1. Extent of Exposure

1.1 Identity

"DDT" is the common name approved by the International Standards Organization for the technical product in which 1,1,1-trichloro-2,2-di-(4-chlorophenyl)ethane (p,p'-DDT) is the predominant component (Table 5.1). Technical DDT is a mixture of isomers containing 65-80% p,p'-DDT and up to 14 other components, including o,p'-DDT (15-21%); p,p'-DDD (up to 4%); 1-(p-chlorophenyl)-2,2,2-trichloroethanol (up to 1.5%); and traces of o,o'-DDT and bis(p-chlorophenyl)sulfone. Up to 1% m,p'-DDT may be present in some samples of technical DDT (IARC 1974; Tomatis et al 1971, 1972).

Samples of technical DDT in Europe and analyzed by Tomatis et al (1971, 1972) contained 0.1-0.5% p,p'-DDE, but 4.08% p,p'-DDE was found in another sample of technical DDT (WHO 1977). One sample of U.S. technical DDT was reported to have contained 15% p,p'-DDE (Peraino et al 1975). The apparently wide variation in the content of p,p'-DDE in technical DDT is of considerable importance, because DDE has a long biologic half-life (see Section 1.5).

Technical DDT has been formulated in almost every conceivable form including solutions in xylene or petroleum distillates, emulsifiable concentrates, water-wettable powders, granules, aerosols, smoke candles, charges for vaporizers, and lotions. Aerosols and other household formulations often are combined with synergized pyrethrins (WHO 1977).

The physical and chemical properties of DDT as well as synonyms and trade names are summarized in Table 5.2, and synonyms and trade names are given in the Table 5.3. The structures of DDT, other compounds that occur in technical DDT, and their metabolites are presented in Table 5.1 (WHO 1977). The structure of the o,p' and m,p' compounds can be inferred from those of the p,p' isomers.

1.2 Discovery and Introduction

Technical DDT is synthesized by condensing chloral hydrate with chlorobenzene in the presence of sulfuric acid, a process first discovered by Zeidler in 1874. However, it was 1939 before the insecticidal applications of DDT were identified, by Muller and his coworkers (IARC 1974). By 1943, low-cost production methods had been developed, and commercial production had begun (IARC 1974).

1.3 Changing Patterns of Use and Production

Before 1945, all of the DDT produced in the USA was used or allocated by the military services for various medical and public health uses. Early in 1945 it became available for experimental work in agriculture, and it was commercially available in limited quantitites early in the autumn of the same year. The results were so spectacular that use in the United States increased until 1959, and in response to a demand for exports production continued to increase until about 1963. Even before 1963 some restrictions were placed on its use in the United States, mainly to minimize residues in food and in the feed of animals that produce milk and meat.

Another important factor reducing the use of DDT was the increasing resistance of pests. After a peak in 1959, the use of DDT in the United States declined steadily, except for its major remaining use on cotton (Table 1.3.1, USEPA 1975).

During 1970-72, over 80% of the DDT used in the United States was applied to cotton crops, with most of the remainder being used on peanut and soybean crops (See Table 1.3.2, USEPA 1975). In June 1972 the U.S. Environmental Protection Agency (EPA) canceled all crop uses of the pesticide. Public health and quarantine uses and exports were exempted. Subsequently, EPA granted temporary registrations of DDT for use against the pea leaf weevil (1973, 1974) and the Douglas-fir tussock moth (1974). In 1975, however, the state of Louisiana was denied a request for emergency use of 2.25 million pounds of DDT to control the tobacco budworm on cotton. The EPA Administrator found "no substantial new evidence which may materially affect the 1972 order with respect to the human cancer risk posed by DDT, the environmental hazards of DDT and the need to use DDT on cotton" (USEPA 1975). In November 1976 EPA issued Toxic Pollutant Effluent Standards prohibiting all direct discharge of DDT into ambient waters (USEPA 1976).

Outside the United States, DDT is still used extensively for agriculture and vector control in many tropical countries (WHO 1977). Although many pests of public health importance have become resistant to DDT in some or all of their range, resistance in vectors of malaria has been less widespread (WHO 1977). Accordingly the use of DDT for

TABLE 1.3.1

DOMESTIC PRODUCTION, CONSUMPTION, AND EXPORTS OF DDT IN THE UNITED STATES, 1950-1972

Year	Production (1,000 lb)	Domestic Consumption (1,000 lb)	Exports (1,000 lb)
1950	67,320	57,638	7,898
1951	97,875	72,686	-
1952	115,717	70,074	32,288
1953	72,802	62,500	31,410
1954	90,712	45,117	42,743
1955	110,550	61,800	50,968
1956	137,747	75,000	54,821
1957	129,730	71,000	61,069
1958	131,862	66,700	69,523
1959	156,150	78,682	76,369
1960	160,007	70,146	86,611
1961	175,657	64,068	103,696
1962	162,633	67,245	106,940
1963	187,782	61,165	113,757
1964	135,749	50,542	77,178
1965	140,785	52,986	90,414
1966	141,349	46,672	90,914
1967	103,411	40,257	81,828
1968	139,401	32,753	109,148
1969	123,103	30,256	82,078
1970	59,316	25,457	69,550
1971	63,134*	18,000*	45,134
1972	57,427*	22,000*	35,424

*EPA estimates

Adapted from USEPA 1975

TABLE 1.3.2

SUMMARY OF 1970 DDT DOMESTIC SALES IN THE UNITED STATES

Item	DDT (lb)
Total DDT sold	11,966,196
Types of DDT formulations sold	
Emulsifiable sprays	10,318,915
Dust	1,506,186
Wettable powder	127,350
Granular	13,736
Use	
Cotton	10,277,258
Soybeans	603,053
Peanuts	937,901
Other	158,853
States	
Alabama	1,139,256
Arkansas	1,193,175
California	2,500
Delaware	21,400
Florida	74,888
Georgia	1,600,556
Louisiana	2,712,347
Maryland	133
Mississippi	3,731,876
Missouri	11,895
North Carolina	426,810
New Jersey	2,352
New Mexico	6,948
New York	2,612
Oklahoma	865
Oregon	200
Pennsylvania	33
South Carolina	1,016,286
Tennessee	207,104
Texas	97,422
Virginia	13,282
Washington	1,000

Adapted from USEPA 1975

malaria control has tended to remain stable. On a worldwide basis, the principal agricultural use of DDT now is on cotton (Goldberg 1975). Estimates of current and future worldwide agricultural use of DDT for the protection of cotton and other crops are given in Tables 1.3.3 and 1.3.4. Table 1.3.5 summarizes data compiled by the Food and Agriculture Organization (FAO) of the United Nations on the use of DDT in various countries between 1961 and 1975.

The demand for DDT as a residual spray against adult mosquitos in antimalarial programs for the decade 1971-81 has been predicted to be 470,000 metric tons or an average of 47,000 metric tons/year, a figure similar to that predicted for agricultural uses. The estimated requirements for six regions of the world (Africa, America, Southeast Asia, Europe, the Eastern Mediterranean, and the Western Pacific) are given in Table 1.3.4. The estimated annual demands tend to increase toward a maximum in 1977, with a subsequent decrease until 1981, the last year of the forecast, when the predicted requirement is 29,000 metric tons (Goldberg 1975).

Production of DDT in the United States between 1950 and 1972 is summarized in Table 1.3.1. U.S. production reached a maximum of about 188 million pounds in 1963. By the late 1960's DDT output had declined by about one-third, for example, to 123 million pounds in 1969. Then production declined precipitously, to an estimated 60 million pounds/year in the early 1970's (Table 1.3.1).

TABLE 1.3.3

ESTIMATED ANNUAL AGRICULTURAL USE OF DDT (METRIC TONS/YEAR)

Region	In Cotton-Producing Countries		In Non-Cotton-Producing Countries	Total
	Cotton	Other Crops	Crops Other Than Cotton	
1973				
Central America	7,580	2,550	383	10,513
South America	18,800	6,200	1,180	26,180
Africa	2,186	729	605	3,520
Asia	5,568	1,523	410	7,501
Total	34,134	11,002	2,578	47,714
1971-81				
Latin America	13,560	1,510	270	15,340
Africa	13,100	1,410	1,170	15,680
Asia	33,500	3,350	905	37,755
Total	60,160	6,270	2,345	68,775

Adapted from Goldberg 1975, derived from data of F.W. Whittemore

TABLE 1.3.4

ESTIMATED DDT REQUIREMENTS (IN METRIC TONS) FOR ANTIMALARIA PROGRAMS

WHO Region	Formulation*	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	Total 1972-81
African	Technical	62	80	90	100	113	114	112	112	112	112	112	1,059
	75% wdp	632	655	697	791	816	829	884	884	884	884	884	8,209
	25% wdp	100	120	133	145	159	175	166	166	166	166	166	1,564
American	Technical	557	558	649	601	560	517	517	505	431	430	354	5,121
	75% wdp	11,286	11,328	11,121	10,427	9,697	8,625	8,425	7,725	6,759	6,564	5,325	85,995
Southeast Asian	75% wdp	16,435	21,425	20,608	21,578	22,388	25,040	30,983	26,348	17,766	18,312	12,710	217,157
	50% wdp	8,000	6,000	6,000	6,000	6,000	5,400	6,000	6,000	6,000	6,000	6,000	59,400
European	75% wdp	700	980	980	880	880	880	200	200	200	200	200	5,600
	50% wdp	500	500	500	500	500	300	300	300	300	300	300	3,800
Eastern Mediterranean	Technical	31	31	31	31	31	31	31	31	31	31	31	310
	75% wdp	14,090	9,084	8,614	8,454	8,454	8,106	7,936	7,426	7,211	7,171	7,171	79,627
Western Pacific	75% wdp	1,235	1,962	2,360	2,438	2,515	3,028	3,375	3,215	2,785	2,610	2,390	26,678
	25% ec	365	367	524	724	715	715	715	715	515	515	515	6,020
Totals	Technical	650	669	771	733	704	662	660	648	574	573	497	6,490
	75% wdp	44,379	45,434	44,380	44,568	44,750	46,507	51,803	45,798	35,604	35,741	28,680	423,266
	25% wdp, ec	465	487	657	869	874	890	881	881	681	681	681	7,584

*wdp = water dispersible powder; ec = emulsion concentrate

Adapted from Goldberg 1975

TABLE 1.3.5

CONSUMPTION OF DDT IN REPORTING COUNTRIES
(in thousands of kg, ie, metric tons)

Country	Year			
	1961-65	1973	1974	1975
Africa				
Burundi	-*	25	23	-
Chad	1	1	-	-
Egypt	2,221	109	109	-
Ivory Coast	-	-	52	-
Madagascar	20	67	-	-
Niger	-	-	2	-
Rwanda	44	94	103	88
Sudan	-	604	650	-
Swaziland	-	2	2	-
North and Central America				
Canada	561	-	-	-
El Salvador	725	-	-	1,133
Mexico	-	8,754	4,096	4,129
U.S.	26,853	478	-	-
South America				
Argentina	231	522	-	-
Bolivia	-	69	-	-
Chile	-	544	290	26
Colombia	350	-	-	-
Uruguay	16	10	-	-
Asia				
Burma	43	18	69	-
Cyprus	124	-	-	-
India	1,770	2,700	4,000	4,360
Iran	-	492	-	-
Israel	138	10	10	-
Japan	723	-	-	-
Jordan	14	1	7	6
Kampuchea	11	-	-	-
Laos	4	-	-	-
Pakistan	-	-	128	-

TABLE 1.3.5 (Continued)

Europe				
Austria	63	19	18	7
Czechoslovakia	360	198	90	10
Germany (Federal Republic)	248	9	-	-
Hungary	3,100	6	2	-
Italy	1,313	2,462	2,019	-
Poland	2,305	72	50	-
Portugal	-	21	-	-
Switzerland	-	-	10	10

*Dash indicates no report was available but does not necessarily indicate that no DDT was used.

