred vision, diplopia, tinnitis, sweating, difficulty in sleeping and bad dreams, nausea, alteration of reflexes, incoordination, nystagmus, and change in personality. Blázquez and Bianchini (1956) reported hepatomegaly in 10 of 22 dieldrin-exposed sparymen, in addition to the symptoms listed by Hayes (1957). In one survey, EEG abnormalities were found in about one-third of spraymen not clinically ill (Hayes 1957). Avar and Czégledi-Jankó (1970) reported preconvulsive changes and EEG abnormalities in one worker with a concentration of HEOD in the blood as low as 0.05 ppm. Prior and Deacon (1969) noted spontaneous sleep in otherwise healthy subjects. Nelson (1953) reported contact dematitis

in workers exposed to 25% aldrin dust, together with "transient bronchial complications due to inhalation of concentrated fumes."

Takahashi et al (1976) reported significantly higher C-reactive protein levels in the sera of workers chronically exposed to dieldrin and pentachlorophenol than in controls. Serum levels of gamma$_2$-globulin were significantly associated with concentrations of dieldrin in serum. Elevated C-reactive protein levels were considered to indicate the presence of tissue inflammation.

In a study of five male farmworkers exposed to a mixture of herbicides and pesticides, including dieldrin, four were found to have suffered impotence after chronic exposure; sexual function was recovered after exposure was terminated (Espir et al 1970). Peck (1970) suggested that their exposure to dieldrin might have induced an increased metabolism of testosterone that led to a deficiency of this hormone.

Dean et al (1975) found no significant increase in the frequency of chromosome abnormalities in lymphocytes from 22 workers occupationally exposed to aldrin and dieldrin.

3.4 Epidemiologic Studies in the General Population

A number of epidemiologic searches for health effects associated with general uses of aldrin/dieldrin have been conducted in various parts of the United States, with generally negative results (USDHEW 1969). However, such studies are difficult to conduct in the general population, ie, in nonoccupationally exposed persons, because residues of dieldrin are widespread in the environment. Virtually everyone is exposed to traces of dieldrin in food, and residues of

dieldrin have been found in the tissues of almost every person examined (Train 1974). Accordingly it is impossible to identify unexposed groups for rigorous comparison with exposed groups.

However, since residues of dieldrin are retained in tissues for months or years after exposure, it is possible to use these residues as indirect measures of the intensity of past exposure. A number of epidemiologic studies have been published in which correlations have been sought between various pathologic conditions and tissue levels of dieldrin.

In a study of 38 autopsy cases, there was an association between high residues of organochlorine compounds and malignant tumors. The highest residues of organochlorine compounds were associated with carcinomas, cachexia, and a variety of focal or generalized abnormalities of the liver. However, these reported associations were with total organochlorine residues, not specifically with dieldrin (Casarett et al 1968).

In another investigation of various pesticides in fat samples taken at autopsy, the average concentration (in ppm) of dieldrin was 0.55 ± 0.34 in 40 cases of carcinoma, 0.47 ± 0.22 in 5 cases of leukemia, 0.51 ± 0.18 in 5 cases of Hodgkin's disease and 0.21 ± 0.15 in 42 "control" cases. Each of the differences from the control level was statistically significant (Radomski et al 1968). The data from this study suggested a relationship between dieldrin levels in adipose tissues and cases of portal cirrhosis and hypertension.

Davies et al (1975) compared levels of dieldrin in the adipose

tissues of 122 cancer victims with those in 122 matched controls. The average dieldrin level was 0.3 ppm in each group. There were no significant differences between dieldrin residue levels in cancer patients and controls, either when the patients were grouped together or divided according to the primary site of cancer. Robinson et al (1965) found no significant differences between dieldrin levels in the fat of 7 cancer victims, 29 victims of cardiovascular diseases, and 7 accident victims sampled at autopsy.

Dacre and Jennings (1970) reported that dieldrin levels were significantly higher in the lung tissues of 26 persons who died of lung canger than in persons who died of other causes. Dieldrin concentrations were significantly higher in cirrhotic than in noncirrhotic livers in an autopsy study of Oloffs et al (1974). However, when expressed on a lipid basis, the dieldrin levels were similar in the two groups.

D'Ercole et al (1976) detected no correlation between dieldrin residues in the blood of newborn infants and maternal age, sex of newborn, birth weight, or incidence of congenital anomalies. Residues were found in premature infants but were not significantly different from those in full-term infants.

4. Correlation of Exposure and Effect

4.1 Effects on Humans

Aldrin is converted to dieldrin both in the environment and by metabolism in mammals. Exposure of mammals to either is reflected by storage of dieldrin in the tissues, including the blood and fat. Where comparative data are available, toxic effects resulting from exposure to aldrin are similar, both qualitatively and quantitatively, to those resulting from exposure to dieldrin. Accordingly the two chemicals are treated together in this section correlating exposure with effect.

Table 4.1.1 summarizes the clinical and case reports of the effects of aldrin/dieldrin on humans and the studies with volunteers, which were cited in Sections 3.1 and 3.2, respectively. There are many reports of human poisonings, including a number of deaths, resulting from accidents or suicides. However, little quantitative information on the doses of aldrin/dieldrin responsible for the poisonings is available, and in some cases even the route of exposure is not clearly established. Many of the poisonings involved exposure to dust or spray formulations, and in these cases exposure may have been by dermal, respiratory, or oral routes. A few accidental poisonings resulted from ingestion, and there was one reported case of suicide by injection.

The AMA Committee on Toxicology (1960) suggested that the median lethal dose by ingestion in humans is probably about 65 mg/kg and "untoward symptoms" will result from a single dose of 10 mg/kg

or more. For long-term exposure, the concentration of HEOD in the blood or fat provides an indirect measure of cumulative exposure (Hunter et al 1969, Jager 1970). Jager (1970) summarized evidence suggesting that a concentration of HEOD in the blood of 0.15-0.20 ppm is the approximate threshold for clinical intoxication and a blood concentration of 0.30 ppm is the approximate threshold for convulsive seizures. According to the pharmacokinetic data summarized in Section 1.5.4, these blood concentrations correspond to about 30-40 ppm of HEOD in fat and to a continuous intake of about 15-20 µg/kg/day. Although a number of factors complicate these pharmacokinetic relationships, including intermittent exposures and interactions with other chemicals, these figures are a rough guide to the tissue levels and exposure that present toxic hazards.

The data in Table 4.1.1 are consistent with these figures but provide little additional quantitative information. One individual who survived a convulsive intoxication had 40 ppm HEOD in his fat 2 weeks after exposure (Bell 1960). A 4-year-old child who survived a severe intoxication had 0.27 ppm HEOD in blood serum and 47 ppm in fat 3 days after exposure (Garrettson and Curley 1969). One individual survived a single dose of 44 mg/kg (Hayes 1963), and another survived a single dose of 25.6 mg/kg (Spiotta 1951). The only report found of accidental long-term exposure was one by Gupta (1975) about two children who died after 6-12 months of exposure to contaminated food. Their average daily intake is

likely to have been less than 1 mg. However, in a study with volunteers, daily intake of 211 µg/day for 2 years by middle-aged men led to no measurable adverse effects (Hunter et al 1969).

Table 4.1.2 summarizes the results of studies of workers occupationally exposed to aldrin/dieldrin. These studies are described more fully in Section 3.3. Incidents of clinical intoxication, including convulsive seizures and at least one death, were frequently recorded in public health programs involving the spraying of liquid formulations containing 0.5-2.5% dieldrin (Hayes 1957, Blázquez and Bianchini 1956, Zavon et al 1961). In contrast, poisonings associated with the use of dust formulations have been much less frequent and have involved observation of inadequate safety precautions (Nelson 1953, Bell 1960). Little quantitative information from these incidents is available, except for an estimate by Fletcher et al (1959) that spraymen came into dermal contact with as much as 1.8 mg/kg/day of dieldrin without showing clinical symptoms. This figure is about 100 times the estimated threshold intake for clinical intoxication derived from the data of Jager (1970).

A few studies listed in Table 4.1.2 included data on tissue levels of HEOD. Blood concentrations as high as 0.14, 0.25, or 0.31 ppm were reported in individual workers with no overt symptoms (Hayes and Curley 1968, Avar and Czégledi-Jankó 1970, Mick et al 1971). However, one worker with a blood concentration of HEOD as low as 0.05 ppm showed clinical symptoms of intoxication and characteristic EEG changes (Avar and Czégledi-Jankó 1970).

In most of the studies summarized in Tables 4.1.1 and 4.1.2, the symptoms of aldrin/dieldrin intoxication involved the central nervous system, including headache, muscular jerking, convulsive seizures, and EEG changes. Other symptoms occasionally reported included dermatitis, enlarged liver, hematuria, transient bronchial complications, and elevated levels of serum enzymes (Avar and Czeglédi-Jankó 1970, Blázquez and Bianchini 1956, Nelson 1953, Jager 1970).

In two cases, biochemical changes occurred in association with low blood levels of HEOD. Hunter et al (1972) reported measurements of D-glutaric acid excretion that indicated significantly elevated microsomal enzyme activity in workers whose mean blood level of HEOD was only 0.026 ppm. Takahashi et al (1976) found elevated serum levels of C-reactive proteins and a correlation between alpha $_2$ globulin and HEOD levels in workers whose mean blood level of HEOD was only 0.012 ppm. These results suggest functional biochemical changes at exposure levels one order of magnitude lower than the threshold for overt intoxication.

Few data were found which can be used to assess the possibility that aldrin/dieldrin has carcinogenic, teratogenic, or mutagenic effects on the human population, or affects human reproduction. In two studies, cancer victims were shown to have higher tissue levels of HEOD than persons without cancer (see Section 3.4). However, these findings do not prove a cause-and-effect relationship. No evidence of chromosome abnormalities was

found in one study of 22 exposed workers (Dean et al 1975). Workers exposed for up to 19 years had no excess incidence of cancer (Jager 1970, Versteeg and Jager 1973), but the number of workers who were "highly exposed" was small and even their exposure appears to have been comparatively modest (see Section 3.3). No studies of female workers or of the reproductive performance of male workers were found.

4.2 Effects on Experimental Animals

Table 4.2.1 summarizes the reported effects of oral exposure to aldrin/dieldrin on experimental animals. Teratogenic, carcinogenic, and mutagenic effects are listed in Tables 4.3.1, 4.3.2, and 4.3.3, respectively. No studies of the effects of dermal exposure of animals to aldrin/dieldrin were found. The only study of the effects of respiratory exposure of animals to aldrin/dieldrin is that of Medved' et al (1964), who reported that exposure of cats to aldrin at a concentration of 0.1 mg/m^3 for an unspecified period caused marked lowering of conditioned and unconditioned reflexes.

At high dietary levels (10-150 ppm), the most striking effects of aldrin/dieldrin were on the central nervous system, the liver, and the kidney. Dose-response relationships for these effects appear to have comparatively small slopes. For example, although rats developed kidney and liver lesions and occasional convulsions at a dietary level of 10 ppm, some rats have survived for up to 2 years at dietary levels of 50, 100, and even 150 ppm (Fitzhugh et al 1964).

At dietary levels between 1 and 10 ppm, the most pronounced effects of aldrin/dieldrin were on the liver and the reproductive system. At a dietary level of 1 ppm dieldrin, reported effects included liver enlargement, liver lesions, and induction of hepatic microsomal enzymes in rats and mice, enzyme induction in rhesus monkeys, and liver enlargement in dogs (Street et al 1969; Wright 1974; Jager 1970; Walker et al 1969, 1972; Treon et al 1955). Adverse effects on reproduction were reported in rats and mice exposed at 2.5 ppm (Cleveland 1966, Virgo and Bellward 1975) and in dogs exposed at about 3 ppm (Deichmann et al 1971, Kitselman 1953). The importance of these observations is that dietary exposure to dieldrin at 1 ppm led to blood levels of HEOD in the range 0.017-0.086 ppm in these species (Table 1.5.4). These blood concentrations are in the lower part of the range observed in occupationally exposed workers (Table 4.1.2).

Several experiments showed effects of aldrin/dieldrin at dietary levels even below 1 ppm. Raccoons exposed at 0.73 ppm in the diet suffered severe adverse effects on reproduction (Frederickson 1973). Rats exposed at 0.5 ppm had increased liver weights and liver lesions (Fitzhugh et al 1964). In another study, rats exposed at 0.31, 0.16, and 0.08 ppm developed brain and vascular lesions, and those exposed at 0.31 and 0.16 suffered impaired reproduction (Harr et al 1970a,b). Mice exposed at 0.1 ppm had an increased incidence of liver tumors (Walker et al 1972).

4.3 Teratogenic, Carcinogenic, and Mutagenic Effects

Table 4.3.1 summarizes the experiments on teratogenesis, which are cited in Section 3.4. Aldrin and dieldrin were teratogenic in mice and Syrian golden hamsters when administered at about one-half the median lethal doses (Ottolenghi et al 1974). However, dieldrin had no effects on mice (other than minor effects on ossification) and no effects in rats exposed at lower doses (Chernoff et al 1975). A third experiment with dieldrin was inconclusive (Boucard et al 1970).

