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,

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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

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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

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.

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.

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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

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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 metabol-

ites were identified in their urine. Of the total urinary excretion, 85%

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

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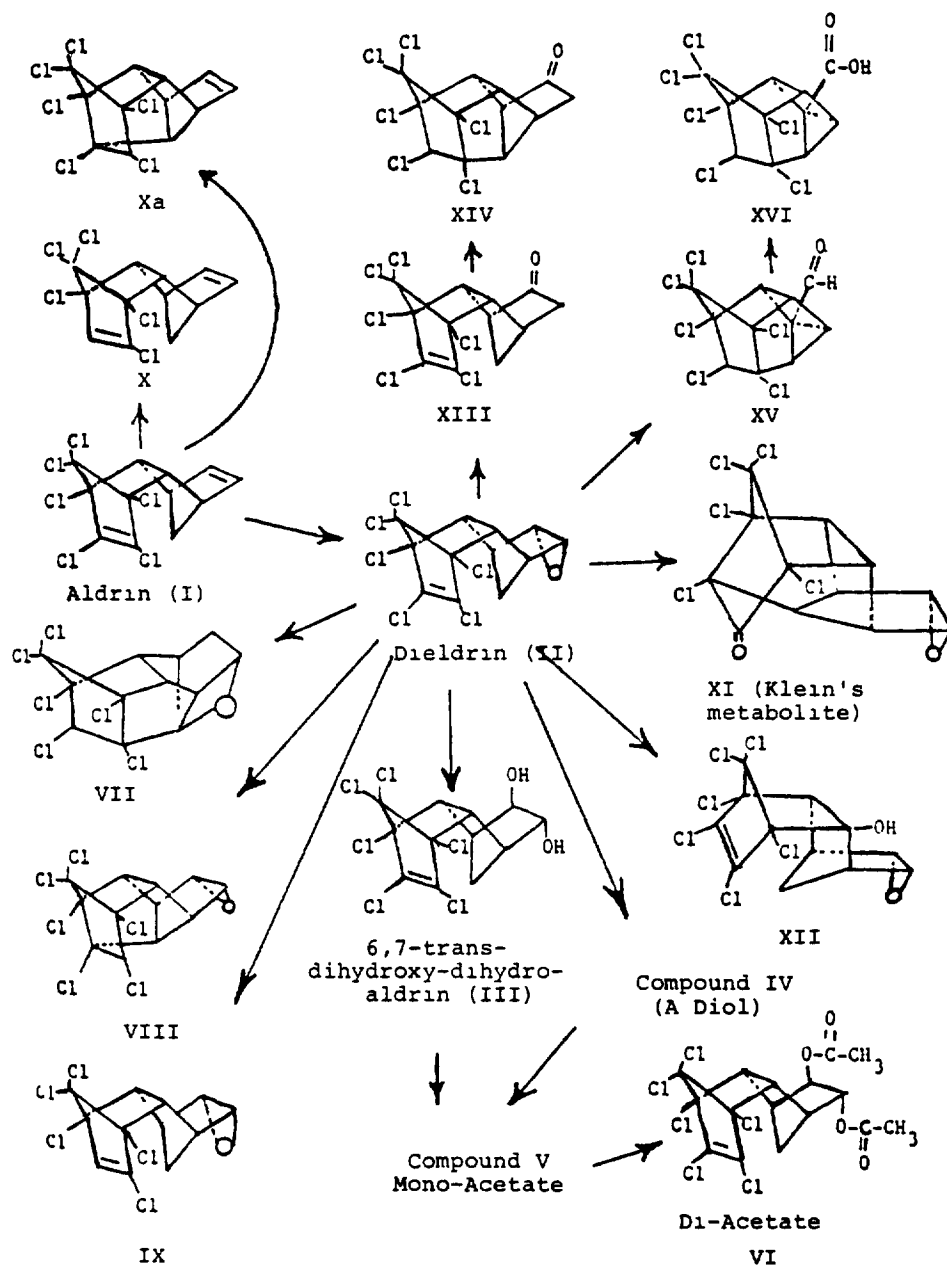
consisted of one of the two enantiomorphic isomers of trans-6,7-dihydroxy-dihydroaldrin ("trans-aldrin-diol" or "trans-dihydro-aldrindiol"; compound III) (Jager 1970).