Adapted from FAO 1977

Use in the United States peaked near 79 million pounds in 1959, and declined to about 18 million pounds in 1971 (22 million pounds in 1972) and to nearly zero after 1972 (USEPA 1975). The amount exported lagged behind domestic consumption until 1958 and did not reach the maximum until 1963. From 1958 onward, the quantity of DDT exported continued to exceed domestic consumption (USEPA 1975).

For the decade 1959-69, the United States was one of the principal world sources of DDT, and production varied between 105 million pounds and 188 million pounds/year. These statistics were assessed by a US group in 1970 (NAS 1971), which concluded that during this period the annual total world production was probably no more than 1.5 times that of the United States. An annual 220 million pounds was taken as a world production figure, and the integrated world production (the total amount since production began) was estimated to be 4,410 million pounds. Much of the pesticide manufactured in the United States was exported; in 1968, 110 of the 140 million pounds manufactured were sold to foreign countries. Of the 83 million pounds exported in 1969, about 31 million pounds were for agricultural purposes and 51 million pounds for public health purposes (Goldberg 1975). About half of the agricultural use was in the southern hemisphere. In 1969, the United States exported DDT (in millions of pounds) for agricultural uses to the following areas: North America, 10; South America, 10; Asia, 4; and Africa, 6 (Goldberg 1975).

In the early 1950's, 13 companies were involved in the manufacture of DDT in the United States. Among the last firms to cease producing DDT were Geigy Corporation (1966), Allied Chemical (1969), Olin Corporation (1969), Diamond Shamrock Corporation (1970), and Lebanon Chemicals (1971). Only one company, Montrose Chemical Corporation of California, still produces DDT in the United States. The U.S. International Tariff Commission did not release production figures for DDT for 1975 (USITC 1977), but the plant capacity had been given as 85 million pounds/year (IARC 1974).

Little published information is available on the production of DDT in countries overseas. Producers of technical DDT in Europe in 1972 or 1973 were as follows (with number of producers in parentheses): France (3), Italy (5), Spain (10), and the United Kingdom (1). However, as of 1972, there were reportedly only two major producers left in Europe. DDT is also known to be produced in: Brazil, where production was 3 million kg in 1969 and is believed to be increasing; Israel, where the total capacity in 1970 was 350 thousand kg; and India, where production for 1971-72 was 4 million kg and was expected to increase. Japan produced 4.6 million kg in 1970 (IARC 1974).

1.4 Exposure

Generally, exposure to DDT is greatest for manufacturers and formulators, moderate for agricultural applicators, less for the general population, and least for special groups whose location or

practices minimize their exposure. However, for brief intervals the exposure of agricultural applicators may exceed anything that good industrial practice would permit (WHO 1977).

Occupational exposure to DDT is reflected quantitatively by the concentration of DDT and DDE in blood and fat and by the concentration of DDA in urine (See Section 1.5.4). Urinary excretion of DDA may be increased for several days after a single exposure to DDT by inhalation or percutaneous absorption (Wolfe et al 1970). In a study of formulators, urinary excretion of DDA was increased for only 1 day after exposure (Table 1.4.1, Edmundson et al 1972a). Similar results were obtained in a study of aircraft sprayers (Edmundson et al 1972b). These results indicated that DDA levels in the urine reflect exposure in the immediately preceding period. DDT levels in blood similarly reflect recent exposure, whereas DDE levels in blood and fat reflect cumulative exposure over a larger period (Edmundson et al 1972c; Section 1.5.4).

Indications of the exposures of workers manufacturing and formulating DDT and of those applying it have been determined in several studies either by direct measurements of the amount reaching the skin or indirectly from DDT levels in blood (Edmundson et al 1972c) or body fat (Hayes et al 1956) or from DDA levels in urine (Durham et al 1965, Laws et al 1967, Ortelee 1958).

Potential dermal exposure was estimated by direct methods of measurement at 84 mg/hr for outdoor spraying (Hayes 1959), 1,755

TABLE 1.4.1

DDT, DDE, AND DDA LEVELS IN THE BLOOD OF SEVEN PESTICIDE FORMULATORS
(South Flordia, 1966-67)

Operator's Age (years)	Experience (months)	Amount Formulated (pounds)	DDT (%) in Formulation		Hours Exposed	Personal Protection	DDT (ppb) in Blood		DDE (ppb) in Blood		DDA (ppb) in Urine	
			Initial	Final			Initial	30 hr	Initial	30 hr	Initial	6-14 hr
31	6	4,050	50	10	3	None	<7	8*	3	6	22	28
25	20	2,500	50	10	3	"	<7	9**	8	11	28	30
28	32	4,050	50	10	3	"	34	54	31	48	9	41
26	24	1,200	50	25	1	Mask, part-time	45	69	20	85	33	197
28	42	1,200	50	25	1	" " "	33	59	25	102	N.D.***	108
32	90	1,200	50	25	1	" " "	43	58	29	93	38	476
28	86	1,200	50	25	1	None	67	129	70	250	54	377

* Highest level, 21 ppb, reached in 6 hr
** Highest level, 22 ppb, reached in 6 hr
***N.D. = not detected

Adapted from Edmundson et al 1972a

mg/hr for indoor spraying (Wolfe et al 1959, 1967), 2.2 mg/hr during forest spraying (Wassermann et al 1960), and 524.5 mg/hr for formulating plant workers (Wolfe and Armstrong 1971, IARC 1974). Estimates of potential respiratory exposure ranged from 0.11 mg/hr for outdoor spraying to 7.1 mg/hr for indoor spraying (Wolfe et al 1959), with values of 4.92 mg/hr for forest spraying (Wassermann et al 1960) and 14.1 mg/hr for formulating plant workers (Wolfe and Armstrong 1971, IARC 1974). These direct measurements of exposure indicate only the amounts of DDT reaching the skin or the lungs and do not necessarily provide a measure of absorption into the body.

Several investigators have emphasized that the use of household insecticides and the concentration of DDT in house dust are positively correlated with the storage of DDT in people (Radomski et al 1968; Davies et al 1969a, 1975; Edmundson et al 1970). A study of dust in 16 urban households, 4 farm households, and 8 households in which at least one member was a pesticide formulator failed to reveal a statistically significant correlation between the level of various pesticides in dust and in the serum of poeple living in the homes. There were striking individual examples of workers whose homes contained high concentrations of the compounds they used professionally and other examples in which there was circumstantial evidence relating household dust residues to body burden (Starr et al 1975). Undoubtedly,

household insecticides have been an important source of intake of DDT in some instances. It is not clear whether the relevant absorption involves mainly the inhalation of dust, the contamination of food within the home, or even dermal absorption.

Table 1.4.2 summarizes measurements of DDT and DDE in the body fat of people in the United States subject to various types of exposure. Two groups of applicators had fat concentrations only 2-3 times those of the general population and comparable to those of volunteers who ingested 3.5 mg daily. However, two formulators had fat concentrations 20 and 100 times higher than those of the general population. The data in Table 1.4.1 indicate that blood levels of DDT and DDE were 4-10 times higher in formulators than in the general population and tended to increase with the number of years of employment (Edmundson et al 1972a). Similarly, blood levels of DDT and DDE and urinary levels of DDA were 2-10 times higher in aircraft sprayers than those in the general population and increased with the duration of exposure (Table 1.4.3, Edmundson et al 1972b).

In a community where DDT was used extensively in agriculture and as a thermal fog for municipal mosquito control, the concentrations of DDT and DDE in the serum of 3 groups of 28 or more men (applicators, farmworkers, and controls) were measured bimonthly throughout 1968. In each sampling period, applicators tended to have the highest storage levels, and the controls the lowest levels.

TABLE 1.4.2

CONCENTRATION OF DDT-DERIVED MATERIAL IN BODY FAT OF PEOPLE IN THE UNITED STATES WITH EXPOSURE TO DDT

Occupation or Other Exposure Circumstance	Year	No. of Samples	DDT (ppm)	DDE as DDT (ppm)	Total as DDT (ppm)	DDE as DDT (% of total)
None*	Before 1942	10	None detected		-	-
Environmental	1954-56	110	6.0	9.6	15.6	62
"	1961-62	28	4.3	8.6	12.9	67
Applicators	1954-56	30	14.0	21.1	35.1	60
"	1961-62	14	10.7	24.1	34.8	69
Formulator	1951	1	122	141	263	54
"	1954	1	648	483	1,131	43
Meat abstainers	1955-56	16	2.3	3.6	5.9	61
Eskimos	1960	20	0.8	2.2	3.0	73
Volunteers given 3.5 mg/d orally	1953-54	2	30	3.9	34	11
"	1957-58	6	50	21	71	30
Volunteers given 35 mg/d orally	1953-54	6	234	24	258	9
"	1957-58	6	281	40	321	12

*Died before DDT commonly used

Adapted from Hayes 1975

TABLE 1.4.3

LEVELS OF BLOOD DDT AND DDE AND URINARY DDA
IN FOUR AIRCRAFT SPRAYERS

Operator Age (years)	Length of Experience (years)	DDT (ppb)	DDE (ppb)	DDA (ppb)	Range in Study (ppb) DDT	DDE	DDA
47	2	<4	13	7	<4	10-13	3-18
37	3	17	15	0			
	3.5	15	12	0			
	4	16	19	22	11-13	16-33	9-37
51	4	20	28	0			
	5	19	42	17	19-49	22-72	17-72
60	12	23	48	0			
	13	34	20	0			
	14	56	37	19	56-87	37-66	19-80

Adapted from Edmundson et al 1972b

Storage in applicators was about four times greater than in the controls. However, all three groups showed a sixfold increase in serum levels of DDT and metabolites between April and August. The seasonal increase was attributed to mosquito control and indoor uses of DDT, although community use of DDT was only 0.2% of that on farms (Perron and Barrentine 1970).