Table 4.3.2 summarizes the experiments on carcinogenesis, which are cited in Section 3.5. Aldrin and dieldrin were carcinogenic in mice, having produced increased incidence of tumors in 20 experiments, usually in males and females independently. The principal site of action is the liver, although treatment with dieldrin was associated with an increase in tumors of the lung and other sites in several experiments for which age-adjusted statistical analysis of tumor incidence was reported. In most of the experiments, dietary levels were 2.5-10 ppm, but in the most extensive experiment dietary exposure to dieldrin at 1 and 0.1 ppm led to significant increases in incidence of liver and lung tumors.

The results of carcinogenicity tests with rats are more equivocal. If several inadequately reported experiments are discounted, aldrin/dieldrin has been tested for carcinogenicity in rats in eight experiments. In six of these experiments, there

was a statistically ($P<0.01$) or marginally significant ($P<0.05$) increase in tumor incidence at one or more of the lower doses (0.1-30 ppm). However, the sites at which these increases were observed were inconsistent (thyroid, lung, adrenal, pancreas, lymphatic system, mammary gland, and liver), and in five cases tumor incidence was reduced at higher doses (10-150 ppm). The only statistically significant effects at these higher doses were liver lesions of disputed biologic significance. If only the data from the higher dose levels were available, the results would be accepted as consistently negative. On the other hand, if only the data from the lower dose levels were available, aldrin and dieldrin would be accepted as strongly carcinogenic, at least on the basis of the NCI experiments. The reasons for the apparent reversal in dose-response relationships are not clear, although the results of one experiment suggested that the pathways of metabolism of dieldrin may be different at low and high dose levels (Mueller et al 1975a,b).

Table 4.3.3 summarizes the experiments on mutagenesis, which are cited in Section 3.6. Several studies indicated that aldrin and dieldrin can damage chromosomes, primarily by causing breaks and gaps, in mammalian cells, both in vitro and in vivo (Ahmed 1975, Majumdar 1976, Georgian 1975). Aldrin and dieldrin yielded consistently negative results in bacterial reversion bioassays, with or without metabolic activation. In other mutagenicity tests, including dominant lethal and host-mediated assays, aldrin and

dieldrin generally gave negative results, although the sensitivity of some of the systems used is questionable. Dieldrin caused unscheduled DNA repair in human fibroblast cultures (Ahmed et al 1977).

Most of the positive results of damage to chromosomes were obtained at high concentrations, close to cytotoxic levels both in vitro and in vivo. However, Majumdar et al (1976) reported statistically significant increases in chromosome aberrations at the lowest doses tested (1 mg/kg in mice exposed in vivo and 1 ppm in human embryonic lung cell cultures).

4.4 Summary

Aldrin is converted to dieldrin in the environment and in mammalian tissues. The toxic effects of the two chemicals are similar, qualitatively and quantitatively.

When mammals are exposed to either aldrin or dieldrin, dieldrin is circulated in their blood and is stored in their tissues, primarily in the fat. After ingestion, humans store dieldrin in their tissues at much higher concentrations than those measured in experimental animals exposed at comparable levels. Consequently, target tissues in humans are exposed to dieldrin at concentrations proportionately higher than in experimental animals that ingest comparable quantities.

Aldrin/dieldrin is neurotoxic, and many cases of poisoning, including a few deaths, caused by accidental or imprudent overexposure have been reported. In a study conducted in a manufacturing plant,

concentrations of dieldrin in the blood were reported to be indicative of toxic hazard. A concentration of 0.15-0.20 ppm in the blood was considered the threshold for EEG changes and other CNS effects, whereas 0.30 ppm was considered the threshold for convulsive seizures. Corresponding average daily intakes were about 15-22 μg/kg and 30 μg/kg, respectively. Only minor biochemical changes (induction of hepatic microsomal enzymes and elevated levels of C-reactive protein in serum) were reported in workers with lower blood concentrations of dieldrin (0.012-0.026 ppm). Although a few workers who were exposed to aldrin/dieldrin for up to 19 years have been studied, the available reports are inadequate for determining whether aldrin/dieldrin may have carcinogenic, mutagenic, or teratogenic effects in humans, or may affect reproduction.

In experimental animals, the most conspicuous effects of aldrin/dieldrin are on the liver and on the CNS. A concentration of 1 ppm in the diet has been reported to be the approximate threshold for induction of hepatic microsomal enzymes in rats and mice. Rats exposed at a dietary concentration of 0.08-0.31 ppm have had brain and vascular lesions and impaired reproduction.

Aldrin/dieldrin is carcinogenic in mice, increasing the incidence of tumors primarily in the liver but also in the lung and perhaps other sites. In one experiment, carcinogenic effects occurred even at 0.1 ppm, the lowest dietary concentration tested. In rats, aldrin/dieldrin appeared to increase the incidence of

tumors at a variety of sites when administered at low dietary concentrations (0.1-30 ppm) but consistently failed to do so when administered at higher concentrations (10-150 ppm). The reasons for this apparent reversal in dose-response relationships are not clear.

Aldrin/dieldrin administered at about one-half the median lethal dose was teratogenic in mice and hamsters, but lower doses had no teratogenic effects in mice and rats. Aldrin/dieldrin has yielded consistently negative results in bacterial mutagenesis bioassays. However, aldrin/dieldrin has repeatedly caused chromosome damage in mammalian cells, even at low exposure levels (1 mg/kg in mice exposed in vivo and 1 ppm in human embryonic lung cultures). Dieldrin caused unscheduled DNA repair in human fibroblast cultures.

TABLE 4.1.1

SUMMARY OF EFFECTS OF ALDRIN/DIELDRIN EXPOSURE ON HUMANS (CLINICAL AND CASE REPORTS)

Substance	Duration and Route of Exposure	Concentration or Dose	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin (aerosol)	84-214 hr respiratory	176 mg/m^3 "per day"	-	No detectable effect	Hodge et al 1967
Dieldrin	Unknown dermal and perhaps oral	4% powder	-	Convulsions, fever, cyanosis, death in 20 hr (9-mo-old girl)	Committee on Toxicology 1960
Aldrin (dust)	2 working days dermal, respiratory (packaging)	-	40 ppm in fat after 2 wk	Convulsions, EEG changes	Bell 1960
Dieldrin	18 hr dermal (dusting sheep)	3% solution	5-7 ppm in fat after 1 mo	Twitching of arms and legs	"
"	6 wk	0.4% solution	1 ppm in fat after 8 mo	"Symptoms of dieldrin poisoning"	"
Aldrin (field residues)	1-2 mo dermal	-	-	Myoclonic jerks, paresthesia, muscle weakness, tachycardia, motor polyneuropathy	Jenkins and Toole 1964

TABLE 4.1.1 (continued)

SUMMARY OF EFFECTS OF ALDRIN/DIELDRIN EXPOSURE ON HUMANS (CLINICAL AND CASE REPORTS)

Substance	Duration and Route of Exposure	Concentration or Dose	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin (impregnated wool)	Unknown dermal	-	-	Nonspecific dermatitis	Ross 1964
"	"	0.1-0.5% in wool	-	No sensitization of skin	Hodge et al 1967
Dieldrin	Single dose oral	5% solution	0.27 ppm in serum, 47 ppm in fat (3 d after ingestion)	Convulsions, death in 2-yr-old girl; convulsions, cyanosis, EEG changes, elevated serum alkaline phosphatase after 6 mo in 4-yr-old boy	Garrettson and Curley 1969
Aldrin	Single dose oral (in food)	20% powder	-	Nausea, vomiting, hyperirritability, convulsions, death in 4/9 cases	Preda et at 1963
Aldrin or dieldrin	Single dose oral	65 mg/kg	-	Estimated median lethal dose	Committee on Toxicology 1960

TABLE 4.1.1 (continued)

SUMMARY OF EFFECTS OF ALDRIN/DIELDRIN EXPOSURE ON HUMANS (CLINICAL AND CASE REPORTS)

Substance	Duration and Route of Exposure	Concentration or Dose	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin	Single dose oral	44 mg/kg	-	Convulsions	Hayes 1963
Aldrin	Single dose oral (attempted suicide)	-	0.279 ppm in plasma	Survived	Hayes and Curley 1968
Aldrin (liquid mixture)	Single dose oral	25.6 mg/kg	-	Convulsions within 20 min, EEG changes, generalized cerebral dysrhythmia, hematuria, albuminuria; treatment with barbiturates, EEG normal within 5 mo	Spiotta 1951
Dieldrin	"	-	-	Convulsions after 30 min, hematuria, amnesia; no EEG abnormalities, normal kidney and liver function	Jacobs 1967

TABLE 4.1.1 (continued)

SUMMARY OF EFFECTS OF ALDRIN/DIELDRIN EXPOSURE ON HUMANS (CLINICAL AND CASE REPORTS)

Substance	Duration and Route of Exposure	Concentration or Dose	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin	6-12 mo oral	About 0.5% dust (mixture of aldrin and HCH) in flour	-	Myoclonic jerks, convulsions, EEG changes, death in 2/12	Gupta 1975
Dieldrin	Single dose oral	10 mg/kg	-	"Untoward symptoms"	Committee on Toxicology 1960
Dieldrin (99% HEOD in gelatin capsules)	2 year oral	50 or 211 ug daily	0.005-0.025 ppm in blood, 0.4-4.9 ppm in fat	None	Hunter et al 1967, 1969
Dieldrin in hydrocarbon solvent	Single dose iv injection (suicide)	5 ml of solution (unspecified concentration)	50 ppm in blood	Convulsions, frothing at the mouth, death within 3 min	Schwar 1965

*Aldrin is converted to dieldrin in the body, and the presence of dieldrin in tissues reflects exposure to either.

TABLE 4.1.2

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE TO ALDRIN/DIELDRIN

Substance	Duration and Route of Exposure	Concentration or Dose	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin	1-5 yr unknown	-	0.024-0.4 ppm in blood	Muscular jerking, myoclonia, convulsions, psychic disturbances, EEG changes; clinical symptoms and EEG changes associated with blood levels of HEOD as low as 0.05 ppm; no symptoms in one worker with HEOD blood level of 0.25 ppm	Avar and Czegledi-Janko 1970
Dieldrin	Unknown dermal, respiratory	2.5% spray applied to surfaces at 0.5 g/m^2	-	Muscle jerking, convulsions, one death	Hayes 1957
"	1-18 mo dermal, respiratory	1.25-2.5% emulsion applied to surfaces at 1 g/m^2	-	Vertigo, nausea, myoclonia, convulsions, tremors, dermatitis, enlarged liver	Blazquez and Bianchini 1956

TABLE 4.1.2 (continued)

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE TO ALDRIN/DIELDRIN

Substance	Duration and Route of Exposure	Concentration or Dose	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin	14-154 d respiratory, dermal	1.25 or 2.5% spary	-	Giddiness, headache, muscle twitching, convulsions, loss of consciousness	Patel and Rao 1958
Aldrin ("empty drums")	-	-	-	Nausea, vomiting, malaise, headache, fainting, convulsions, hematuria, EEG changes	Nelson 1953
Aldrin and dieldrin (technical product and various formulations; also exposure to Telodrin and Endrin in some cases)	1-13 yr respiratory, dermal	-	0.022-0.078 ppm in blood in most workers; occasionally up to 0.23 ppm in blood in highly exposed workers	No significant effects in most workers, adverse effects associated with blood levels of dieldrin 0.05-0.20 ppm: convulsions in 15; headache, dizziness, drowsiness, hyperirritability, malaise in 8 others; EEG abnormalities; elevated serum alkaline phosphatase and SGOT levels, increased urinary excretion of D-glutaric acid	Hoogendam et al 1962, 1965; Jager 1970; Hunter et al 1972

TABLE 4.1.2 (continued)

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE TO ALDRIN/DIELDRIN

Substance	Duration and Route of Exposure	Concentration or Dose	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin or dieldrin	Long-term respiratory, dermal	30 µg/kg/d (estimated)	0.30 ppm in blood	Threshold for convulsive seizures	Jager 1970
"	"	15-20 µg/kg/d (estimated)	0.15-0.20 ppm in blood	Threshold for EEG changes and other CNS effects	Brown et al 1964, Jager 1970
Aldrin	1-2 yr respiratory, dermal	25% dust	-	Contact dermatitis, furunculi, "transient bronchial complications"	Nelson 1953
Aldrin and dieldrin (manufacture)	-	-	-	No significant increase in chromosome abnormalities	Dean et al 1974
Dieldrin	180 d dermal (estimated as 1.8 mg/kg/d)	0.55-1.1% emulsions, sprayed on surfaces at 0.5-1.0 g/m^2	-	No clinical symptoms	Fletcher et al 1959

TABLE 4.1.2 (continued)

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE TO ALDRIN/DIELDRIN

Substance	Duration and Route of Exposure	Concentration or Dose	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin technical (formulating plant)	5 wk dermal, respiratory	-	0.100-0.312 ppm in plasma	No complaints or health problems reported to the company physician	Mick et al 1971
Aldrin and dieldrin (manufacture)	1-19 yr dermal, respiratory	-	0.0012-0.137 ppm (mean 0.025 ppm) in plasma; 0.60-32 ppm (mean 6.1 ppm) in fat; 0.0014-0.066 ppm (mean 0.028 ppm) in urine	No meaningful association of tissue levels with history of sick leave	Hayes and Curley 1968
Dieldrin (also exposure to pentachlorophenol)	Long-term unknown	-	Mean 0.012 ppm in blood	Elevated levels of C-reactive protein in serum; significant correlation between alpha-2-globulin and dieldrin levels in serum	Takahashi et al 1976

TABLE 4.1.2 (continued)

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE TO ALDRIN/DIELDRIN

Substance	Duration and Route of Exposure	Concentration or Dose	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin (spray)	1-8 yr dermal, respiratory	-	0.001-0.009 ppm in blood	No symptoms	Morgan and Hickin 1966

*Aldrin is converted to dieldrin in the body, and the presence of dieldrin in tissues reflects exposure to either.