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

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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

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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 erythro-

cytes and the blood plasma but not in the leucocytes, the platelets,

or the erythrocyte stroma. The distribution between plasma and red cells

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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}.
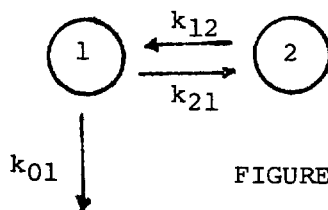

FIGURE 1.5.2 (Moriarty 1975)

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:

$$Q_1 = X_1 e^{-\lambda_1 t} + X_2 e^{-\lambda_2 t}$$

$$Q_2 = X_3 e^{-\lambda_1 t} + X_4 e^{-\lambda_2 t}$$

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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 impli-

citly 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).

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FIGURE 1.5.3 (Moriarty 1975)

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

$$C = 689 - 234e^{-0.400t} - 470e^{-0.00774t}$$

———— Line derived from equation with
two exponential terms

- - - - Line derived from equation with
one exponential term

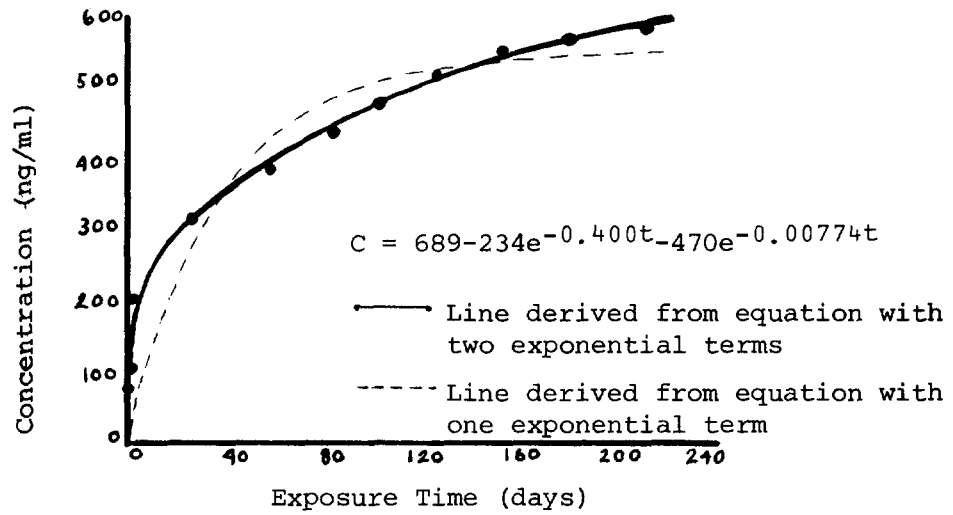Concentration (ng/ml)

Exposure Time (days)

FIGURE 1.5.4 (Moriarty 1975)