Laws et al (1967) measured DDT and DDE in the fat and serum and DDA in the urine of 35 workers with long-term exposure to DDT in a manufacturing plant. Group mean residue levels, which are summarized in Table 1.4.4, were only slightly higher than those in the formulators and applicators listed in Tables 1.4.1 and 1.4.3, ranging from 4 to 20 times those in the general population. The highest values reported were 647 ppm in fat, 2,200 ppb in serum, and 2.67 ppm in urine. From the previously estabished relationships between intake, storage, and excretion (see Section 1.5.4), the authors estimated that the workers had an intake of DDT in the range 3.6-18 mg/man/day (Table 1.4.5).

Poland et al (1970) sampled tissues from 18 workers at the same factory and reported tissue residues somewhat higher than detected by Laws et al (1967). The mean residue levels were 307 ppm in adipose tissue (30% DDE) and 1,360 ppb in serum (37% DDE).

Ortelee (1958) measured DDA levels in the urine of 20 formulators (from 2 plants) and of 20 workers in a manufacturing plant. The men involved had worked with DDT for periods of 0.5-8 years. DDA levels

TABLE 1.4.4

MEASURES OF EXPOSURE TO DDT IN WORKERS EMPLOYED FOR 11-19 YEARS IN A DDT MANUFACTURING PLANT

Exposure Category	No. of Men	Total DDT* in Fat (ppm)	% as DDE	Total DDT* in Serum (ppb)	% as DDE	DDA in Urine (ppm)
High	20	263±34	35	740±110	38	1.27±.43
Medium	12	130±16	48	360± 70	40	0.60±.12
Low	3	98±24	45	540±130	36	0.41±.24
Total	35	204±23	36	590± 70	38	0.97±.11
General population	13	13± 8	43	73± 1	38	-

*DDT plus metabolites; mean ± SD

Adapted from Laws et al 1967

in the urine in workers classified as having slight, moderate, and heavy exposure averaged 0.53, 1.5, and 2.8 ppm, respectively, corresponding to estimated intakes of about 14, 30, and 42 mg/man/day, up to 200 times the exposure of the general population. The highest residues (averaging 2.4 ppm DDA in the urine) were found in the manufacturing workers.

Two reported studies indicated the extent of exposure of spraymen involved in malaria control projects (WHO 1973). In Brazil, 202 spraymen who had been exposed for 6-13 years were examined; analysis of blood from a small number of men showed mean serum levels of DDT and metabolites about 3 times higher than those in controls. In a study in India, the serum levels of DDT and metabolites in 100 spraymen averaged 1.273 ppm, 7.5 times higher than those in controls. These levels in malaria control workers are similar to the levels found in manfacturing workers (Laws et al 1967, Poland et al 1970), and the daily intakes would be expected to be similar, in the range 3.6-18 mg/man/day.

WHO (1977) summarized a study conducted in the USSR of workers exposed to DDT, polychloropinene (toxaphene), and BHC (Table 1.4.6). Total residues in blood were analyzed by a total chloride method. Organochlorine levels (expressed on a lipid basis) were reported to be as high as 38.4 ppm in the blood of a pilot and as high as 19.5 ppm in the blood of warehousemen (WHO 1977). However, only a small number of individuals (8/134 pilots, 13/133 technicians, and 3/55

TABLE 1.4.5

ESTIMATED MEAN DAILY INTAKE OF DDT
BY WORKERS IN A DDT PLANT

Exposure Category	No. of Men	Intake of DDT (mg/man/day) Based On:	
		DDT in Fat	DDA in Urine
High	20	18	17.5
Medium	12	6.2	8.4
Low	3	3.6	6.3

Adapted from Laws et al 1967

TABLE 1.4.6

ORGANOCHLORINE RESIDUES IN BLOOD OF OCCUPATIONALLY EXPOSED WORKERS

Group	No. in Group	Percentage of Samples in Various Concentration Ranges (ppm in lipids)					
		0	0.2-0.9	1.0-3.0	4-9	10-50	>50
Controls	47	21.3	44.7	23.4	10.6	0	0
Pilots*	134						
Group A		19.1	35.3	25.0	14.7	5.9	0
Group B		22.9	27.1	40.6	7.4	2.0	0
Technicians*	133						
Group A		26.2	16.4	39.3	8.2	9.9	0
Group B		39.4	31.2	25.7	3.7	0	0
Agricultural workers**	55	13.0	43.5	31.0	7.0	2.0	3.5

*Results of investigation at the time of work for Group A and before work or a few months after termination for Group B
**Studied only during work

Adapted from WHO 1977

agricultural workers) had residue levels outside the range observed in controls.

The potential for human exposure to DDT and related pesticides under various circumstances of use has been measured directly by Wolfe and others (see Table 1.4.7). The figures for potential dermal exposure to DDT range from 30 to 1,750 mg/hr, which is far higher than occupational exposure assessed indirectly from tissue residues. Presumably only a fraction of the DDT contacting the skin is actually absorbed into the body. The direct measurements of potential respiratory exposure are more in accord with tissue residue measurements and indicate that potential exposure to DDT is particularly high in indoor house spraying (Table 1.4.7).

1.5 Metabolism and Pharmacokinetics

1.5.1 Metabolism in Mammals

The metabolism of DDT has been reviewed by Hayes (1965) and IARC (1974) and in more detail by Menzie (1969). Figure 1.5.1 shows the principal metabolic pathways, and Table 1.5.1 lists the principal metabolites with the conventional abbreviations that are used in this report.

DDT is metabolized in a variety of mammalian species, initially by reductive dechlorination or dehydrochlorination of the trichloroethane moiety to yield either DDD or DDE (Menzie 1969, Datta et al 1964, Peterson and Robison 1964). These and other metabolic reactions are common to the p,p' and the o,p' isomers of DDT. However,

TABLE 1.4.7

SUMMARY OF PUBLISHED STUDIES ON POTENTIAL OCCUPATIONAL EXPOSURE TO DDT AND RELATED COMPOUNDS USED BY DIRECT METHODS

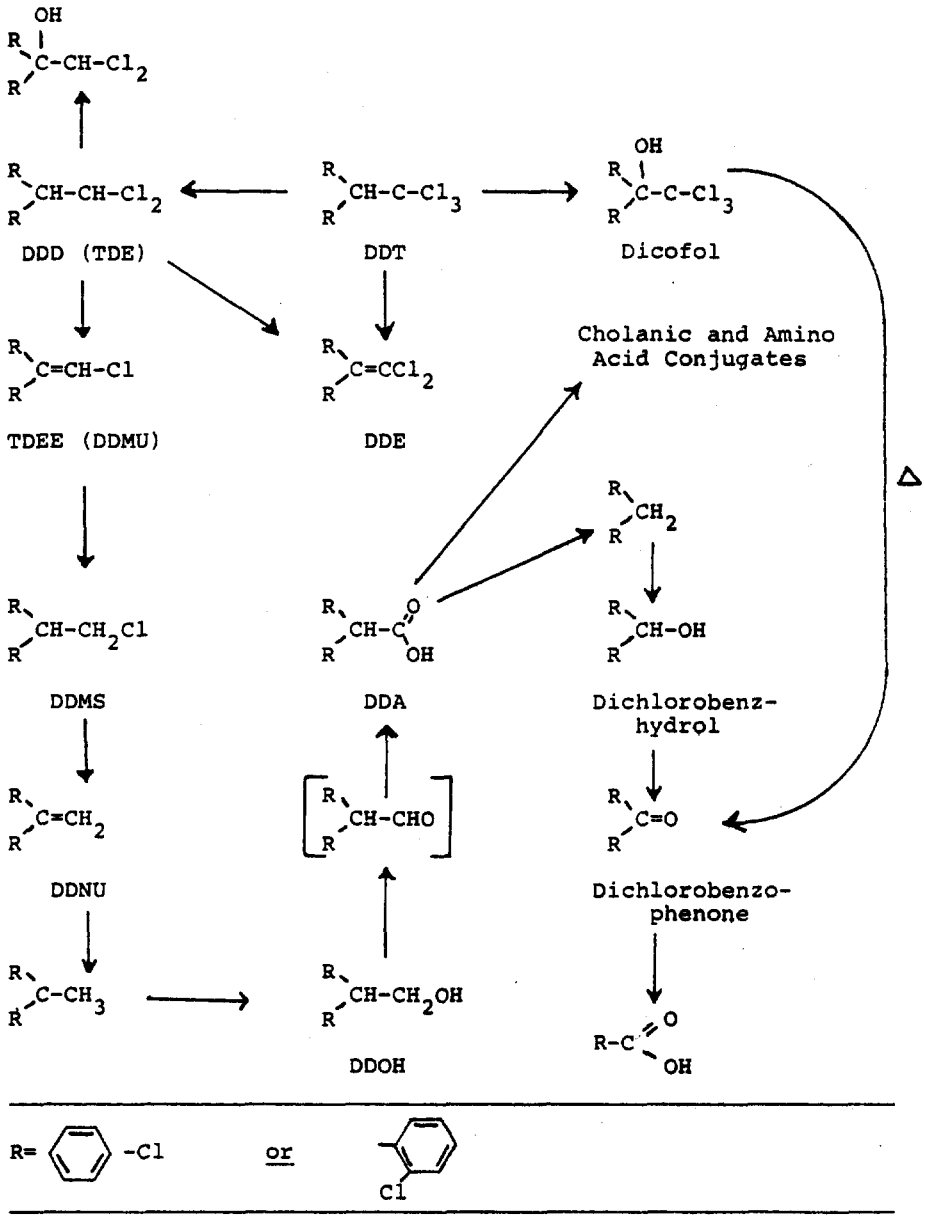
Compound	Activity	Exposure*			Reference
		Respiratory (mg/hr)	Dermal (mg/hr)	Total (% toxic dose/hr)	
DDT	Indoor house spraying		543	>0.31	Hayes 1959
DDT	Indoor house spraying	3.4**	1,755	1.02	Wolfe et al 1959
DDT	Outdoor house spraying		84	>0.05	Hayes 1959
DDT	Outdoor house spraying	0.11	243	0.14	Wolfe et al 1959
DDT	Spraying forests	4.92	212	0.15	Wasserman et al 1960
Dicofol	Air blast spraying fruit orchards	0.05	30.5	0.04	Wolfe et al 1972
Dilan	Air blast spraying fruit orchards	0.26	75.1	0.02	Wolfe et al 1972
Perthane	Air blast spraying fruit orchards	0.14	59.4	<0.01	Wolfe et al 1972