TABLE 4.2.1

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin or dieldrin (99% pure)	Rat	50, 100, or 150 ppm 2 yr	-	Dose-related reduction in survival, increased liver weight, liver lesions, nephritis, renal necrosis, distended and hemorrhagic urinary bladders	Fitzhugh et al 1964, Reuber 1974
Dieldrin	"	75 ppm 396-440 d	-	Increased liver weight, liver cell changes, nephritis	Ferrigan et al 1965
Dieldrin (technical)	"	50 or 100 ppm 8 wk	-	Increase in smooth endoplasmic reticulum, atypical mitochondria	Kimbrough et al 1971
Dieldrin	"	40 ppm 2 yr	-	Reduced survival, convulsions, reproductive failure, brain and vascular lesions	Harr et al 1970a,b
"	"	25 or 50 ppm 60 d	-	Reduced muscular performance (as measured by speed of pulling a weight along a runway)	Khairy 1960

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin or dieldrin	Rat	25 ppm 2 yr	-	Increased liver weight, liver lesions	Treon et al 1955
"	"	12.5 or 25 ppm 3 generations	-	Inconsistent effects on pregnancy rates, severe reduction in survival of offspring	Treon and Cleveland 1955, Cleveland 1966
Aldrin	"	3-4.5 mg/kg/day 13 mo	-	Increased chronaxy	London and Pallade 1964
Dieldrin	"	20 ppm 2 yr	-	Reduced survival, convulsions, reproductive failure, brain and vascular lesions	Harr et al 1970a,b
Aldrin or dieldrin	"	12.5 ppm 2 yr	-	Increased liver weight, liver lesions	Treon et al 1955
Dieldrin (99% pure)	"	10 ppm 2 yr	0.03-0.11 ppm in blood, 8-50 ppm in fat	Increased liver weight in females, lesions, irritability, convulsions	Walker et al 1969

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin or dieldrin (99% pure)	Rat	10 ppm 2 yr	-	Increased liver weight, liver lesions, nephritis	Fitzhugh et al 1964
Dieldrin	"	"	-	Neural spasms, severely impaired reproduction, brain and vascular lesions	Harr et al 1970a,b
"	"	6.2 ppm 5 d	-	Increased level of serum luteinizing hormone, decreased prostate weight	Blend and Lehnert 1973
"	"	5 ppm 2 yr	-	Severely impaired reproduction, brain and vascular lesions	Harr et al 1970a,b
Aldrin or dieldrin	"	2.5 ppm 2 yr	-	Increased liver weight, liver lesions	Treon et al 1955
"	"	2.5 ppm 3 generations	-	Slightly decreased pregnancy rate, slightly to moderately decreased survival of offspring	Treon and Cleveland 1955, Cleveland 1966

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin or dieldrin (99% pure)	Rat	2 ppm 2 yr	-	Increased liver weight, liver lesions	Fitzhugh et al 1964, Reuber 1974
Dieldrin (99% pure)	"	1 ppm 2 yr	0.009-0.069 ppm in blood, 1.3-16 ppm in fat	Increased liver weight in females	Walker et al 1969
Dieldrin	"	1 ppm 2 wk	-	"Threshold" level for induction of hepatic microsomal enzymes	Street et al 1969
"	"	0.7 ppm 5 d	-	Decreased prostate weight	Blend and Lehnert 1973
"	"	0.31, 0.63, 1.25, or 2.5 ppm 2 yr	4-50 ppm in fat	Impaired reproduction; brain and vascular lesions	Harr et al 1970a,b

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN IN ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissues Levels of Dieldrin*	Reported Effects	Reference
Dieldrin (99% pure)	Rat	0.1 ppm 2 yr	0.003-0.013 ppm in blood, 0.17-3.1 ppm in fat	No significant effects	Walker et al 1969
Dieldrin	"	0.08 or 0.16 ppm 2 yr	1-2 ppm in fat	Impaired reproduction in second breeding, brain and vascular lesions	Harr et al 1970a,b
Aldrin or dieldrin (99% pure)	"	0.5 ppm 2 yr	-	Increased liver weight, liver lesions	Fitzhugh et al 1974, Reuber 1974
Dieldrin (99% pure)	"	1 ppm	-	Increased hepatic microsomal enzyme activity	Wright 1974
Aldrin	Mouse	2 or 4 mg/kg/d 7 d late in pregnancy	-	Significant reduction in body weight and significant increase in electroshock seizure threshold in offspring tested at 38 d	Al-Hachim 1971

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin	Mouse	1.25, 2.5, or 5 mg/kg/d 5 d	-	Increased hepatic microsomal protein and cytochrome P-450, alteration in uptake and metabolism of testosterone	Schein and Thomas 1975
Dieldrin (technical)	"	10 or 15 ppm 76 d	-	Reduced fertility and litter size, 100% mortality of offspring	Virgo and Bellward 1975
Aldrin or dieldrin	"	10 or 25 ppm 6 generations	-	Reductions in fertility, lactation indices, and viability of pups	Deichmann and MacDonald 1971, Keplinger et al 1966, 1968
Dieldrin (99% pure)	"	10 ppm 2 yr	0.42-0.52 in blood, 11-12 ppm in fat	Reduced survival, enlarged livers, liver lesions	Walker et al 1972, Thorpe and Walker 1973

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin (99% pure)	Mouse	5 ppm 2 yr	-	Reduced survival, enlarged livers, liver lesions	Walker et al 1972
Dieldrin (technical)	"	5 ppm 90 d	-	Reduced litter size	Good and Ware 1969
Aldrin or dieldrin	"	1 mg/kg single dose	-	Reduced toxic reaction to parathion and paraoxon 1-12 days later	Triolo and Coon 1966a,b
"	"	3 ppm 6 generations	-	No significant effect on reproduction	Deichmann and MacDonald 1971
Dieldrin (technical)	"	2.5 or 5 ppm 76 d	-	Increased mortality of offspring	Virgo and Bellward 1975
Dieldrin (99% pure)	"	2.5 ppm 2 yr	-	Reduced survival in females, enlarged livers, liver lesions	Walker et al 1972
"	"	1.25 ppm 2 yr	-	Enlarged livers, liver lesions	"

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin (99% pure)	Mouse	1.0 ppm 2 yr	0.044 ppm in blood, 1.27-1.55 ppm in fat	Enlarged livers, liver lesions	Walker et al 1972
Dieldrin	"	1 ppm	-	Increased hepatic microsomal enzyme activity	Wright 1974
Dieldrin (99% pure)	"	0.1 ppm 2 yr	0.0026-0.0039 ppm in blood, 1.27-1.55 ppm in fat	Enlarged livers, liver lesions	Walker et al 1972
Aldrin or dieldrin	Dog	2-10 mg/kg/d 2-5 wk	-	Fatty changes in liver and renal tubules; death in 9/10	Fitzhugh et al 1964
Dieldrin (99% pure)	"	2 mg/kg/d 1 wk	-	Proliferation of smooth endoplasmic reticulum, increased hepatic microsomal enzyme activity	Wright 1974

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin or dieldrin	Dog	1 mg/kg/d 12-49 wk	-	Fatty change in liver and renal tubules; reduced number of erythrocytes in bone marrow; death in 4/4	Fitzhugh et al 1964
Aldrin or dieldrin (recrystal-lized)	"	0.6 or 2.0 mg/kg/d 1 yr	-	36/37 pups stillborn or died within 3 d of birth	Kitselman 1953
Aldrin	"	0.5 mg/kg/d up to 2 yr	-	Convulsions; death	Fitzhugh et al 1964
Dieldrin	"	"	-	Convulsions; survival for 2 yr in 3 of 4	"
"	"	0.2 mg/kg/d 6 yr	-	Increased serum alkaline phosphatase activity, increased bromosulphthalein clearance	Jager 1970

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Aldrin or dieldrin	Dog	0.2 mg/kg/d 2 yr	-	No clinical effects	Fitzhugh et al 1964
Aldrin or dieldrin (recrystal-lized)	"	0.2 mg/kg/d 1 yr	-	10/16 pups stillborn or died within 3 d of birth	Kitselman 1953
Aldrin (technical)	"	0.15 or 0.3 mg/kg/d 14 mo	0.012-0.14 ppm in blood, 11-150 ppm in fat	Reduced fertility, mammary development, and lactation; stillbirths and increased pup mortality	Deichmann et al 1971
Aldrin	"	3 ppm 15 mo	-	Increased liver weight; liver cell changes	Treon et al 1955
Dieldrin	"	"	-	Increased liver weight	"
Aldrin	"	1 ppm 15 mo	-	No reported effects	"

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin	Dog	1 ppm 15 mo	-	Increased liver weight	Treon et al 1955
Dieldrin (recrystallized)	"	0.05 mg/kg/d 2 yr	0.03-0.087 ppm in blood	Increased serum alkaline phosphatase activity, increased liver weight in females	Walker et al 1969
"	"	0.005 mg/kg/d 2 yr	0.005-0.024 ppm in blood	No reported effects	"
Dieldrin	Rhesus monkey	5 ppm 6 yr	-	Increased hepatic microsomal enzyme activity; death in 2/5	Jager 1970, Wright 1974
"	"	1.75 ppm 6 yr	0.075 ppm in blood, 19 ppm in fat	Increased hepatic microsomal enzyme activity	"
"	"	1 ppm 6 yr	0.033 ppm in blood, 8.3 ppm in fat	Increased hepatic microsomal enzyme activity, marginal increase in microsomal protein	"

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF ORAL ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin	Rhesus monkey	0.01, 0.10, or 0.50 ppm 6 yr	0.004-0.022 ppm in blood, 0.39-5.0 ppm in fat	No reported effects	Jager 1970, Wright 1974
Dieldrin (technical)	Squirrel monkey	0.1 mg/kg/d 55-109 d	-	Impaired learning of a discrimination reversal task	Smith et al 1976
"	"	0.01 mg/kg/d 55-109 d	-	No measurable effect on learning	"
Dieldrin	Sheep	10 mg/kg/d 30 d	-	Impaired learning	Van Gelder et al 1970
"	"	25 ppm 40 mo	-	Death of all lambs shortly after birth	Harris and Greenwood 1963
"	"	1 or 5 ppm 40 mo	-	No measurable effects on reproduction	"

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Dietary Concentration or Oral Dose and Duration	Tissue Levels of Dieldrin*	Reported Effects	Reference
Dieldrin	White-tailed deer	25 ppm 3 yr	-	Reported growth, increased liver weight, reduced pituitary weight, increased thyroid size, reduced size of fawns at birth, increased postpartum mortality	Murphy and Korschgen 1970
"	"	5 ppm 3 yr	-	Increased postpartum mortality in offspring	"
"	Raccoon	2.2 ppm 2 yr	-	Death of most females under the stress of breeding	Frederickson 1973
"	"	0.73 ppm 2 yr	-	Reduced pregnancy rate and litter size, fetal deaths and resorption of embryos; adverse effects on sperm production and fertility in males	"
"	Cottontail rabbit	0.07-0.25 ppm 1 yr	0.11-0.66 ppm in brain	No measurable effect on reproduction	Malecki et al 1974

*Aldrin is converted to dieldrin in the body, and the presence of dieldrin in tissues reflects exposure to either.