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

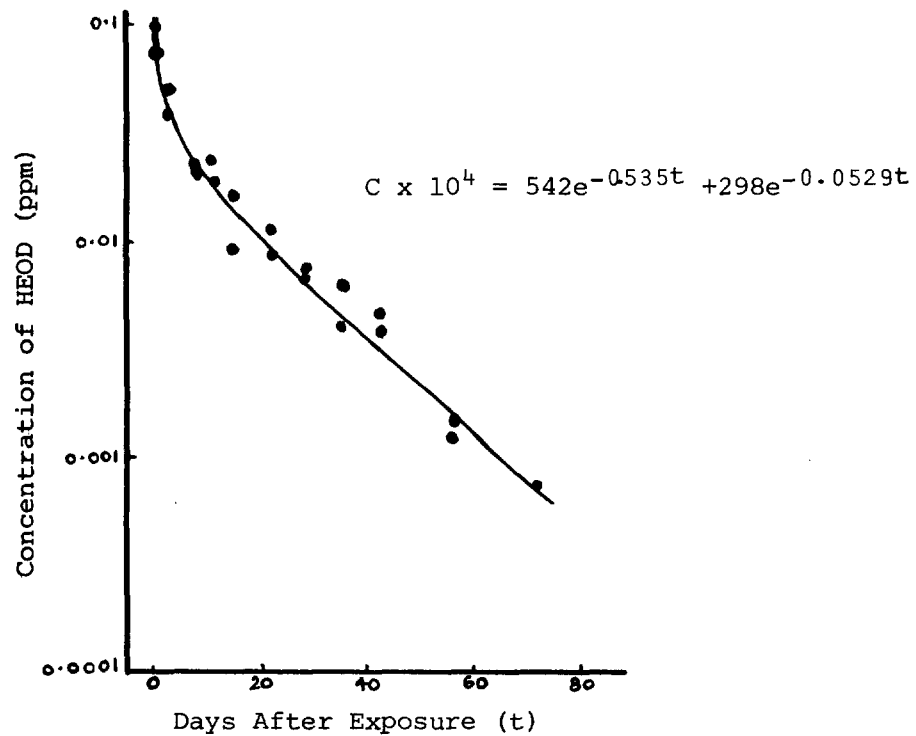(Data fitted to an equation with two exponential terms)

$$C \times 10^4 = 542e^{-0.535t} + 298e^{-0.0529t}$$

Concentration of HEOD (ppm)

Days After Exposure (t)

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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

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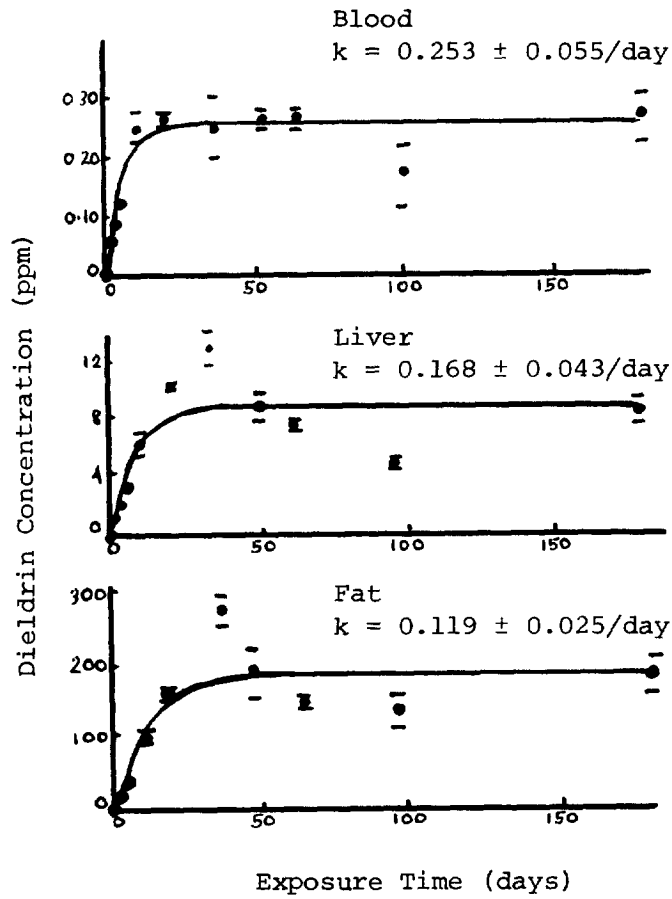
(Data fitted to equations with one exponential
term; horizontal bars indicate the standard
error of the means)

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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
		0.01	0.00026	0.0038	0.386	1.18	0.0245	(Tunstall
		0.1	0.0033	0.0075	1.01	1.20	0.0344	Laboratory)
		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 Workmen, Pernis***		0.006	0.00013	(0.0011)**	0.17	0.03	0.0053	de Vlieger et al 1968
1964		0.535	0.01146	0.069	(10.9)	(1.81)	(0.34)	
Formulators		0.791	0.01694	0.102	(16.1)	(2.68)	(0.50)	
pre-1960		(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 di-

vided 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), amino-

pyrine, 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 radio-labeled 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

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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.