*Measured by direct methods
**7.1 mg/m^3

Adapted from Hayes 1975

Figure 1.5.1 Metabolic Pathways of DDT in Mammals

See Table 1.5.1 for chemical names abbreviated in this figure.



p,p'-DDE is the most stable metabolite and is retained most strongly in mammalian tissues, whereas o,p'-DDE is much less persistent (Hayes 1975, Menzie 1969). As demonstrated in rats, further conversion of DDE in the liver proceeds slowly via DDMS and DDMU to DDNU (Datta 1970). Further metabolism of DDNU seems to occur primarily in the kidney (Datta and Nelson 1970) to yield DDOH, DDCHO, and DDA (IARC 1974). DDA is readily excreted in the urine, either free or as a conjugate with cholanic acid or amino acids in the bile (Durham et al 1963, Pinto et al 1965). A similar metabolic pathway has been demonstrated for o,p'-DDD (Reif and Sinsheimer 1975).

DDT is converted to DDD by the intestinal flora of rats (Mendel and Walton 1966) and in the rumen of cattle (McCully et al 1966). DDCN is formed under anaerobic conditions in the environment (Albone et al 1972, Jensen et al 1972) but is not known to be formed in vivo.

Phenolic metabolites of DDT have also been reported (Morello 1965). Phenolic metabolites of o,p'-DDD in rats include 3-hydroxy, 4-hydroxy, and 3,4-dihydroxy derivatives of o,p'-DDA (Reif and Sinsheimer 1975). Two phenolic metabolites of p,p'-DDE were identified in bile of wild seals (Jansson et al 1975). Also, at least two methyl sulfone derivatives of p,p'-DDE were detected at relatively high levels (about 4 ppm) in the fat of seals (Jensen and Jansson 1976). These stable methyl sulfone derivatives have

TABLE 1.5.1

ABBREVIATIONS USED FOR DDT AND METABOLITES

p,p'-DDT:	1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane
p,p'-DDD (TDE):	1,1-dichloro-2,2-bis(p-chlorophenyl)ethane
p,p'-DDE:	1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene
p,p'-DDMU (TDEE):	1-chloro-2,2-bis(p-chlorophenyl)ethylene
p,p'-DDMS:	1-chloro-2,2-bis(p-chlorophenyl)ethane
p,p'-DDNU:	2,2-bis(p-chlorophenyl)ethylene
p,p'-DDOH:	2,2-bis(p-chlorophenyl)ethanol
p,p'-DDCHO:	2,2'-bis(p-chlorophenyl)acetaldehyde
p,p'-DDA:	2,2'-bis(p-chlorophenyl)acetic acid
p,p'-DCBP:	4,4'-dichlorobenzophenone
p,p'-DDCN:	bis(p-chlorophenyl)acetonitrile

Note: o,p' isomers of most of these components and metabolites are known in addition to the more abundant p,p' derivatives

TABLE 1.5.2

LIVER RESIDUES OF DDT, DDE, AND DDD IN ANIMALS EXPOSED TO TECHNICAL DDT BY LONG-TERM FEEDING

Species	Dietary Level (ppm)	Feeding Period (ppm)	Residues in Liver (ppm)			Reference
			DDT	DDE	DDD	
Mouse	250	42	25	13	25	IARC 1974
Hamster	250	42	4.2	0.08	4.2	IARC 1974
Rat	200	90	4	1.5	-	Dale et al 1962

high gas-chromatographic retention times and may have been missed by other investigators.

Species differ in the relative importance of the two initial pathways of metabolism of DDT. After long-term feeding of DDT, the ratio of liver residues of DDE:DDD was 0.5 in mice, versus 0.02 in hamsters (Gingell and Wallcave 1974, IARC 1974). DDE comprised about 20% of all DDT-derived residues in the livers of rats and mice fed DDT, versus 2% in hamsters (Tomatis et al 1971, Dale et al 1962, Gingell and Wallcave 1974; See Table 1.5.2). When fed DDT, rhesus monkeys did not store DDE at detectable amounts in fat or liver, although they did excrete DDA; they stored DDE when fed DDE (Durham et al 1963). This suggests that rhesus monkeys metabolize DDT to DDA almost exclusively via the DDD pathway.

1.5.2 Metabolism in Humans

After absorption into the human body, DDT is metabolized primarily to DDD, which is further degraded and readily excreted in the urine as DDA (Roan et al 1971). DDT is also slowly converted, by dehydrochlorination, into DDE (Morgan and Roan 1971), which is retained in adipose tissue (Hayes 1975, USEPA 1975). No increase in the urinary excretion of DDA was noted after the oral ingestion of DDE by human volunteers; however, such an increase was observed after ingestion of DDD or DDT (Roan et al 1971). The observations by Laws et al (1967) of occupationally exposed people indicate that urinary levels of DDA are correlated with the levels

of exposure to technical DDT and that DDT and its metabolites are stored in adipose and other tissues. These results suggest that humans metabolize DDT via DDD to DDA and excrete it as DDA or conjugates thereof, whereas they do not metabolize DDE at a measurable rate and retain it whether it is itself ingested or is produced in the body by metabolism.

Urine from patients given o,p'-DDD for therapeutic treatment of adrenal cortical carcinoma was analyzed for water-soluble metabolites. After a methylation procedure, methyl derivatives of o,p'-DDA and its glycine conjugate were identified. In addition, methyl derivatives of 3-mono-, 4-mono-, and 3,4-dihydroxy-o,p'-DDA were identified, indicating hydroxylation of the ortho-substituted chlorophenyl ring, probably via epoxidation at the 3,4 position (Reif et al 1974).

1.5.3 Pharmacokinetics in Experimental Animals

Data on the pharmacokinetics of DDT in mammals were summarized by USDHEW (1969) and Hayes (1975) and were critically reviewed by Moriarty (1975). Several mathematical models have been proposed and used to describe experimental data (USDHEW 1969, Moriarty 1975).

DDT is absorbed into the body by ingestion and dermal absorption (Hayes 1965, 1975) and by inhalation (Atallah and Dorough 1975). After absorption it is circulated through the body in the blood and is transferred in and out of other organs throughout the body (USDHEW 1969). Substantial quantities are also absorbed into

the lymphatic system and are presumably circulated through the body in lymph (Hayes 1965, Sieber 1976). In rats given a single oral dose at 150 mg/kg, DDT concentrations in the brain reached a peak after about 12 hours and declined thereafter, while concentrations in fat continued to rise (Dale et al 1963). After oral administration of radiolabeled DDT, levels of radioactivity in liver, kidney, heart, brain, lung, and spleen reached a peak after 48 hours, followed by a redistribution to fat (Yoshioka 1974). Results of earlier studies had suggested that DDT administered orally reaches peak levels in blood within 2 hours and in other organs within 2-5 hours (Hayes 1965).

When DDT is administered in large oral doses, some of it is not absorbed but is passed unaltered into the feces. However, after administration by other routes, only traces of unmetabolized DDT are found in the feces and most of the excreted material is in the form of metabolites (Hayes 1965). In bile-duct-cannulated rats, 65% of the injected dose of radiolabeled DDT was recovered as metabolites in the bile, 2% in the urine, and only 0.3% in the feces. Only traces of unmetabolized DDT and DDE were found in bile (Jensen et al 1957).

Data on the uptake and excretion of DDT and its metabolites have been fitted to "one-compartment" models, in which the whole body is treated as a single unit (USDHEW 1969). However, "two-compartment" models, in which the blood and the remainder of the

body are treated separately, are usually needed to fit experimental data (Moriarty 1975). Figure 1.5.2 shows a two-compartment model for the loss of DDT from the body after exposure has stopped. In this model, compartment 1 is identified with the blood, and compartment 2 with the remainder of the body (Moriarty 1975).

Table 1.5.3 summarizes data on the loss of DDT from animals after exposure has ceased, as fitted to one- and two-compartment models by Moriarty (1975). "Half-lives" for loss of DDT from the body range from 15 to 131 days with the exception of a longer half-life for a minor component of the residues in rhesus monkeys, which Moriarty regarded as questionable.

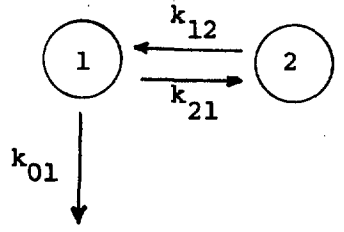
Data on the rate of uptake of DDT by mammals are very scanty. The only set of data sufficient for analysis is that of Laug et al (1950) for technical DDT in rats. When analyzed with a one-compartment model it yielded rate constants (λ) in the range 0.0066-0.013 for females and 0.025-0.026 for males, corresponding to half-times for uptake of 53-105 days and 26-27 days, respectively (Moriarty 1975). These rate constants for uptake are higher than those for loss, at least for males (Table 1.5.3).

No data on the pharmacokinetics of DDD or DDE in experimental animals that are adequate for numerical analysis were found.

The compartmental models of Moriarty (1975) and other assume implicity that the physiologic state of the animals remains constant for times much longer than λ^{-1}. Accordingly, they predict

FIGURE 1.5.2 (Moriarty 1975)

TWO-COMPARTMENT MODEL FOR LOSS OF DDT FROM THE BODY



If Q_1 is the amount of DDT in the blood, the model predicts:

$$Q_1 = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$$

where A_1 and A_2 are constants and λ_1 and λ_2 depend in a complex way on the rate constants k_{12}, k_{21}, and k_{01}. These equations provide a good description of data on loss of DDT from animals (Figures 1.5.3, 1.5.4).