TABLE 4.3.1

TERATOGENIC EFFECTS OF ALDRIN/DIELDRIN ADMINISTERED TO ANIMALS BY ORAL INTUBATION

Substance	Species	Dose and Time of Administration*	Reported Effects	Reference
Aldrin (recrystallized)	Rat	25 mg/kg d 9	Anomalies in 33%: open eye, webbed foot, cleft palate	Ottolenghi et al 1974
Dieldrin (recrystallized)	"	15 mg/kg d 9	Anomalies in 17%: webbed foot, cleft palate	"
Dieldrin (technical)	"	6 mg/kg/d d 7-16	Maternal deaths and weight loss; no anomalies in offspring	Chernoff et al 1975
"	"	1.5 or 3.0 mg/kg/d d 7-16	None	"
Dieldrin	"	3.4 mg/kg/d d 6, 6-14, or 1-14	Nonsignificant increase in anomalies	Boucard et al 1970
"	"	2.5 µg/kg/d d 6, 6-14, or 1-14	"	"
Photodieldrin	"	0.15, 0.3, or 0.6 mg/kg/d d 7-16	15% maternal mortality at 0.6 mg/kg/d, no increase in anomalies in offspring	Chernoff et al 1975

TABLE 4.3.1 (continued)

TERATOGENIC EFFECTS OF ALDRIN/DIELDRIN ADMINISTERED TO ANIMALS BY ORAL INTUBATION

Substance	Species	Dose and Time of Administration*	Reported Effects	Reference
Dieldrin (technical)	Mouse	3.0 or 6.0 mg/kg/d d 7-16	Increased maternal liver weight; increase in supernumerary ribs and decrease in caudal ossification centers in offspring	Chernoff et al 1975
"	"	1.5 mg/kg/d d 7-16	No significant effects	"
Dieldrin	"	3.4 mg/kg/d d 6, 6-14, or 1-14	Nonsignificant increase in anomalies	Boucard et al 1970
"	"	2.5 µg/kg/d d 6, 6-14, or 1-14	"	"
Photo-dieldrin	"	0.15, 0.30, or 0.60 mg/kg/d d 7-16	No significant effects	Chernoff et al 1975
Aldrin (recrystallized)	Hamster	50 mg/kg d 7, 8, or 9	Anomalies in 11-22%: open eye, webbed foot, cleft palate, cleft lip, others	Ottolenghi et al 1974

TABLE 4.3.1 (continued)

TERATOGENIC EFFECTS OF ALDRIN/DIELDRIN ADMINISTERED TO ANIMALS BY ORAL INTUBATION

Substance	Species	Dose and Time of Administration*	Reported Effects	Reference
Dieldrin (recrystal-lized)	Hamster	30 mg/kg d 7, 8, or 9	Anomalies in 4-33%: open eye, cleft lip, cleft palate, exencephaly, platycrania, micrognathia, ectrodactyly	Ottolenghi et al 1974

*Day of pregnancy

TABLE 4.3.2

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Concentration and Duration	Reported Effects	Reference
Aldrin (technical)	Rat	30 or 60 ppm 74 wk followed by 37-38 wk observation for females, 80 wk followed by 32-33 wk observation for males	At 60 ppm, no significant increases in tumor incidence; at 30 ppm, significant increases (compared to pooled controls) in three types of tumor: thyroid follicular cell tumors and adrenal cortical adenomas in both sexes, pancreatic islet tumors in males	NCI 1978a
Dieldrin (technical)	"	"	Significant dose-related increase in thyroid follicular cell tumors in females; at 30 ppm, significant increase (compared to pooled controls) in incidence of adrenal cortical adenomas and carcinomas in females	"
Aldrin	"	5 ppm 25 mo	No significant increase in tumor incidence	Deichmann et al 1967
Dieldrin (recrystallized)	"	2, 10, or 50 ppm 104-105 wk	"	NCI 1978b

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Concentration and Duration	Reported Effects	Reference
Dieldrin	Rat	1 ppm	Significant increase in lung and other tumors in males; nonsignificant incidence of liver lesions of disputed significance	Reuber 1974, Epstein 1975
Aldrin (recrystallized)	"	0.5, 2, 10, 50, 100, or 150 ppm 2 yr	Reduced survival at 50, 100, and 150 ppm; significant increase in lymphatic and mammary tumors at 0.5, 2, and 10 ppm (25/60 in pooled groups vs 2/17 in controls) but not at higher doses, significant increase in liver lesions of disputed significance (probably neoplastic or preneoplastic)	Fitzhugh et al 1964, Reuber 1974, Epstein 1975, Thorpe 1974
Dieldrin (recrystallized)	"	"	Reduced survival at 50, 100, and 150 ppm; marginally significant increase in lymphatic and mammary tumors at 0.5, 2, and 10 ppm (16/63 in pooled groups vs 2/17 in controls) but not at higher doses; significant increase in liver lesions of disputed significance (probably neoplastic or preneoplastic)	"

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Concentration and Duration	Reported Effects	Reference
Dieldrin (recrystallized)	Rat	0.1, 1.0, or 10 ppm 2 yr	Marginally significant increase in thyroid and mammary tumors in females exposed at 1.0 and 0.1 ppm (15/23 and 14/23 vs 19/43 in controls) but not at 10 ppm; liver lesions at 10 ppm	Walker et al 1969, Gross 1974, Stevenson et al 1975
Photodieldrin (recrystallized)	"	5 or 10 ppm (males); 3.4 or 7.5 ppm time-weighted average (females) 80 wk followed by 30 wk observation	No significant increases in tumor incidence	NCI 1977
Dieldrin (recrystallized)	Mouse	10 ppm 2 yr (series of nine experiments)	Increased incidence of liver tumors in males and females in nine independent experiments; lung metastases from 0-17% of tumors; some tumors successfully transplanted; significant increase in age-adjusted incidence of lung tumors in three experiments; increase in lymphoid and other tumors in two experiments	Walker et al 1972, Thorpe and Walker 1973, Hunt 1974, Epstein 1975, Gross 1974

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Concentration and Duration	Reported Effects	Reference
Dieldrin	Mouse	10 ppm 2 yr	Mean survival time 51 wk vs 59.8 wk in controls, 24% incidence of liver tumors vs 7% in controls	Davis and Fitzhugh 1962
Dieldrin (recrystallized)	"	10 ppm 2, 4, 8, 16, 32, or 64 wk sacrifice at 104 wk	Increased incidence of liver tumors, which was statistically significant in 64-wk group; malignant tumors in 64-, 8-, and 4-wk groups	Walker et al 1972
Aldrin	"	10 ppm 2 yr	Mean survival time 51.6 wk vs 59.8 wk in controls, 23% incidence of liver tumors vs 7% in controls	Davis and Fitzhugh 1962
Dieldrin	"	10 ppm 2 yr	Reduced survival, 39% vs 64% in controls at 2 yr; increased incidence of liver tumors, 87% in males and 87% in females vs 30% in male and 4% in female controls; lung metastases in 5% of exposed females; 8/9 tumors transplanted successfully	Davis 1965, Reuber 1974, Epstein 1975

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Concentration and Duration	Reported Effects	Reference
Aldrin	Mouse	10 ppm 2 yr	Reduced survival, 31% at 2 yr vs 64% in controls, increased incidence of liver tumors, 82% in males and 85% in females vs 30% in male and 4% in female controls; lung metastases in 4% of exposed males; 9/10 tumors transplanted successfully	Davis 1965, Reuber 1974, Epstein 1975
Dieldrin (recrystallized)	"	5 ppm (with 50 ppm DDT) 2 yr	Incidence of liver tumors 58% in males and 94% in females vs 0 in controls, 6% in males exposed to DDT only, and 16% in females exposed to DDT only	Walker et al 1972, Reuber 1974, Epstein 1975
Aldrin (technical)	"	4 or 8 ppm (males) 3 or 6 ppm (females) time-weighted average 80 wk followed by 10-13 week observation	Hepatocellular carcinomas in 56% of males at 8 ppm, 33% of males at 4 ppm, and 18% of pooled control males; non-significant increase in females	NCI 1978a

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Concentration and Duration	Reported Effects	Reference
Dieldrin	Mouse	3 or 10 ppm lifetime	Marked increase in liver lesions, including some diagnosed as hepatocellular carcinomas	MacDonald et al 1972, 1973; Reuber 1974; Epstein 1975
Dieldrin (technical)	"	2.5 or 5 ppm time-weighted average 80 wk followed by 10-13 wk observation	Hepatocellular carcinomas in 36% of males at 5 ppm, 24% of males at 2.5 ppm, and 18% of pooled control males; non-significant increase in females	NCI 1978a
Dieldrin (recrystallized)	"	1.25, 2.5, or 5 ppm 2 yr	Increased incidence of liver tumors in both sexes in all exposed groups; lung metastases from 3 tumors in exposed mice; significant dose-related increase in age-adjusted incidence of lung tumors	Walker et al 1972, Hunt 1974
"	"	0.1 or 1 ppm 2 yr	Increased incidence of liver tumors in both sexes at both dose levels independently; lung metastases from 3 tumors in exposed mice; increased incidence of pulmonary adenomas and carcinomas in males and females	Walker et al 1973, Gross 1974, Epstein 1975

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF ALDRIN/DIELDRIN TO ANIMALS

Substance	Species	Concentration and Duration	Reported Effects	Reference
Photo-dieldrin	Mouse	0.32 or 0.64 ppm 80 wk followed by 10-13 wk observation	No statistically significant increases in tumor incidence	NCI 1977

TABLE 4.3.3

SUMMARY OF MUTAGENIC EFFECTS OF ALDRIN/DIELDRIN

Substance	Species or System	Strain	Dose	Reported Effects	Reference
Aldrin or dieldrin (technical)	Salmonella typhimurium	TA 1535 TA 1536 TA 1537 TA 1538	20 µg in DMSO	No increase in number of revertants without microsomal activation	Shirasu et al 1976
Dieldrin	"	"	1,000 µg	No increase in number of revertants with and without rat liver microsomal activation	Marshall et al 1976
Aldrin or dieldrin	"	-	-	No increase in number of revertants with mouse liver microsomal activation	Van Dijck and Van de Voorde 1976
Dieldrin	"	TA 1535 TA 1536 TA 98 TA 100	10 mg	No increase in number of revertants with and without rat liver microsomal activation	McCann et al 1975
"	"	5 unspecified strains	-	No increase in number of revertants with and without microsomal activation (no details given in abstract)	Bidwell et al 1975

TABLE 4.3.3 (continued)

SUMMARY OF MUTAGENIC EFFECTS OF ALDRIN/DIELDRIN

Substance	Species or System	Strain	Dose	Reported Effects	Reference
Aldrin or dieldrin (technical)	Bacillus subtilis	H17 Rec^+ M45 Rec^-	20 µg in DMSO	Negative results in recombination assays	Shirasu et al 1976
Aldrin or dieldrin	Escherichia coli	B/r try WP2 WP2 try hcr	20 µg in DMSO	No increase in number of mutants without microsomal activation	"
Aldrin	Saccharomyces cerevisiae	-	5 and 50 µg/ml	Significant mutagenic activity	Guerzoni et al 1976
Dieldrin	Chinese hamster cells	V79	0.1, 0.3, 1.0, or 3.0 mM	Negative results in vitro in alkaline elution assay for DNA damage, with rat liver microsomal activation	Swenberg et al 1976
"	"	"	-	Significant increase in ouabain resistant mutants	Ahmed 1975
Dieldrin (recrystallized)	Chinese hamster	-	30 or 60 mg/kg single dose in DMSO	Nonsignificant decrease in polyploidy in bone marrow cells, no increase in chromatid gaps	Dean et al 1975

TABLE 4.3.3 (continued)

SUMMARY OF MUTAGENIC EFFECTS OF ALDRIN/DIELDRIN

Substance	Species or System	Strain	Dose	Reported Effects	Reference
Aldrin	Human lymphocytes	-	19 or 38 µg/ml	Increase in chromosome aberrations: gaps, breaks, deletions, fragments, and interchanges	Georgian 1975
Aldrin or dieldrin	Human fibroblasts	VA-4	1, 10, 100, or 1,000 µM	Induction of unscheduled DNA repair in VA-4 cells transformed by SV-40 virus, with and without rat liver microsomal activation	Ahmed et al 1977
Dieldrin (purified)	Human lung cells	WI-38	1, 10, or 30 µg/ml	Significant dose-related increases in chromosome abnormalities: breaks, fragments, interchanges, and rings	Majumdar et al 1976
Dieldrin (technical)	Duck lymphocytes	-	0.1, 1, 10, or 100 µg/ml	Significant increase in chromosomal aberrations, including gaps and breaks, at 100 µg/ml; mitotic indices reduced at all concentrations	Bunch and Low 1973
Dieldrin (recrystallized)	Saccharomyces cerevisiae (host-mediated assay in CF1 mice)	D4	25 or 50 mg/kg single dose or repeated doses of 0.2, 3, or 10 mg/kg/d	No changes in rate of mitotic gene conversion	Dean et al 1975

TABLE 4.3.3 (continued)

SUMMARY OF MUTAGENIC EFFECTS OF ALDRIN/DIELDRIN

Substance	Species or System	Strain	Dose	Reported Effects	Reference
Dieldrin (purified)	Mouse	STS	1, 30, or 50 mg/kg single ip injection	Pronounced mitotic inhibition and significant 2- to 6-fold increases in chromosome abnormalilities in bone marrow cells	Majumdar et 1976
Aldrin or dieldrin	"	-	1.2 or 2 mg/kg single dose	Mitotic inhibition, chromosome aberrations including breaks, fragments, chromosome and chromatid bridges, and stickiness	Markaryan 1966
Dieldrin (recrystallized)	Mouse (dominant lethal assay)	CF1	12.5, 24, or 50 mg/kg single dose in DMSO	Negative results in one assay, reduced number of fetal implantations in another	Dean et al 1975
Aldrin	Mouse	-	9.6, 19, or 38 mg/kg single ip injection	Dose-related increase in chromosome and chromatid aberrations; no effect at 9.6 mg/kg	Georgian 1975
"	Rat	-	"	Significant increase in chromosome and chromatid aberrations at 19 mg/kg; inconclusive results at 38 mg/kg	"

TABLE 4.3.3 (continued)