FIGURE 1.5.3 (Moriarty 1975)

DECREASE IN CONCENTRATION OF DDT IN
STEERS' OMENTAL FAT AFTER EXPOSURE
(Data fitted to an equation with two exponential terms)

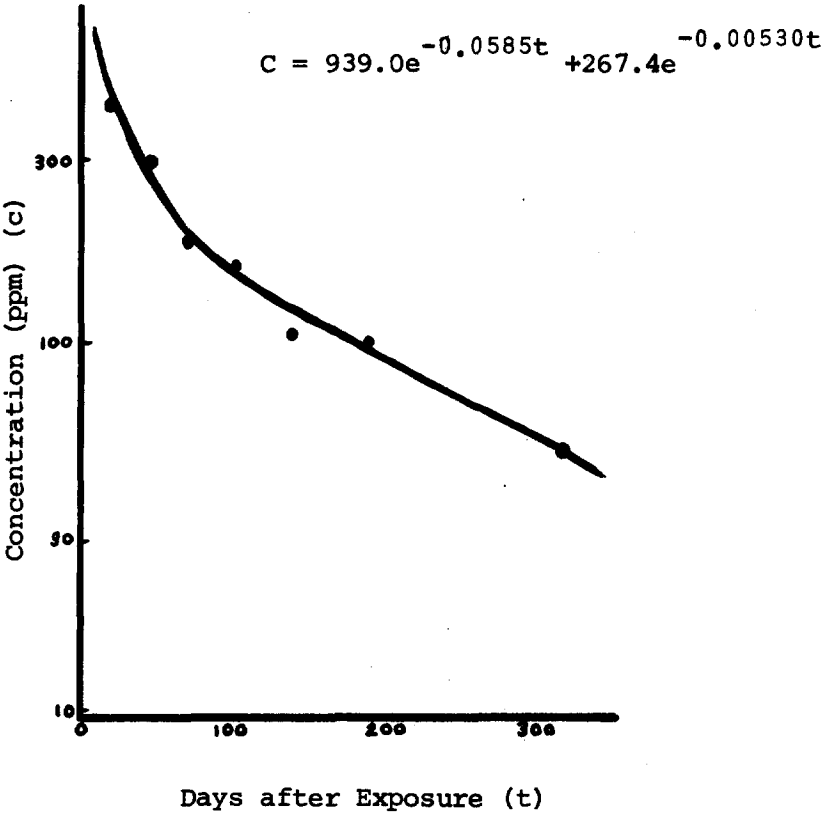


FIGURE 1.5.4 (Moriarty 1975)

DECREASE IN THE DDT CONCENTRATION IN THE BODY FAT OF RHESUS MONKEYS AFTER EXPOSURE ENDED

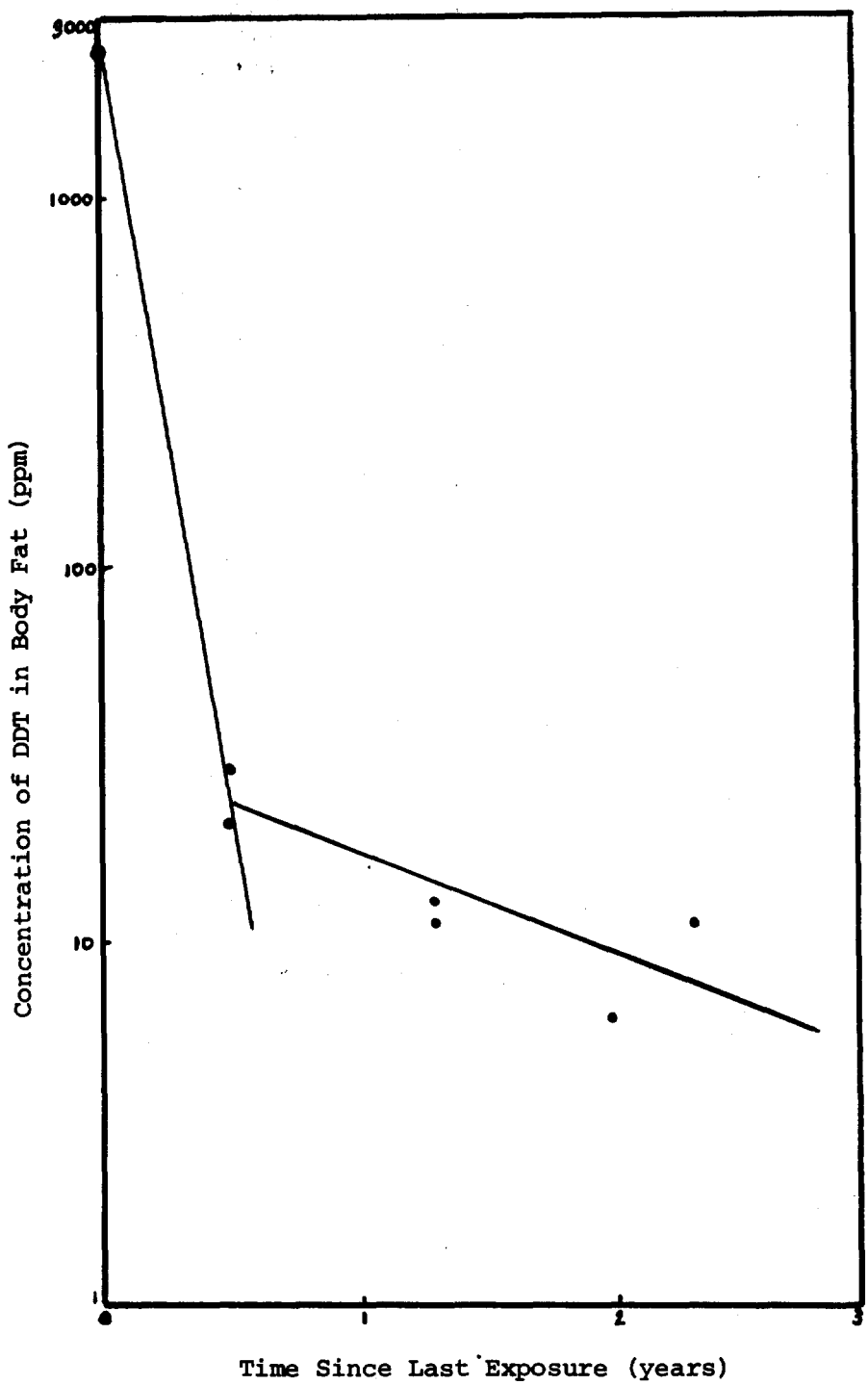


TABLE 1.5.3

LOSS OF DDT BY MAMMALS AFTER CESSATION OF EXPOSURE

Species	Sex	Tissue	Initial Level (ppm)	Period	No. of Experimental Terms*	λ (d^{-1})	$t_{\frac{1}{2}}$ (days)
Rat	M	Fat	896	425	1	0.012	57
Rat	M	Fat	540	425	1	0.012	59
Rat	M	Fat	234	243	1	0.0097	72
Rat	M	Fat	115	425	1	0.0066	105
Rat	F	Fat	3,028	243	1	0.011	61
Rat	F	Fat	4,190	425	1	0.0085	82
Rat	F	Fat	459	425	1	0.0065	107
Rat	F	Fat	337	425	1	0.0093	75
Dog	-	Fat	1,295**	243	1	0.017	42
Dog	-	Fat	539	121	1	0.040	17
Cattle	M	Fat	419	308	2	0.058	12
						0.0053	131
Rhesus monkey	-	Fat	2,650***	1,065	2	0.022	32
						0.00046	1,520
Bat (Pipistrelle)	-	Whole body	ca. 5***	125	1	0.046	15

*Equal to the number of compartments in the model
**Fed technical DDT + aldrin
***Fed p,p'-DDT; all others fed technical DDT

Adapted from Moriarty 1975

an ultimate steady state concentration of DDT (and metabolites) in the tissues of animals constantly exposed. However, the few long-term studies available do not demonstrate convincingly that a true steady state is reached (Figures 1.5.5, 1.5.6).

For other chlorinated hydrocarbons, especially dieldrin, data show that no true steady state is reached (Moriarty 1974, 1975). Thus the data in the literature should be interpreted as describing "quasi-steady" states reached after long-term exposure, and they may underestimate the potential for storage after exposure of more than 1-2 years.

Data for a number of species suggest that residues in tissues increase with increasing dietary concentrations but not in direct proportion to rates of intake (Figures 1.5.7-1.5.9, USDHEW 1969, Hayes 1975, Moriarty 1975). These data have been evaluated and summarized by Hayes (1975). Additional data for mice are summarized in Table 1.5.4. Storage factors for three species at medium exposure rates (about 1 mg/kg/day or 10 ppm in the diet) are shown in Table 1.5.5. A "storage factor" is defined as the concentration of DDT in the fat of an animal after long-term exposure divided by the concentration in the diet. These storage factors range between 2 and 24. Although data for other species refer only to higher dose ranges, storage factors for dogs, cattle, and hamsters appear to be lower than those for rats and mice in comparable conditions (Figure 1.5.8, Gingell and Wallcave 1974).

FIGURE 1.5.5 (USDHEW 1969)

INCREASE OF THE CONCENTRATION OF DDT IN THE BODY FAT OF MALE RATS FED TECHNICAL DDT AT 5 PPM IN THEIR DIET FOR 6 MONTHS

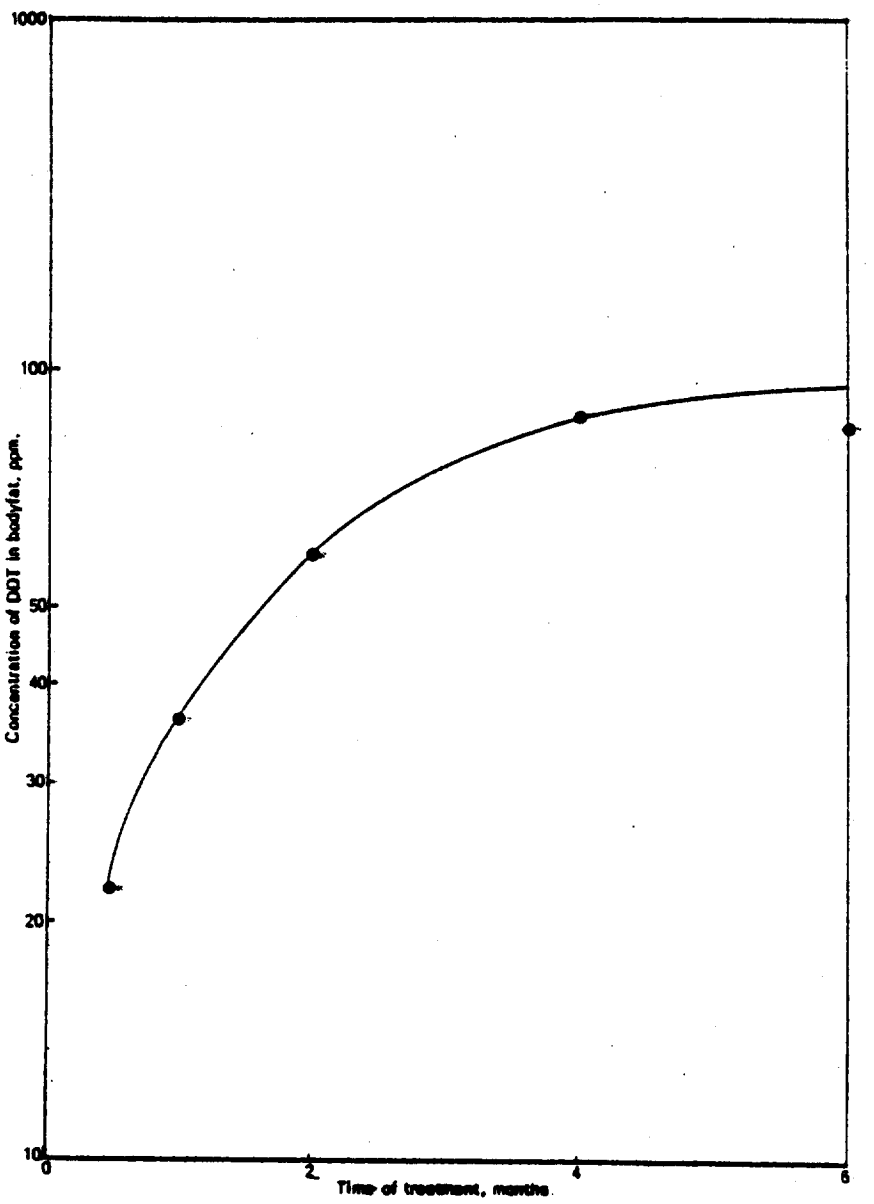


FIGURE 1.5.6 (USDHEW 1969)

INCREASE OF THE CONCENTRATION OF DDT IN THE BODY FAT OF RHESUS MONKEYS WITH CONTINUING EXPOSURE TO DDT

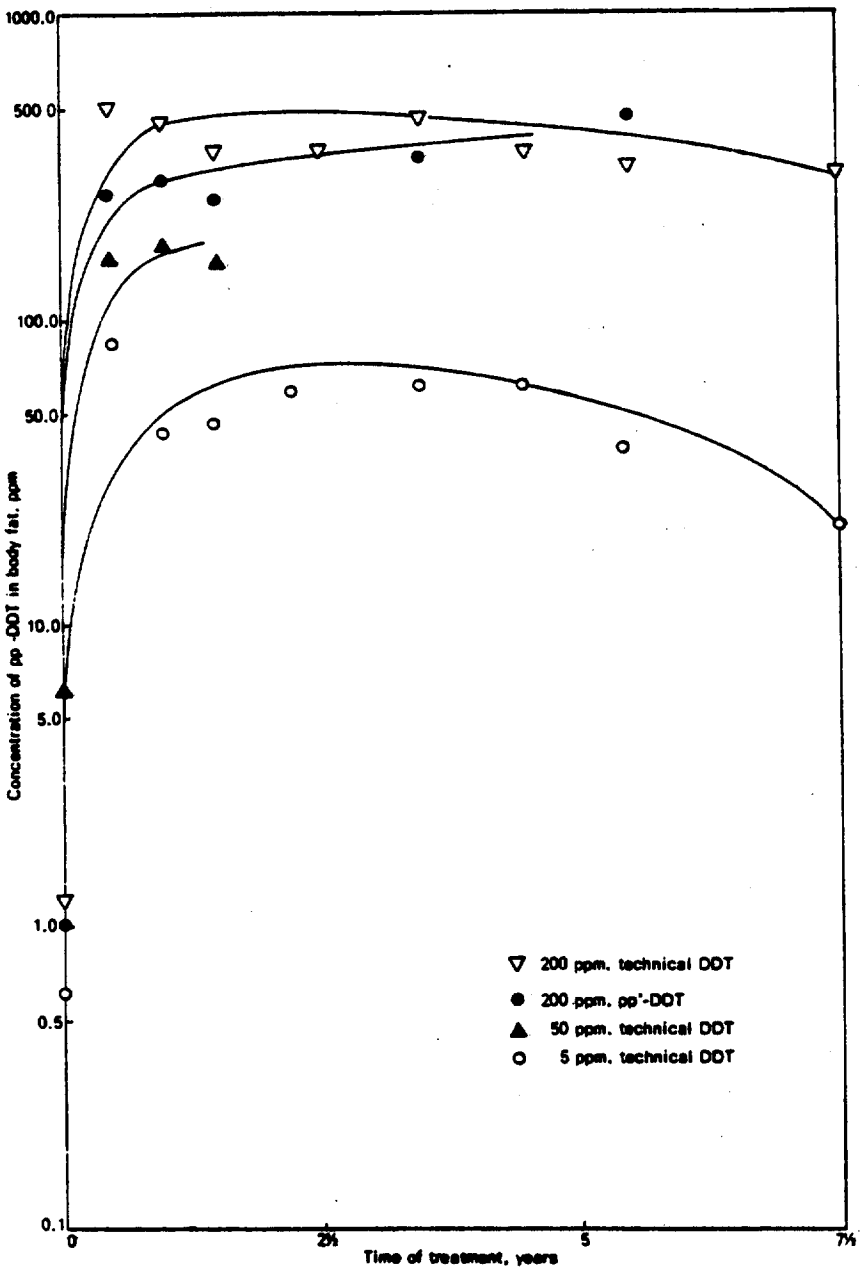


FIGURE 1.5.7 (USDHEW 1969).

STORAGE OF DDT IN THE TISSUES OF RATS FED DIETS CONTAINING DDT AT DIFFERENT CONCENTRATIONS

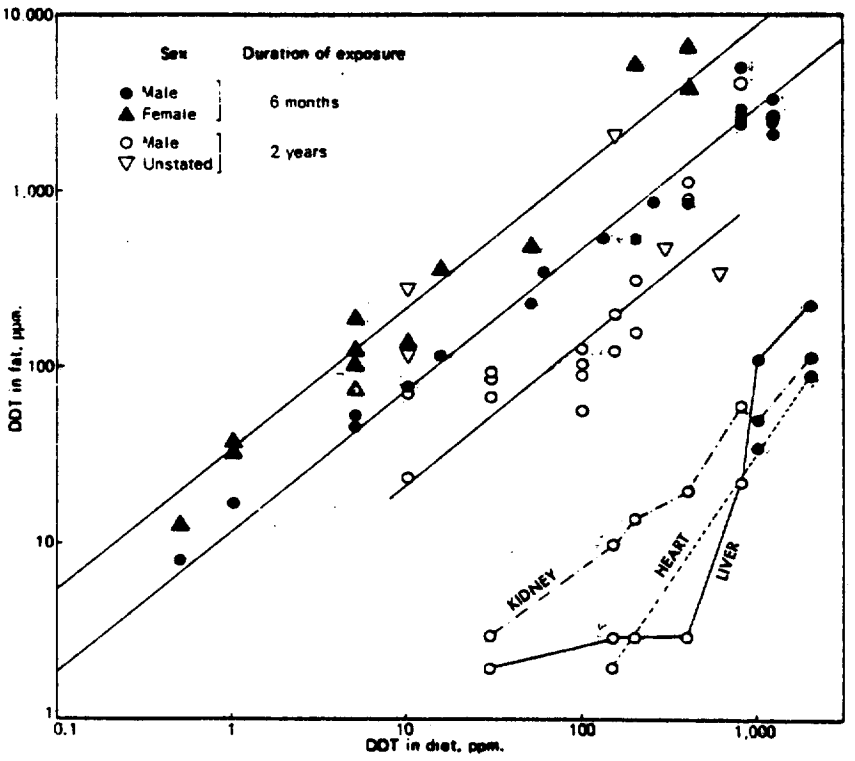


FIGURE 1.5.8 (USDHEW 1969)

STORAGE OF DDT IN THE ADIPOSE TISSUE OF SEVERAL SPECIES OF ANIMALS GIVEN DDT AT DIFFERENT DAILY DOSES

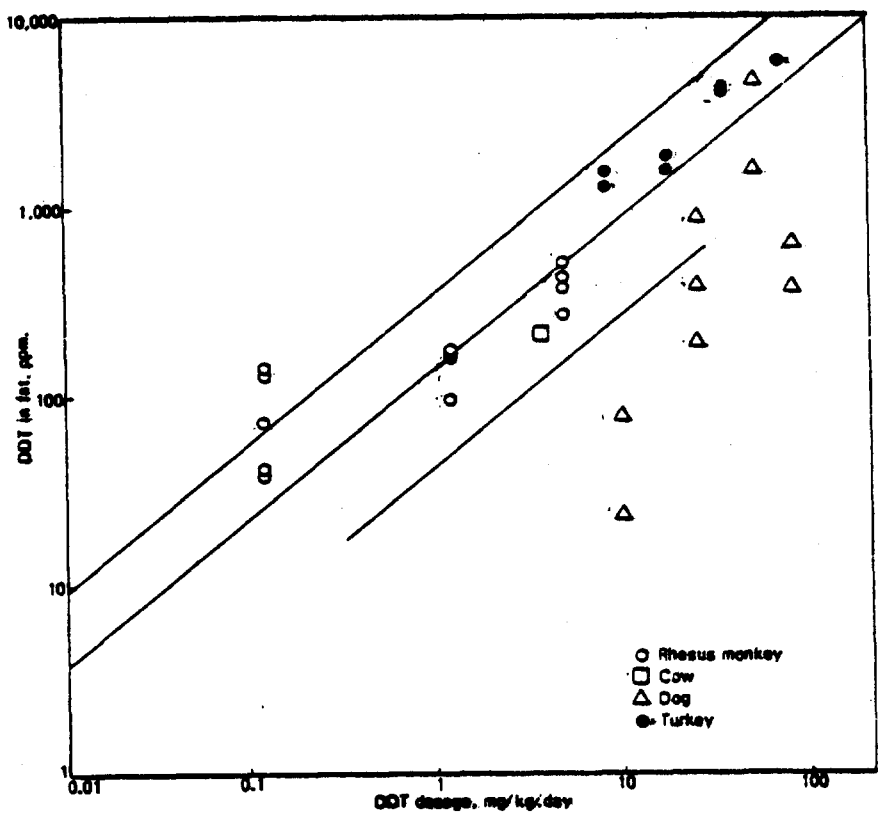


FIGURE 1.5.9 (USDHEW 1969)