SUMMARY OF MUTAGENIC EFFECTS OF ALDRIN/DIELDRIN

Substance	Species or System	Strain	Dose	Reported Effects	Reference
Dieldrin	Mammal (unspecified)	-	0.08, 0.8, or 8 mg/kg by	Negative for mutagenicity in 4 tests (unspecified)	Bidwell et al 1975
Dieldrin (technical)	Mallard duck	-	4, 10, or 30 ppm in diet for 60 days	No significant increase in chromosome aberrations	Bunch and Low 1973

TABLE 5.1

VON BAEYER/IUPAC NAMES OF DIELDRIN

Abbreviated Chemical Names and Other Designations	Von Baeyer/IUPAC Name
Aldrin HHDN SD 2794	1,8,9,10,11,11-Hexachloro-2,3-7,6-endo-2,1-7,8-exo-tetracyclo-(6.2.1.$1^{3,6}$.$0^{2,7}$)dodeca-4,9-diene
Dieldrin HEOD SD 3417	1,8,9,10,11,11-Hexachloro-4,5-exo-epoxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo(6.2.1.$1^{3,6}$.$0^{2,7}$)dodec-9-ene
cis-4,5-Dihydroxy-dihydroaldrin "Aldrin cis-diol" WL 43020	1,8,9,10,11,11-Hexachloro-4,5-(exo)cis-dihydroxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo-(6.2.1.$1^{3,6}$.$0^{2,7}$)dodec-9-ene
trans-4,5-Dihydroxy-dihydro-aldrin "trans-6,7-Dihydroxy-dihydro-aldrin" "Aldrin trans-diol" WL 40549	1,8,9,10,11,11-Hexachloro-4,5-trans-dihydroxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo-(6.2.1.$1^{3,6}$.$0^{2,7}$)dodec-9-ene
4,5-Dihydroaldrin	1,8,9,10,11,11-Hexachloro-2,3-7,6-endo-2,1-7,8-exo-tetracyclo-(6.2.1.$1^{3,6}$.$0^{2,7}$)dodec-9-ene
4-Ketodihydroaldrin	1,8,9,10,11,11-Hexachloro-2,3-7,6-endo-2,1-7,8-exo-tetracyclo-(6.2.1.$1^{3,6}$.$0^{2,7}$)dodec-9-en-4-one

(HEOD) AND RELATED COMPOUNDS

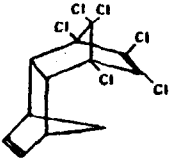
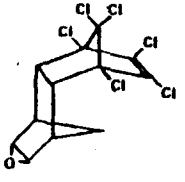
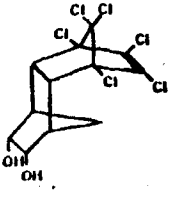
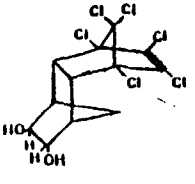
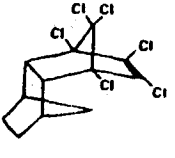
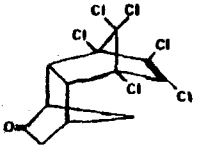
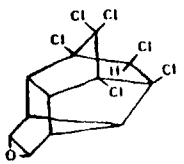
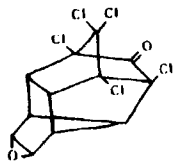
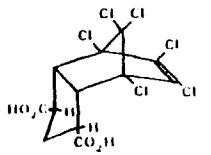
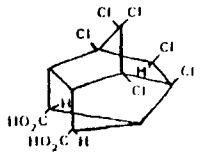
CAS No.*	Molecular Weight	Molecular Formula	Structure
309-00-2	364.9	$C_{12}H_8Cl_6$	
60-57-1	380.9	$C_{12}H_8Cl_6O$	
30460-74-3	398.9	$C_{12}H_{10}Cl_6O_2$	
3106-29-4	398.9	$C_{12}H_{10}Cl_6O_2$	
10059-65-1	366.9	$C_{12}H_{10}Cl_6$	
34022-77-0	380.9	$C_{12}H_8Cl_6O$	

TABLE 5.1 (continued)

VON BAEYER/IUPAC NAMES OF DIELDRIN (HEOD) AND RELATED COMPOUNDS

Abbreviated Chemical Names and Other Designations	Von Baeyer/IUPAC Name	CAS No.*	Molecular Weight	Molecular Formula	Structure
Photodieldrin "Photoisomer of dieldrin" "Photo-HEOD" BL 6623	3,exo-4,5,6,6,7-Hexachloro-11,12-exo-epoxy-pentacyclo-($6.4.0.0^{2,10}.0^{3,7}.0^{5,9}$)dodecane INCORRECT NAME: 1,9,10,10,11-exo-12-Hexachloro-4,5-exo-epoxy-8,3-7,6-endo-8,9-7,11-exo-pentacyclo-($7.3.0.0^{2,6}.0^{3,8}.0^{7,11}$)dodecane	13366-73-9	380.9	$C_{12}H_8Cl_6O$	
4-Keto-4-dechloro-photodieldrin "HEOD Pentachloroketone" "Ketophotodieldrin" "Klein's metabolite"	3,5,6,6,7-Pentachloro-11,12-exo-epoxy-pentacyclo-($6.4.0.0^{2,10}.0^{3,7}.0^{5,9}$)dodecan-4-one INCORRECT NAME: 1,9,10,10,11-Pentachloro-4,5-exo-epoxy-8,9-7,11-exo-pentacyclo-($7.3.0.0^{2,6}.0^{3,8}.0^{7,11}$)dodecan-12-one	21038-31-3	360.5	$C_{12}H_7Cl_5O_2$	
4,5-seco-Aldrin-4,5-dicarboxylic acid (seco-ADA) "Aldrin dicarboxylic acid" "Dihydrochlordene dicarboxylic acid" "Aldrin-derived acid" "ADA" SD 2878	1,7,8,9,10,10,Hexachloro-2,3-6,5-endo-tricyclo($5.2.1.0^{2,6}$)dec-8-ene-3,5-exo,exo-dicarboxylic acid	5103-66-2	428.9	$C_{12}H_8Cl_6O_4$	
11,12-seco-Photoaldrin-11,12-dicarboxylic acid "Acid from oxidation of photoaldrin"	1,7,8,exo-9,10,10-Hexachlorotetracyclo($5.2.1.0^{2,6}.0^{4,8}$)decane-3,5-exo,exo-dicarboxylic acid		428.9	$C_{12}H_8Cl_6O_4$	

Adapted from Bedford 1974

TABLE 5.1 (continued)

VON BAEYER/IUPAC NAMES OF DIELDRIN (HEOD) AND RELATED COMPOUNDS

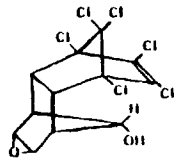
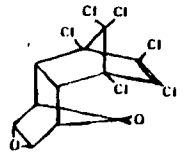
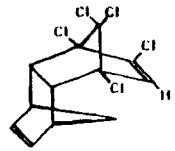
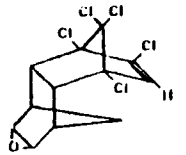
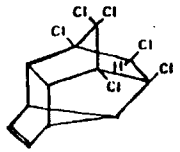
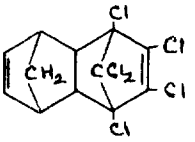
Abbreviated Chemical Names and Other Designations	Von Baeyer/IUPAC Name	CAS No.*	Molecular Weight	Molecular Formula	Structure
syn-12-Hydroxy-dieldrin "9-Hydroxy HEOD" WL 40231	1,8,9,10,11,11-Hexachloro-4,5-exo-epoxy-12-(syn-epoxy)hydroxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo-(6.2.1.1^{3,6}.0^{2,7})dodec-9-ene	26946-01-0	396.9	$C_{12}H_8Cl_6O_2$	
12-Ketodieldrin "9-Keto-HEOD" WL 42170	1,8,9,10,11,11-Hexachloro-4,5-exo-epoxy-2,3-7,6-endo-2,1-7,8-exo-tetracyclo(6.2.1.1^{3,6}.0^{2,7})dodec-9-en-12-one		394.9	$C_{12}H_6Cl_6O_2$	
9-Dechloroaldrin "Pentachloro photoproduct of aldrin"	1,8,10,11,11-Pentachloro-2,3-7,6-endo-2,1-7,8-exo-tetracyclo-(6.2.1.1^{3,6}.0^{2,7})dodeca-4,9-diene	21939-95-6	330.5	$C_{12}H_9Cl_5$	
9-Dechlorodieldrin "Pentachloro photoproduct of HEOD" "pentachlorodieldrin"	1,8,10,11,11-pentachloro-4,5-exo-epoxy-2,3-7,6-endo-2,1-7,6-exo-tetracyclo(6.2.1.1^{3,6}.0^{2,7})dodec-9-ene		362.5	$C_{12}H_9Cl_5O$	
Photoaldrin "Photoisomer of aldrin" SD 18303	3,exo-4,5,6,6,7-Hexachloropentacyclo-(6.4.0.0^{2,10}.0^{3,7}.0^{5,9})dodec-11-ene	13366-64-8	364.9	$C_{12}H_8Cl_6$	

TABLE 5.2

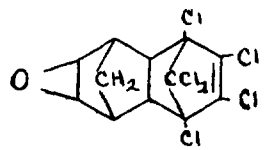
PHYSICAL AND CHEMICAL PROPERTIES OF ALDRIN

Appearance	Brown to white crystalline solid
Empirical formula	$C_{12}H_8Cl_6$
Structure	
Molecular weight	364.93
Melting point	104-105.5 C
Vapor pressure	2.31×10^{-5} mm Hg at 20 C
Octanol/water partition coefficient	5.00
Solubility	Insoluble in water; very soluble in most organic solvents
Stability	Stable in the presence of organic and inorganic alkalis; stable to the action of hydrated metal chlorides

From IARC 1974, Condensed Chemical Dictionary 1977, Merck 1976

TABLE 5.3

PHYSICAL AND CHEMICAL PROPERTIES OF DIELDRIN

Appearance	Light tan, flaked solid
Empirical formula	$C_{12}H_8OCl_6$
Structure	
Molecular weight	380.93
Melting point	175 C
Vapor presure	1.78×10^{-7} mm Hg at 20 C
Octanol/water partition coefficient	4.56
Solubility	Practically insoluble in water (0.25 mg/liter); moderately soluble in common organic solvents except aliphatic petroleum solvents and methyl alcohol
Stability	Stable in organic and inorganic alkalis and acids commonly used in agriculture

From IARC 1974, Condensed Chemical Dictionary 1977, Merck 1976

TABLE 5.4

SYNONYMS AND TRADE NAMES FOR ALDRIN AND DIELDRIN

Aldrin

1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene

Compound 118

Octalene

HHDN

SD 2794

Dieldrin

3,4,5,6,9,9-Hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-2,7:3,6-dimethanonaphth[2,3-b]oxirene

1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo, exo-1,4:5,8-dimethanonaphthalene

Compound 497

Insecticide No. 497

HEOD

Octalox

SD 3417

From Condensed Chemical Dictionary 1977, Merck 1976

6. REFERENCES

AHMED, F.E. 1975. Environmental genetics: A model to investigate pollutants producing genetic damage. Diss. Abstr. Int. B 36:3737 (Abstract)

AHMED, F.E., HART, R.W., and LEWIS, N.J. 1977. Pesticide induced DNA damage and its repair in cultured human cells. Mutat. Res. 42:161-174

AL-HACHIM, G.M. 1971. Effect of aldrin on the condition avoidance response and electroshock seizure threshold of offspring from aldrin-treated mother. Psychopharmacologia 21:370-373

ASPELIN, A.L. 1975. Statement of testimony at public hearings on suspension of registrations of chlordane/heptachlor (EPA Exhibit 26). U.S. Environmental Protection Agency, Washington, D.C.