RELATIONSHIP BETWEEN THE CONCENTRATION OF DDT IN THE BODY FAT OF RHESUS MONKEYS AND THE CONCENTRATION OF DDT IN THE DIET

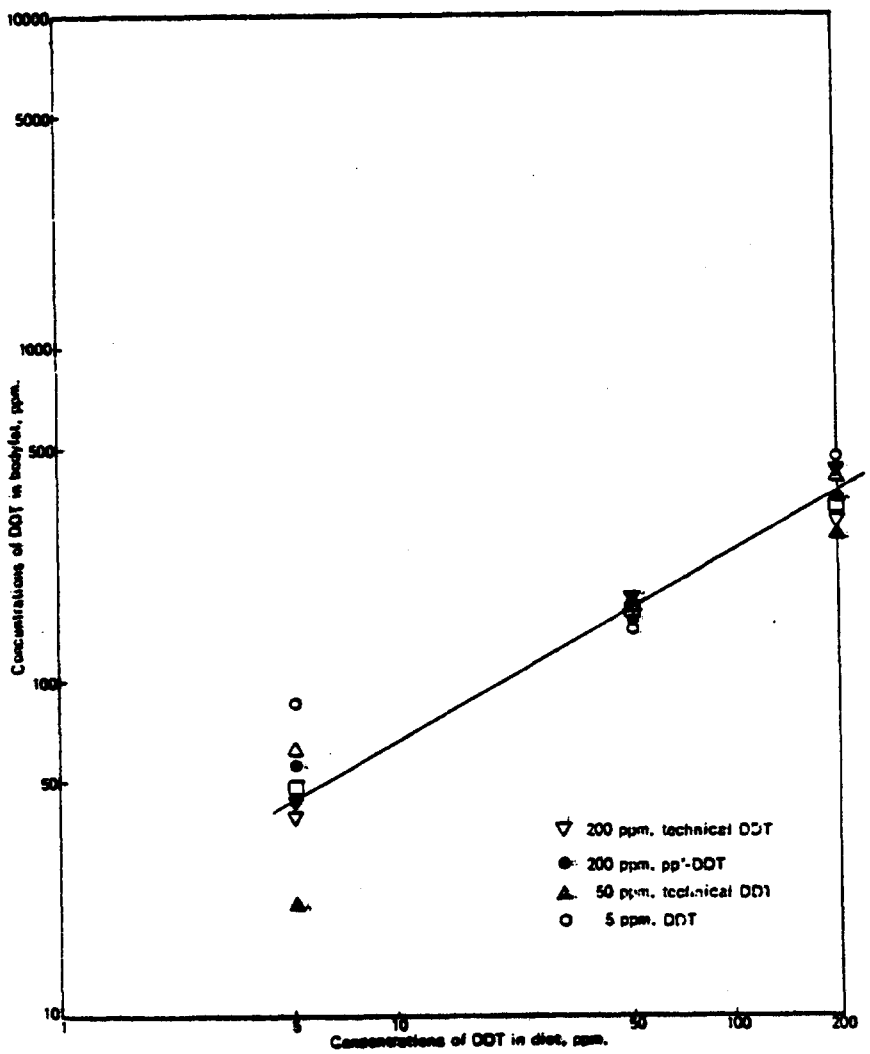


TABLE 1.5.4

DDT RESIDUES IN FAT AND LIVER OF CF1 MICE
EXPOSED TO TECHNICAL DDT FOR 16-30 WEEKS

Exposure Group	Concentration (ppm) in Interscapular Fat		Concentration (ppm) in Liver	
	Average	Range	Average	Range
Controls	1.76	(1.18-2.35)	0.73	(0.18-2.09)
2 ppm	5.17	(3.05-8.15)	2.76	(0.45-15.89)
50 ppm	106.68	(53.69-220.38)	6.05	(3.41-10.52)
250 ppm	455.68	(214.83-722.19)	42.20	(19.45-86.67)

From Tomatis et al 1971, IARC 1974

Analysis of residue storage and kinetics is complicated by the variance in the amount of administered DDT stored as DDE and DDD (see Table 1.5.2). When p,p'-DDT is administered, stored p,p'-DDE must derive primarily from metabolism. However, technical DDT contains small quantities of p,p'-DDE, which appears to be stored much more efficiently than p,p'-DDT. The only experiment in which the storage of DDE and DDD has been measured directly is that of Tomatis et al (1974a). Table 1.5.6 compares the storage of DDT, DDE, and DDD in mice fed technical DDT, p,p'-DDE, or p,p'-DDD at 250 ppm.

Storage of DDT and DDE is modified by interaction with other chemicals, especially enzyme inducers. (The effects of diphenylhydantoin on DDT storage in man are discussed in Section 1.5.4.) Administration of aldrin increased storage of DDT and DDE in the blood and fat of dogs (Deichmann et al 1971), but administration of dieldrin did not affect storage of DDT or DDE in rats (Street 1964). Gingell and Wallcave (1974) showed that DDT enhanced its own metabolism in hamsters; pretreatment with DDT at 250 ppm increased the metabolism of radiolabeled DDT to two to three times that in controls. No such effect was observed in mice, which correlates with the fact that DDT is a poor enzyme inducer in mice (Thorpe and Walker 1973). DDT at a dietary level of 250 ppm decreased hexobarbital sleeping time in hamsters but not in mice (Gingell and Wallcave 1974).

DDT, DDE and DDD cross the placenta in a number of animal species and are excreted in milk (Hayes 1964, 1975; IARC 1974). Female rats given DDT at 32 mg/kg/day secreted about 25% of the

TABLE 1.5.5

STORAGE FACTORS (PPM IN FAT/PPM IN DIET) FOR DDT
IN ANIMALS EXPOSED AT A DIETARY LEVEL OF 10 PPM OR EQUIVALENT

Species	Sex	Exposure Period	Storage Factor	Reference
Rat	M	6 mo	2	Figure 1.5.7, USDHEW 1969
"	"	2 yr	7	"
"	F	6 mo	15	"
"	M	"	12	Moriarty 1975
"	F	"	24	"
Mouse	-	16-30 wk	2	Table 1.5.3, Moriarty 1975
Rhesus monkey	-	1-7 yr	5	Figure 1.5.9, USDHEW 1969

TABLE 1.5.6

LEVELS OF DDT AND METABOLITES STORED IN THE FAT OF MICE AFTER
LONG-TERM EXPOSURE TO TECHNICAL DDT, p,p'-DDE, AND p,p'-DDD

Compound (dietary concentration)	Mean Concentrations (ppm) in Fat (range in parentheses)			
	p,p'-DDT	o,p'-DDT	p,p'-DDE	p,p'-DDD
Technical DDT (250 ppm)	455 (271-629)	8.9 (6.5-13.1)	21.7 (5.8-37.1)	35.4 (17.5-48.6)
p,p'-DDE (250 ppm)	< 0.01	< 0.01	222 (78-434)	< 0.01
p,p'-DDD (250 ppm)	1.3 (0.3-5.1)	0.21 (0-0.58)	2.72 (0.5-5.6)	2.58 (0.71-5)
Controls	0.07 (0-0.19)	0.07 (0-0.16)	4.37 (0-19.2)	0.10 (0.04-0.17)

Adapted from Tomatis et al 1971, 1974a

ingested dose into their milk (Hayes 1976). Cows usually secreted more than 10% of the daily dose in their milk and sometimes as much as 32% (Hayes 1965, 1975).

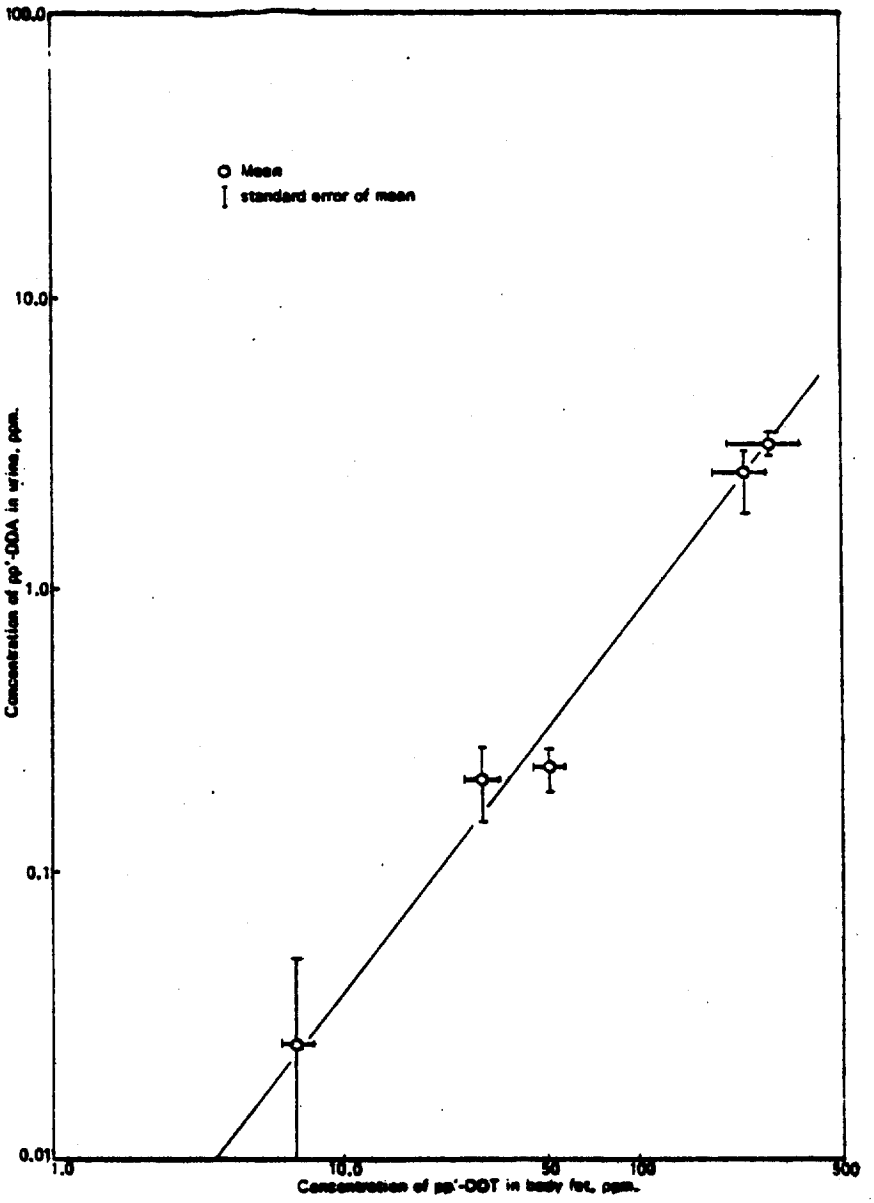
1.5.4 Pharmacokinetics in Humans

Ingested DDT, DDE, and DDD are absorbed into the human body (Hayes et al 1956, 1971; Morgan and Roan 1971). The compounds are probably also absorbed by inhalation and from the surface of the skin, although precise measurements are lacking. When absorbed, they are circulated throughout the body in the blood and stored in other tissues, especially the fat (Hayes 1975). The distribution of DDT, DDE, and DDD in various organs of the body generally parallels their fat content (Table 1.5.7). Less than 18% of the p,p'-DDT and p,p'-DDE in the blood is carried in the erythrocytes; most is bound to low density lipoproteins in the plasma (Morgan et al 1972). DDT, DDE, and DDD are also found in the lymph nodes (Table 1.5.7) and may be circulated in the lymph.