AVAR, P., and CZEGLÉDI-JANKÓ, G. 1970. Occupational exposure to aldrin: Clinical and laboratory findings. Brit. J. Ind. Med. 27:279-282

BALDWIN, M.K., ROBINSON, J. and PARKE, D.V. 1972. A comparison of the metabolism of HEOD (dieldrin) in the CF1 mouse with that in the CFE rat. Food Cosmet. Toxicol. 10:333-351

BARNES, J.M., and HEATH, D.F. 1964. Some toxic effects of dieldrin in rats. Brit. J. Ind. Med. 21:280-282

BEDFORD, C.T. 1974. Von Baeyer/IUPAC names and abbreviated chemical names of metabolites and artifacts of aldrin (HHDN), dieldrin (HEAD) and endrin. Pestic. Sci. 5:473-489

BELL, A. 1960. Aldrin poisoning: A case report. Med. J. Austr. 2:698-700

BIDWELL, K., WEBER, E., NEINHOLD, I. CONNOR, T., and LEGATOR, M.S. 1975. Comprehensive evaluation for mutagenic activity of dieldrin. Mutat. Res. 31:314 (Abstract)

BLÁZQUEZ, J., and BIANCHINI, C. 1956. [Chronic occupational poisoning with dieldrin in humans.] Gac. Med. Caracas 63:1-39 (Spanish)

BLEND, M.J., and LEHNERT, B.E. 1973. Luteinizing hormone (LH) serum levels and body weight/organ weight ratios in male rats fed low levels of dieldrin. In W.B. Deichman, ed., Pesticides and the Environment: A Continuing Controversy. Intercontinental Medical Book Corporation, New York. Pp 189-198

BLEND, M.J., and SCHMIDT, T.J. 1971. In vitro uptake of steroid hormones and dieldrin by rats and canine prostatic tissue. Fed. Proc. 30:577 (Abstract)

BOUCARD, P.M., BEAULATON, I-S., MESTRES, R., and ALLIEU, M. 1970. [An experimental study in teratogenesis: Effect of timing and duration of treatment.] Thérapie 25:907-913 (French, translation included)

BROWN, V.K.H., HUNTER, C.G., and RICHARDSON, A. 1964. A blood test diagnostic of exposure to aldrin and dieldrin. Brit. J. Ind. Med. 21:283-286

BROWN, V.K.H., ROBINSON, J., and RICHARDSON, A. 1967. Preliminary studies on the acute and subacute toxicities of a photoisomerization product of HEOD. Food Cosmet. Toxicol. 5:771-779

BUNCH, T.D., and LOW, J.B. 1973. Effects of dieldrin on chromosomes of semi-domestic mallard ducks. J. Wildl. Mgmt. 37:51-57

BUNDREN, J., HOWELL, D.E., and HELLER, V.G. 1952. Absorption and toxicity of dieldrin. Proc. Exp. Biol. Med. 79:236-238

CASARETT, L.J. FRYER, G.C., YAUGER, W.L., Jr., and KLEMMER, H.W. 1968. Organochlorine pesticide residues in human tissue--Hawaii. Arch. Environ. Health 17:306-311

CHAN, T., and TERRIERE, L.C. 1969. Aldrin epoxidase activity of rat liver and rat liver microsomes under various conditions of storage. Biochem. Pharmacol. 18:1061-1070

CHERNOFF, N., KAVLOCK, R.J., KATHREIN, J.R., DUNN, J.M., and HASEMAN, J.K. 1975. Prenatal effects of dieldrin and photodieldrin in mice and rats. Toxicol. Appl. Pharmacol. 31:302-308

CHUNG, R.A., HUANF, I-L., BROWN, R.W. 1967. Studies of DNA, RNA, and protein synthesis in HeLa-S cells exposed to DDT and dieldrin. J. Agr. Food Chem. 15:497-500

CLEVELAND, F.P. 1966. A summary of work on aldrin and dieldrin toxicity at the Kettering Laboratory. Arch. Environ. Health 13:195-198

COLE, J.F., KLEVAY, L.M., and ZAVON, M.R. 1968. Endrin and dieldrin: A comparison of hepatic excretion rates in the rat. Toxicol. Appl. Pharmacol. 12:298 (Abstract)

COMMITTEE ON TOXICOLOGY, A.M.A. 1960. (Conley, B.E., Secretary). Occupational dieldrin poisoning. J. Am. Med. Assoc. 172:2077-2080

CONDENSED CHEMICAL DICTIONARY. 1977. 9th ed. Hawley, G.G. co-ed. Van Nostrand Reinhold Company, New York. Pp 24, 284

CONNEY, A.H. 1967. Pharmacological implications of microsomal enzyme induction. Pharmacol. Rev. 19:317-366

CONNEY, A.H. 1969. Drug metabolism and therapeutics. New England J. Med. 280:653-660

CONNEY, A.H., WELCH, R.M., KUNTZMAN, R., and BURNS, J.J. 1967. Effects of pesticides on drug and steroid metabolism. Clin. Pharmacol. Ther. 8:2-10

CUETO, C., Jr. and BIROS, F.J. 1967. Chlorinated insecticides and related materials in human urine. Toxicol. Appl. Pharmacol. 10:261-269

CUETO, C., Jr. and HAYES, W.J., Jr. 1962. The detection of dieldrin metabolites in human urine. J. Agric. Food Chem. 10:366-369

CUETO, C., Jr. and HAYES, W.J., Jr. 1965. Effect of phenobarbital on the metabolism of dieldrin. Toxicol. Appl. Pharmacol. 7:481 (Abstract)

DACRE, J.C., and JENNINGS, R.W. 1970. Organochlorine insecticides in normal and carcinogenic human lung tissues. Toxicol. Appl. Pharmacol. 17:277 (Abstract)

DAVIES, J.E., BARQUET, A., MORGADE, C., and RAFFONELLI, A. 1975. Epidemiological studies of DDT and dieldrin residues and their relationship to human carcinogenesis. In Recent Advances in the Assessment of the Health Effects of Environmental Pollution, International Symposium Proceedings (WHO, CEC, EPA) 2:695:-702

DAVIES, J.E., EDMUNDSON, W.F., MACEO, A., IRVIN, G.L. III, CASSADY, J., and BARQUET, A. 1971. Reduction of pesticide residues in human adipose tissue with diphenylhydantoin. Food Cosmet. Toxicol. 9:413-423

DAVIS, K.J. 1965. Pathology report on mice exposed to aldrin, dieldrin, heptachlor epoxide for two years. Internal memo to A.J. Lehman, July 19, 1965. U.S. Food and Drug Administration, Washington, D.C. (included as an exhibit by Reuber, 1974, and summarized by Epstein, 1975).

DAVIS, K.J., and FITZHUGH, O.G. 1962. Tumorigenic potential of aldrin and dieldrin for mice. Toxicol. Appl. Pharmacol. 4:187-189

DAVISON, V.L. 1970. Dieldrin accumulation in tissues of sheep. J. Agric. Food Chem. 18:1156-1160

DEAN, B.J., DOAK, S.M.A., and SOMERVILLE, H. 1975. The potential mutagenicity of dieldrin (HEOD) in mammals. Food Cosmet. Toxicol. 13:317-323

DEICHMANN, W.B., and KEPLINGER, M.L. 1966. Effect of combinations of pesticides on reproduction of mice. Abstracts of Fifth Annual Meeting of Society of Toxicology, Williamsburg, Virginia, March 14-16, 1966. Toxicol. Appl. Pharmacol. 8:337-338 (Abstract)

DEICHMANN, W.B., KEPLINGER, M., SALA, F., and GLASS, E. 1967. Synergism among oral carcicogens: IV. The simultaneous feeding of four tumorigens to rats. Toxicol. Appl. Pharmacol. 11:88-103

DEICHMANN, W.B., and MACDONALD, W.E. 1971. Organochlorine pesticides and human health. Food Cosmet. Toxicol. 9:91-103

DEICHMANN, W.B., MACDONALD, W.E., BEASLEY, A.G., and CUBIT, D. 1971. Subnormal reproduction in beagle dogs induced by DDT and aldrin. Industr. Med. 40:10-18

DEICHMANN, W.B., MACDONALD, W.E., BLUM, E., BEVILACQUA, M., RADOMSKI, J., KEPLINGER, M.L., and BALKAS, M. 1970. Tumorigenicity of aldrin, dieldrin, and endrin in the albino rat. Indust. Med. 39:37-44

DEN TONKELAAR, E.M. and VAN ESCH, G.J. 1974. No-effect levels of organochlorine pesticides based on induction of microsomal liver enzymes in short-term toxicity experiments. Toxicology 2:371-380

D'ERAMO, N., and CROCE, E. 1960. Acute erythemato-bullous dermatitis caused by contact with aldrin. Riv. Infort. Prof. 47:534-537

D'ERCOLE, A.J., ARTHUR, R.D., CAIN, J.D., and BARRENTINE, B.F. 1976. Insecticide exposure of mothers and newborns in a rural agricultural area. Pediatrics 57:869-874

DE VLIEGER, M., ROBINSON, J., BALDWIN, M.K., CRABTREE, A.N., and VON DIJK, M.C. 1968. The organochlorine insecticide content of human tissues. Arch. Environ. Health. 17:759-767

EPSTEIN, S.S. 1975. The carcinogenicity of dieldrin: Part I. Sci. Total Environ. 4:1-52

ESPIR, M.L., HALL, J.W., SHIRREFFS, J.G., and STEVENS, D.L. 1970 Impotence in farm workers using toxic chemicals. Brit. Med. J. 1:423-425

FELDMANN, R.J., and MAIBACH, H.I. 1974. Percutaneous penetration of some pesticides and herbicides in man. Toxicol. Appl. Pharmacol. 28:126-132

FERRIGAN, L.W., HUNTER, G.C., and STEVENSON, D.E. 1965. Observations on the effects of continued oral exposure of rats to dieldrin. Food Cosmet. Toxicol. 3:149-150

FITZHUGH, O.G., NELSON, A.A., and QUAIFE, M.L. 1964. Chronic oral toxicity of aldrin and dieldrin in rats and dogs. Food Cosmet. Toxicol. 2:551-561

FLETCHER, T.G., PRESS, J.M., and WILSON, D.B. 1959. Exposure of spraymen to dieldrin in residual spraying. Bull. WHO 20:15-25

FOOD AND AGRICULTURAL ORGANIZATION OF THE UNITED NATIONS (FAO) 1977. FAO Production Yearbook 1976. FAO Statistics Series No. 7. Rome, Italy. Table 102, p 259

FOOD AND AGRICULTURE ORGANIZATION/WORLD HEALTH ORGANIZATION (FAO/WHO) 1971. 1970 Evaluations of Some Pesticide Residues in Food, The Monographs. Rome, Italy, Pp 177-238

FOUTS, J.R. 1963. Factors influencing the metabolism of drugs in liver microsomes. Ann. N.Y. Acad. Sci. 104:875-880

FREDERICKSON, L.G. 1973. Statement of testimony at public hearings on suspension of registrations of aldrin/dieldrin (EPA Exhibit 34). U.S. Environmental Protection Agency, Washington, D.C.

FRY, D.R. 1964. Human dieldrin poisoning. Lancet 1:764

GARRETTSON, L.K., and CURLEY, A. 1969. Dieldrin: Studies in a poisoned child. Arch. Environ. Health 19:814-822

GEORGIAN, L. 1975. The comparative cytogenic effects of aldrin and phosphamidon. Mutat. Res. 31:103-108

GHIASUDDIN, S.M., and MENZER, R.E. 1976. Microsomal epoxidation of aldrin to dieldrin in rats. Bull. Environ. Contam. Toxicol. 15:324-329

GILBERT, D., and GOLDBERG, L. 1967. BHT oxidase: A liver microsomal enzyme induced by the treatment of rats with butylated hydroxytoluene. Food. Cosmet. Toxicol. 5:481-490

GILLETT, J.W., CHAN, T.M., and TERRIERE, L.C. 1966. Interactions between DDT analogs and microsomal epoxidase systems. J. Agric. Food Chem. 14:540-545

GOOD, E.E., and WARE, G.W. 1969. Effects of insecticides on reproduction in the laboratory mouse: IV. Endrin and dieldrin. Toxicol. Appl. Pharmacol. 14:201-203

GOWDEY, C.W., and STAVRAKY, G.W. 1955. A study of the automatic manifestations seen in acute aldrin and dieldrin poisoning. Can. J. Biochem. Physiol. 33:272-282

GROSS, A. 1974. Statement of testimony at public hearings on suspension of registrations of aldrin/dieldrin (EPA Exhibit S-9). U.S. Environmental Protection Agency, Washington, D.C.

GUERZONI, M.E., DEL CUPOLO, L., and PONTI, I. 1976 [Mutagenic activity of pesticides.] Riv. Sci. Tecnol. Alimenti. Nutr. Um. 6:161-166 (Italian)

GUPTA, P.C. 1975. Neurotoxicity of chronic chlorinated hydrocarbon insecticide poisoning: A clinical and electroencephalographic study in man. Indian J. Med. Res. 63:601-606

HARR, J.R., CLAEYS, R.R., BONE, J.F., and McCORELE, T.W. 1970a. Dieldrin toxicosis: Rat reproduction. Amer. J. Vet. Res. 31: 181-189

HARR, J.R., CLAEYS, R.R., and BENEDICT, N. 1970b. Dieldrin toxicosis in rats: Long-term study of brain and vascular effects. Amer. J. Vet. Res. 31:1853-1862

HART, L.G., and FOUTS, J.R. 1963. Effects of acute and chronic DDT administration on hepatic microsomal drug metabolism in the rat. Toxicol. Appl. Pharmacol. 5:371-385

HART, L.G., SHULTICE, R.W., and FOUTS, J.R. 1963. Simulatory effects of chlordane on hepatic microsomal drug metabolism in the rat. Toxicol. Appl. Pharmacol. 5:371-385

HATHWAY, D.E., and MALLINSON, A. 1964. Chemical studies in relation to convulsive conditions: Effects of Telodrin on the liberation and utilization of ammonia in the rat brain. Biochem. J. 90:51-60

HAYES, W.J., Jr. 1957. Dieldrin poisoning in man. Public Health Reports 72:1087-1091

HAYES, W.J., Jr. 1963. Clinical Handbook on Economic Poisons. Public Health Service Publ. No. 476, U.S. Government Printing Office, Washington, D.C.

HAYES, W.J., Jr., and CURLEY, A. 1968. Storage and excretion of dieldrin and related compounds. Arch. Environ. Health 16:155-162

HEATH, D.F., and VANDEKAR, M. 1964. Toxicity and metabolism of dieldrin in rats. Brit. J. Ind. Med. 21:269-279

HODGE, H.C., BOYCE, A.M., DEICHMANN, W.B., and KRAYBILL, H.F. 1967. Toxicology and no-effect levels of aldrin and dieldrin. Toxicol. Appl. Pharmacol. 10:613-675

HOOGENDAM, I., VERSTEEG, J.P.J., and DE VLIEGER, M. 1962. Electroencephalograms in insecticide toxicity. Arch. Environ. Health. 4:92-100

HOOGENDAM, I., VERSTEEG, J.P.J., and DE VLIEGER, M. 1965. Nine years' toxicity control in insecticide plants. Arch. Environ. Health. 10: 441-448

HUNT, P.F. 1974. Statement of testimony at public hearings on suspension of registrations of aldrin/dieldrin (Shell exhibit S-33). U.S. Environmental Protection Agency, Washington, D.C.

HUNTER, C.G., and ROBINSON, J. 1967. Pharmacodynamics of dieldrin (HEOD): Part I. Ingestion by human subjects for 18 months. Arch. Ind. Health 15:614-626

HUNTER, C.G., ROBINSON, J., and ROBERTS, M. 1969. Pharmacodynamics of dieldrin (HEOD): Part II. Ingestion by human subjects for 18-24 months, and post-exposure for 8 months. Arch. Ind. Health 18:12-21

HUNTER, J., MAXWELL, J.D., STEWART, D.A., WILLIAMS, R., ROBINSON, J., and RICHARDSON, A. 1972. Increased hepatic microsomal enzyme activity from occupational exposure to certain organochlorine pesticides. Nature 237:399-401

HUTSON, D.H. 1976. Comparative metabolism of dieldrin in the rat (CFE) and in two strains of mouse (CFI and LACG). Food Cosmet. Toxicol. 14:577-592

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). 1974. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Vol 5: Some Organochlorine Pesticides. Lyon, France. Pp 31-33, 134-145

JACOBS, P., and LURIE, J.B. 1967. Acute toxicity of the chlorinated hydrocarbon insecticides. S. Afr. Med. J. 41:1147-1150

JAGER, K.W. 1970. Aldrin, Dieldrin, Endrin and Telodrin: An Epidemiological and Toxicological Study of Long-Term Occupational Exposure. Elsevier Publishing Company, Amsterdam, London, New York

JEFFERIES, D.J., and FRENCH, M.C. 1972. Changes induced in the pigeon thyroid by p,p-DDE and dieldrin. J. Wildl. Mgmt. 36:24-30

JENKINS, R.B., and TOOLE, J.F. 1964. Polyneuropathy following exposure to insecticides. Arch. Intern. Med. 113:691-695

JOHNSON, O. 1972. Pesticides 72. Chemical Week, June 21, p 57

KAZANTZIS, G., McLAUGHLIN, A.I.G., and PRIOR, P.F. 1964. Poisoning in industrial workers by the insecticide aldrin. Brit. J. Ind. Med. 21:46-51

KEPLINGER, M.L., DEICHMANN, W.B., and SALA, F. 1970. Effects of combinations of pesticides on reproduction in mice. In Deichmann, W.B., ed., Pesticides Symposia. Halos and Associates, Inc., Miami. Pp 125-138

KHAIRY, M. 1960. Effects of chronic dieldrin ingestion on the muscular efficiency of rats. Brit. J. Ind. Med. 17:146-148

KIMBROUGH, R.D., GAINES, T.B., and HAYES, W.J. 1968. Combined effect of DDT, pyrethrum and piperonyl butoxide on rat liver. Arch. Environ. Health 16:333-341

KIMBROUGH, R.D., GAINES. T.B., and LINDER, R.E. 1971. The ultra-structure of livers of rats fed DDT and dieldrin. Arch. Environ. Health 22:459-467

KITSELMAN, C.H. 1953. Long-term studies on dogs fed aldrin and dieldrin in sublethal dosages with reference to histopathological findings and reproduction. J. Amer. Vet. Med. Assoc. 123:28-30

KUPFER, D. 1967. Effects of some pesticides and related compounds on steriod function and metabolism. Residue Rev. 19:11-30

LINDSTROM, F.T., GILLETT, J.W., and RODECAP, S.E. 1975. Distribution of HEOD (dieldrin) in mammals: II. Some applications of the preliminary model. Arch. Environ. Contam. Toxicol. 3:166-182

LINDSTROM, F.T., GILLETT, J.W., and RODECAP, S.E. 1976. Distribution of HEOD (dieldrin) in mammals: III. Transport--transfer. Arch. Environ. Contam. Toxicol. 4:257-288

LONDON, M., and PALLADE, S. 1964. [Nervous excitability in rats intoxicated with aldrin.] Med. Lavoro. 55:589-597 (French)

LUDWIG, G., WEISS, J., and KORTE, F. 1964. Metabolism of insecticides: VII. Excretion and distribution of aldrin-^{14}C and its metabolites after oral administration for a long period of time. Life Sci. 3:123-130

McCANN, J., and AMES, B.N. 1976. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Discussion. Proc. Nat. Acad. Sci. USA 73:950-954

McCANN, J., CHOI, E., YAMASAKI, E., and AMES, B. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Nat. Acad. Sci. USA 72:5135-5139

MACDONALD, W.E., ANDERSON, W.A.D., BEVILACQUA, M., BLUM, E., and DEICHMANN, W.B. 1972. The tumorigenicity of dieldrin in the Swiss-Webster mouse. Unpublished report (with addendum dated September 1973), University of Miami (included as exhibit to Reuber, 1974, and summarized by Epstein, 1975)

MAJUMDAR, S.K., KOPELMAN, H.A., and SCHNITMAN, J.J. 1976. Dieldrin-induced chromosome damage in mouse bone-marrow and WI-38 human lung cells. J. Hered. 67:303-307

MALECKI, R.A., ALLEN, S.H., ELLISTON, J.O., SADLER, K.C., GOFARTH, W.R., and BASKETT, T.S. 1974. Cottontail reproduction related to dieldrin exposure. U.S. Department of Interior, Bureau of Sport Fisheries and Wildlife, Special Sci. Rep.--Wildlife, No. 177, Washington, D.C.

MARKARYAN, D.S. 1966. [Cytogenic effect of some chloroganic insecticides on the nuclei of mouse bone marrow cells.] Genetika 1:132-137 (Russian)

MARSHALL, T.C., DOROUGH, H.W., and SWIM, H.E. 1976. Screening of pesticides for mutagenic potential using Salmonella typhimurium mutants. J. Agric. Food Chem. 24:560-563

MEDVED', L.I. SPYNU, E.I., and KAGAN, Iu.S. 1964. The method of conditioned reflexes in toxicology and its application for determining the toxicity of small quantities of pesticides. Residue. Rev. 6:42-74

MEHENDALE, H.M., EL-BASSIOUNI, E.A., and MCKINNEY, J.D. 1974. Disposition of aldrin by isolated perfused rabbit lung preparations. Fed. Proc. 33:534 (Abstract)

MENZIE, C. 1969. Metabolism of Pesticides. Department of Interior, Bureau of Sport Fisheries and Wildlife, Special Sci. Rep.--Wildl. No. 127. Washington, D.C. Pp 128-135

MERCK INDEX. 1976. An Encyclopedia of chemicals and drugs. 9th ed. Windholz, M., ed. Merck and Co., Inc., Rahway, N.J. Pp 32, 409-410

MICK, D.L., LONG, K.R., DRETCHEN, J.S., and BONDERMAN, D.P. 1971. Aldrin and dieldrin in human blood components. Arch. Environ. Health 23:177-180

MORGAN, D.P., ROAN, C.C., and PASCHAL, E.H. 1972. Transport of DDT DDE, and dieldrin in human blood. Bull. Environ. Contam. Toxicol. 8:321-326

MORGAN, J.E. and HICKIN, N.E. 1966. An assessment of the health of operators concerned with the conservation of wood in buildings in Great Britain. J. Inst. Wood Sci. 17:27-37

MORIARTY, F. 1975. Exposure and residues. In Moriarty, F., ed., Organochlorine Insecticides: Persistent Organic Pollutants. Academic Press, New York and London. Pp 29-72

MORIARTY, F. 1974. Residues in animals during chronic exposure to dieldrin. Environ. Qual. Safety 3:104-110

MOSS, J.A., and HATHWAY, D.E. 1964. Transport of organic compounds in the mammal: Partition of dieldrin and telodrin between the cellular components and soluble proteins of blood. Biochem. J. 91:384-393

MUELLER, W., WOODS, G., KORTE, F., and COULSTON, F. 1975a. Metabolism and organ distribution of dieldrin-^{14}C in rhesus monkeys after single oral and intravenous administration. Chemosphere 2:93-98

MUELLER, W., NOHYNEK, G., WOODS, G., KORTE, F., and COULSTON, F. 1975b. Comparative metabolism of dieldrin ^{14}C in mouse, rat, rabbit, rhesus monkey and chimpanzee. Chemosphere 2:98-92

MURPHY, D.A., and KORSCHGEN, L.F. 1970. Reproduction, growth and tissue residues of deer fed dieldrin. Wildlife Mgmt. 34:887-903

NAKATSUGAWA, T., ISHIDA, J., and DAHM, P.A. 1965. Microsomal epoxidation of cyclodiene insecticides. Biochem. Pharmacol. 14:1853-1865

NATIONAL CANCER INSTITUTE (NCI). 1977. Bioassay of photodieldrin for possible carcinogenicity. CAS No. 13366-73-9. NCI Carcinogenesis Technical Report Series No. 17. Bethesda, Md.

NATIONAL CANCER INSTITUTE (NCI). 1978a. Bioassay of aldrin and dieldrin for possible carcinogenicity. CAS Nos. 309-00-2 and 60-57-1. NCI Carcinogenesis Technical Report Series No. 21. Bethesda, Md.

NATIONAL CANCER INSTITUTE (NCI). 1978b. Bioassay of dieldrin for possible carcinogenicity. CAS No. 60-57-1. NCI Carcinogenesis Technical Report Series No. 22. Bethesda, Md.

NELSON, E. 1953. Aldrin poisoning. Rocky Mt. Med. J. 50:483-486

OBERHOLSER, K.M., WAGNER, S.R., and GREENE, F.E. 1977. Factors affecting dieldrin metabolism by rat liver microsomes. Drug Metab. Dispos. 5:302-309

OLOFFS, P.C., HARDWICK, D.F., SZETO, S.Y., and MOERMAN, D.G. 1974. DDT, dieldrin, and heptachlor epoxide in humans with liver cirrhosis. Clin. Biochem. 7:297-306

ORTEGA, P., HAYES, W.J., Jr., and DURHAM, W.F. 1956. Pathologic changes in the liver of rats after feeding low levels of various insecticides. Arch. Path. 64:614-622

OTTOLENGHI, A.D., HASEMAN, J.K., and SUGGS, F. 1974. Teratogenic effects of aldrin, dieldrin, and endrin in hamsters and mice. Teratology 9:11-16

PASCHAL, E.H., ROAN, C.C., and MORGAN, D.P. 1974. Evidence of excretion of chlorinated hydrocarbon pesticides by the human liver. Bull. Environ. Contam. Toxicol. 12:547-554

PATEL, T.B., and RAO, V.N. 1958. "Dieldrin" poisoning in man: A report of 20 cases observed in Bombay State. Brit. Med. J. 1: 919-921

PAUL, A.H. 1959. Dieldrin poisoning--report of a case. New Zealand Med. J. 58:393

PECK, A.W. 1970. Impotence in farm workers. Brit. Med. J. 2:690

POLISHUK, Z.W., RON, M., WASSERMANN, M., CUCOS, S., WASSERMANN, D., and LEMESCH, C. 1977a. Pesticides in people: Organochlorine compounds in human blood plasma and milk. Pestic. Monit. J. 10:121-129

POLISHUK, Z.W., WASSERMANN, D., WASSERMANN, M., CUCOS, S., RON, M. 1977b. Pesticides in people: Organochlorine compounds in mother and fetus during labor. Environ. Res. 13:278-84

PREDA, I., MORARU, I., MANOLESCU, A., and RADOVICI, L. 1963. Aspects morphopathologiques de l'intoxication aigue par l'aldrine. Ann. Med. Lég. 43:483-485

PRIBILLA, O. 1963. Akute todliche Dieldrinvergiftung. Arch. Toxikol. 20:61-71

PRINCI, F. 1957. Toxicology, diagnosis and treatment of chlorinated hydrocarbon insecticide intoxications. Arch. Ind. Health 16: 333-336

PRIOR, P.F., and DEACON, P.A. 1969. Spontaneous sleep in healthy subjects in long-term serial electroencephalographic recordings. Electroenceph. Clin. Neurophysiol. 27:422-424

RADOMSKI, J.L., DEICHMANN, W.B., CLIZER, E.E., and REY, A. 1968. Pesticide concentrations in the liver, brain and adipose tissue of terminal hospital patients. Food Cosmet. Toxicol. 6:209-220

REMMER, H. 1967. Die Induktion arzneimittelabbauender Enzyme im endoplasmatischen Retikulum der Leberzelle durch Pharmaka. Dtsch. Med. Wschr. 92:2001-2008

REUBER, M.D. 1974. Statement of testimony at public hearings on cancellation of registrations of aldrin/dieldrin (EPA Exhibit 42) U.S. Environmental Protection Agency, Washington, D.C.

REUBER, M.D. 1975. Histogenesis of hyperplasia and carcinomas of the liver arising around central veins in mice ingesting chlorinated hydrocarbons. Path. Microbiol. 43:287-298

REUBER, M.D. 1976. Histopathology of carcinomas of the liver in mice ingesting dieldrin or aldrin. Tumori 62:463-472

RICHARDSON, A., and ROBINSON, J. 1971. The identification of a major metabolite of HEOD (dieldrin) in human faeces. Xenobiotica 1:213-219

RICHARDSON, L.A., LANE, J.R., GARDNER, W.S., PEELER, J.T., and CAMPBELL, J.E. 1967. Relationship of dietary intake to concentration of dieldrin and endrin in dogs. Bull. Environ. Contam. Toxicol. 2:207-219

ROBINSON, J., RICHARDSON, A., HUNTER, C.G., CRABTREE, A.N., and REES, H.J. 1965. Organo-chlorine insecticide content of human adipose tissue in south eastern England. Brit. J. Ind. Med. 22:220-229

ROBINSON, J., ROBERTS, M., BALDWIN, M., and WALKER, A.I.T. 1969. The pharmacokinetics of HEOD (dieldrin) in the rat. Food Cosmet. Toxicol. 7:317-332

ROSS, C.M. 1964. Sock dermatitis from dieldrin. Brit. J. Derm. 76:494-495

RUBIN, E., HUTTERER, F., and LIEBER, C.S. 1968. Ethanol increases hepatic smooth endoplasmic reticulum and drug-metabolizing enzymes. Science 159:1469-1470

SCHEIN, L.G., and THOMAS, J.A. 1975. Effects of dieldrin on the uptake and metabolism of testosterone-1,2-^{3}H by rodent sex accessory organs. Environ. Res. 9:26-31

SCHEIN, L.G., and THOMAS, J.A. 1976. Dieldrin and parathion interaction in the prostate and liver of the mouse. J. Toxicol. Environ. Health 1:829-838

SCHEIN, L.G., THOMAS, J.A., KLASE, P., and EDWARD, W. 1976. Interaction of carbaryl and dieldrin on the metabolism of [^{3}H] testosterone (^{3}H-T). Toxicol. Appl. Pharmacol. 37:167-168 (Abstract)

SCHWAR, T.G. 1965. Intravenous dieldrin solution administration. J. Forensic Med. 12:142-145

SEIDMAN, H. 1974. Statement of testimony at public hearings on cancellation of registrations of aldrin/dieldrin (EPA Exhibit 49). U.S. Environmental Protection Agency, Washington, D.C.

SHEINMAN, R., and YANNAI, S. 1974. Toxicity of dieldrin to primary culture of rat fetal liver cells and human kidney cell line. Toxicol. Appl. Pharmacol. 30:266-274

SHIRASU, Y., MORIYA, M., KATO, K., FURUHASHI, A., and KADA, T. 1976. Mutagenicity screening of pesticides in the microbial system. Mutat. Res. 40:19-30

SMITH, R.M., CUNNINGHAM, W.L., Jr., VAN GELDER, G.A., and KARAS, G.G. 1976. Dieldrin toxicity and successive discrimination reversal in squirrel monkeys (Saimiri sciureus). J. Toxicol. Environ. Health 1:737-747

SONG, J., and HARVILLE, W.E. 1964. Carcinogenicity of aldrin and dieldrin on mouse and rat liver. Fed. Proc. 23:336 (Abstract)

SPIOTTA, E.J. 1951. Aldrin poisoning in a man. Arch. Ind. Health 4:560-566

SQUIRE, R.A., and LEVITT, M. 1975. Report of a workshop on classification of specific hepatocellular lesions in rats. Cancer Res. 35:3214-3223

STARR, H.G., Jr., and CLIFFORD, N.J. 1971. Absorption of pesticides in a chronic skin disease. Arch. Environ. Health 22:396-400

STERNBERG, S. 1974. Statement of testimony at public hearings on suspension of aldrin/dieldrin (Shell exhibit S-8). U.S. Environmental Protection Agency, Washington, D.C.

STEVENSON, D.E. 1974. Statement of testimony at public hearings on suspension of registrations of aldrin/dieldrin (Shell exhibit S-3). U.S. Environmental Protection Agency, Washington, D.C.

STEVENSON, D.E., THORPE, E., HUNT, P.F., and WALKER, A.I.T. 1976. The toxic effects of dieldrin in rats: A reevaluation of data obtained in a two-year feeding study. Toxicol. Appl. Pharmacol. 36:247-254

STREET, J.C. 1964. DDT antagonism to dieldrin storage in adipose tissue of rats. Science 146:1580-1581

STREET, J.C., and CHADWICK, R.W. 1967. Stimulation of dieldrin metabolism by DDT. Toxicol. Appl. Pharmacol. 11:68-71

STREET, J.C., MAYER, F.L., and WAGSTAFF, D.J. 1969. Ecological significance of pesticide interactions. Ind. Med. 38:91-96

STREET, J.C., WANG, M., and BLAU, A.D. 1966. Drug effects on dieldrin storage in rat tissue. Bull. Environ. Contam. Toxicol. 1:6

SWENBERG, J.A., PETZOLD, G.L., and HARBACH, P.R. 1976. In vitro DNA damage/alkaline elution assay for predicting carcinogenic potential. Biochem. Biophys. Res. Commun. 72:732-738

SYMANSKI, H.J. 1970. A case of fatal occupational aldrin intoxication. In Deichmann, W.B., ed. Pesticides Symposia. Halos and Associates, Medical Books Division, Miami, Fla. P 63 (Abstract)

TAKAHASHI, W., REICHERT, E.R., FUNG, G.C., and HOKAMA, Y. 1976. Acute phase proteins and pesticide exposure. Life Sci. 19:1645-1651

THAN PE, U., and VENKAT RAO, V. Dieldrin spraying operations in the Arakan Region of Burma, with special references to precautions taken against toxic hazards. Bull. WHO 22:582-583

THOMAS, J.A., and LLOYD, J.W. 1973. Organochlorine pesticides and sex accessory organs of reproduction. In Deichmann, W.B., ed. Pesticides and the Environment: A Continuing Controversy. Intercontinental Medical Book Corporation, New York. Pp 43-51

THOMAS, J.A., LLOYD, J.W., SMITH, M.T., MAWHINNEY, M.G., and SMITH, C.G. 1973. Effect of dieldrin on the accumulation and biotransformation of radioactive testosterone by the mouse prostate gland. Toxicol. Appl. Pharmacol. 26:523-531

THOMAS, J.A., SCHEIN, L.G., COLBY, H.D., and CANADY, W.J. 1975. Interaction of dieldrin and parathion on androgen metabolism in the prostate and on hepatic P-450 activity in mice. Pharmacologist 16:229 (Abstract)

THORPE, E. 1974. Statement of testimony at public hearings on suspension of registrations of aldrin/dieldrin (Shell exhibit S-5). U.S. Environmental Protection Agency, Washington, D.C.

THORPE, E. and WALKER, A.I.T. 1973. The toxicology of dieldrin (HEOD): II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, β-BHC and γ-BHC. Food Cosmet. Toxicol. 11:433-441

TRAIN, R. 1974. Opinion of the Administrator, Environmental Protection Agency; Consolidated Aldrin/Dieldrin Hearing (FRL 278-7; FIFRA Dockets Nos. 145, etc.). Federal Register 39:37246-37272

TREON, J.F., and CLEVELAND, F.P. 1955. Toxicity of certain chlorinated insecticides for laboratory animals, with special reference to aldrin and dieldrin. Agric. Food Chem. 3:402-408

TRIOLO, A.J., and COON, J.M. 1966a. Toxicologic interactions of chlorinated hydrocarbon and organophosphate insecticides. J. Agr. Food Chem. 14:549-555

TRIOLO, A.J., and COON, J.M. 1966b. The protective effect of aldrin against the toxicity of organophosphate anticholinesterases. J. Pharmacol. Exp. Ther. 154:613-622

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE (USDHEW). 1969. Report of the Secretary's Commission on Pesticides and their Relationship to Environmental Health. USDHEW, Washington, D.C. Pp 263-442

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1977. Toxic Pollutant Effluent Standards. Standard for Aldrin/Dieldrin, Benzidine, DDT, (DDD, DDE), Endrin and Toxaphene; Final Decision. Federal Register 42: Pp 2588-2621 (January 12, 1977)

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1974. Concentration of HEOD in tissues of experimental animals. Shell Exhibit S-14 at public hearings on suspension of registrations of aldrin/dieldrin. Washington, D.C.

U.S. TARIFF COMMISSION. 1951. Synthetic Organic Chemicals, United States Production and Sales, 1950. Second Series, Report No. 173. Washington, D.C. U.S. Government Printing Office. P 127

VAN DIJCK, P. and VAN DE VOORDE, H. 1976. [Mutagenicity versus carcinogenicity of organochlorine insecticides.] Meded. Fac. Landbouwwet., Rijksunic. Gent 41:1491-1498 (Abstract)

VAN GELDER, G.A., SANDLER, B.E., BUCK, B., MALAND, J.B., and KARAS, G.G. 1969. Behavioral and electrophysiological effects of dieldrin in sheep. Ind. Med. 38:64-67

VERSTEEG, J.P.J., and JAGER, K.W. 1973. Long-term occupational exposure to the insecticides aldrin, dieldrin, endrin, and telodrin. Brit. J. Ind. Med. 30:201-202

VIRGO, B.B., and BELLWARD, G.D. 1975a. Effect of dietary dieldrin on the liver and drug metabolism in the female Swiss-Vancouver mouse. Can. J. Physiol. Pharmacol. 53:903-911

VIRGO, B.B., and BELLWARD, G.D. 1975b. Effects of dietary dieldrin on reproduction in the Swiss-Vancouver (SWV) mouse. Environ. Physiol. Biochem. 5:440-450

WAKELING, A.E., SCHMIDT, T.J., and VISEK, W.J. 1972. Evidence for influence of dieldrin on binding of 5α-dihydrotestosterone in the rat ventral prostate. Fed. Proc. 31:725 (Abstract)

WAKELING, A.E. and VISEK, W.J. 1973. Insecticide inhibition of 5α-ηdihydrotestosterone binding in the rat ventral prostate. Science 181:659-661

WALKER, A.I.T., STEVENSON, D.E., ROBINSON, J., THORPE, E., and ROBERTS, M. 1969. The toxicology and pharmacodynamics of dieldrin (HEOD): Two-year oral exposures of rats and dogs. Toxicol. Appl. Pharmacol. 15:345-373

WALKER, A.I.T., THORPE, E., and STEVENSON, D.E. 1972. The toxicology of dieldrin (HEOD): I. Long-term oral toxicity studies in mice. Food Cosmet. Toxicol. 11:415-432

WALKER, E.M., Jr., GALE, G.R., ATKINS, L.M., and GADSDEN, R.H. 1977. Some effects of dieldrin and mirex on Ehrlich ascites tumor cells in vivo and in vitro. Arch. Environ. Contam. Toxicol. 5:333-341

WANG, C.M., NARAHASHI, T., and YAMADA, M. 1971. The neurotoxic action of dieldrin and its derivatives in the cockroach. Pestic. Biochem. Physiol. 1:84-91

WEINIG, E., MACHBERT, G., and ZINK, P. 1966. Über den Nachweis des Dieldrins bei einer Dieldrinvergiftung. Arch. Toxikol. 22:115-124

WHETSTONE, R.R. 1964. Chlorocarbons and chlorohydrocarbons: Chlorinated derivatives of cyclopentadiene. In Kirk, R.E., and Othmer, E.F., eds., Encyclopedia of Chemical Technology, 2nd ed. New York, John Wiley and Sons 5:240-252

WOLFE, H.R., DURHAM, W.F., and ARMSTRONG, J.F. 1963. Health hazards of the pesticides endrin and dieldrin: Hazards in some agricultural uses in the Pacific Northwest. Arch. Environ. Health 6:458-464

WOLFE, H.R., DURHAM, W.F., and ARMSTRONG, J.F. 1967. Exposure of workers to pesticides. Arch. Environ. Health 14:622-633

WONG, D.T., and TERRIERE, L.C. 1965. Epoxidation of aldrin, isodrin, and heptachlor by rat liver microsomes. Biochem. Pharmacol. 14: 375-377

WRIGHT, A.S. 1974. Statement of testimony at public hearings on suspension of registrations of aldrin/dieldrin (Shell exhibit S-6). U.S. Environmental Protection Agency, Washington, D.C.

ZAVON, M.R. 1960. Dieldrin intoxication. J. Am. Med. Assn. 173:190

ZAVON, M.R., and HAMMAN, R.E. 1961. Human experience with dieldrin in malaria control programs. Am. J. Pub. Health 51:1026-1034

☆ U S GOVERNMENT PRINTING OFFICE 1978— 757-141/1838

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
ROBERT A. TAFT LABORATORIES
4676 COLUMBIA PARKWAY CINCINNATI OHIO 45226

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE $300

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF H.E.W.
HEW 396

DHEW (NIOSH) Publication No. 78-201