As noted in Section 1.5.2, DDT is excreted mainly as DDA or water-soluble conjugates of DDA in the urine. Figure 1.5.10 shows that the rate of excretion of DDA is approximately proportional to the concentration of p,p'-DDT in body fat. Small quantities of DDT are also excreted in the bile. In one pest-control operator sampled at surgery, concentrations of DDT were 2.2 ppm in adipose lipids, 11 ppb in blood serum, and 11 ppb in bile. Those of DDE were 11.3 ppm, 60 ppb, and 35 ppb (Paschal et al 1974).

FIGURE 1.5.10 (USDHEW 1969)

RELATIONSHIP BETWEEN THE CONCENTRATION OF p,p'-DDA IN THE URINE OF MAN AND THE CONCENTRATION OF p,p'-DDT IN BODY FAT



The intake and storage of DDT and metabolites during and after controlled exposures of volunteers have been studied (Hayes et al 1956, 1971; Morgan and Roan 1971). In a study of volunteers who received DDT (in capsules or in emulsion form in milk) at rates of 0, 3.5, and 35 mg/man/day, the average intakes, including the doses and traces of DDT in food, were 0.0025, 0.05, and 0.5 mg/kg/day. The storage of DDT was roughly proportional to dosage (Table 1.5.8), but there was an unexpected difference between the storage of recrystallized p,p'-DDT and that of technical DDT. For example, after 12 months of exposure, the average concentration of DDT in fat was 304 ppm in men given p,p'-DDT but only 234 ppm in men given technical DDT (Hayes et al 1956).

Men who ingested p,p'-DDT showed a significant increase in residues of DDE. After 6 months at a dosage of 35 mg/man/day, eight men showed an average level of DDE in their fat of 32.6±7.0 ppm, compared with 12.3±1.5 ppm for the same individuals at the beginning of the study. DDE storage increased as exposure progressed, but DDT residues increased more rapidly. Initially 65% of the residues consisted of DDE, but after 6 months at a DDT dosage of 35 mg/man/day, the percentage of DDE in the stored material had declined to 14%. Thus the ratio of DDT to DDE in fat increased more than tenfold after prolonged oral exposure to p,p'-DDT.

The storage of DDE by men who ingested technical DDT presented a different picture. There was no clear evidence of increased storage of DDE until 18 months of exposure. However, at 18 months

TABLE 1.5.7

AVERAGE CONCENTRATIONS OF DDT, DDE, AND DDD IN VARIOUS TISSUES FROM AUTOPSIES OF 44 PEOPLE IN THE GENERAL POPULATION

Tissue	No. Analyzed	Lipid Content (%)	Concentrations (ppm) DDT	DDE	DDD
Perirenal fat	30	55.7	1.33	4.64	0.0110
Mesenteric fat	29	54.2	1.35	4.40	0.0470
Panniculus fat	30	60.6	1.16	4.48	0.0180
Bone marrow	19	20.6	0.411	2.08	0.0760
Lymph node	11	8.6	0.892	1.38	0.0100
Adrenal	18	10.5	0.125	0.875	0.0570
Kidney	38	3.2	0.0827	0.209	0.0022
Liver	42	2.1	0.0467	0.200	0.0326
Brain	32	7.9	0.0105	0.0831	0.0020
Gonad	36	1.3	0.0150	0.0688	0.0015
Lung	25	0.7	0.0147	0.0585	0.0009
Spleen	27	0.6	0.0112	0.0305	0.0031

Adapted from Casarett et al 1968

TABLE 1.5.8

STORAGE OF DDT IN EXPOSED VOLUNTEERS

Type of DDT	Dosage (mg/man/d)	Concentration (ppm) of DDT* First Study 11 months or more	Second Study 21.5 months
Technical	0	8- 17 (12.5±4.5)	16- 30 (22.0±2.9)
	3.5	26- 33 (23.8±1.4)	59- 76 (50.2±5.6)
	35	101-367 (234±21.4)	105-619 (281±79.5)
Recrystallized	35	216-466 (340±36.4)	129-659 (325±62.2)

*Range (mean and standard error)

Adapted from Hayes et al 1956, 1971

DDE concentrations ranged from 28 to 85 ppm, substantially above the initial levels. Thus, both the total amount stored and the rate at which DDT was converted to DDE distinguished the metabolism of p,p'-DDT from that of technical DDT in man (Hayes et al 1956).

In a second study, volunteers received the same doses used in the first study. Again, storage of DDT was approximately proportional to dosage. Although residue storage resulting from ingested technical DDT was less than that from p,p'-DDT, the difference was not statistically significant in the second experiment. The slow, steady accumulation of DDE was confirmed (Hayes et al 1971).

An approximately steady state of residue storage was said to have been reached after about 20 months in the first study and after about 12 months in the second study (Figures 1.5.11 and 1.5.12). After dosing was stopped, DDT was slowly lost from storage in fat. The concentration remaining after 25.5 months was 32-35% of the maximum for those who had received 35 mg/man/day but was 66% of the maximum for those who had received 3.5 mg/man/day. This indicates slower loss at lower storage levels (Hayes et al 1971). The data also indicate that loss of DDT from the human body follows a two-phase pattern, similar to that observed in animals.

Morgan and Roan (1971) fed volunteers technical DDT and also p,p'-DDE and p,p'-DDD. They found that DDE was stored at higher levels than the other compounds in man, the order being p,p'-DDE > p,p'-DDT > o,p'-DDT ≥ p,p'-DDD. The slow metabolism of DDT to DDE

FIGURE 1.5.11 (USDHEW 1969)

INCREASE OF THE CONCENTRATION OF p,p'-DDT IN THE BODY FAT OF MEN WITH CONTINUING INTAKE OF p,p'-DDT

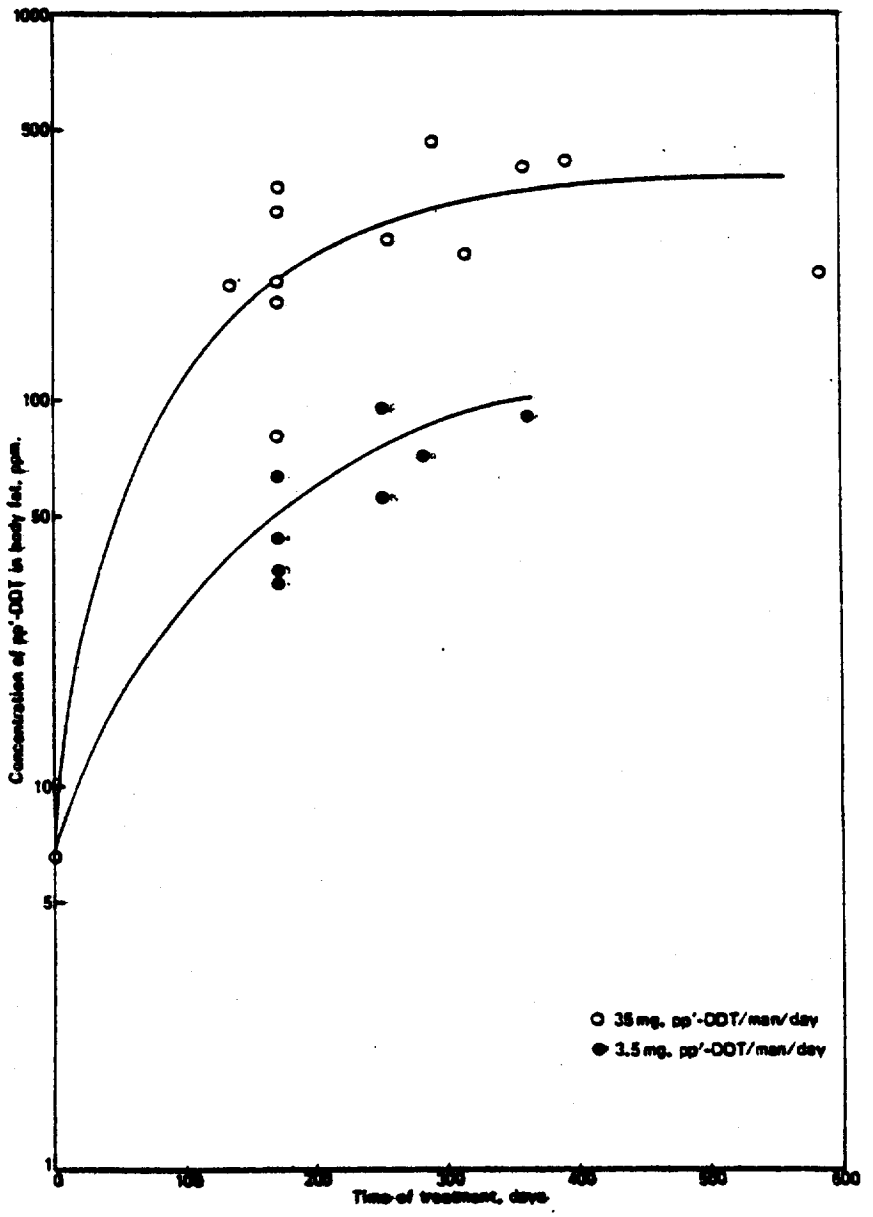
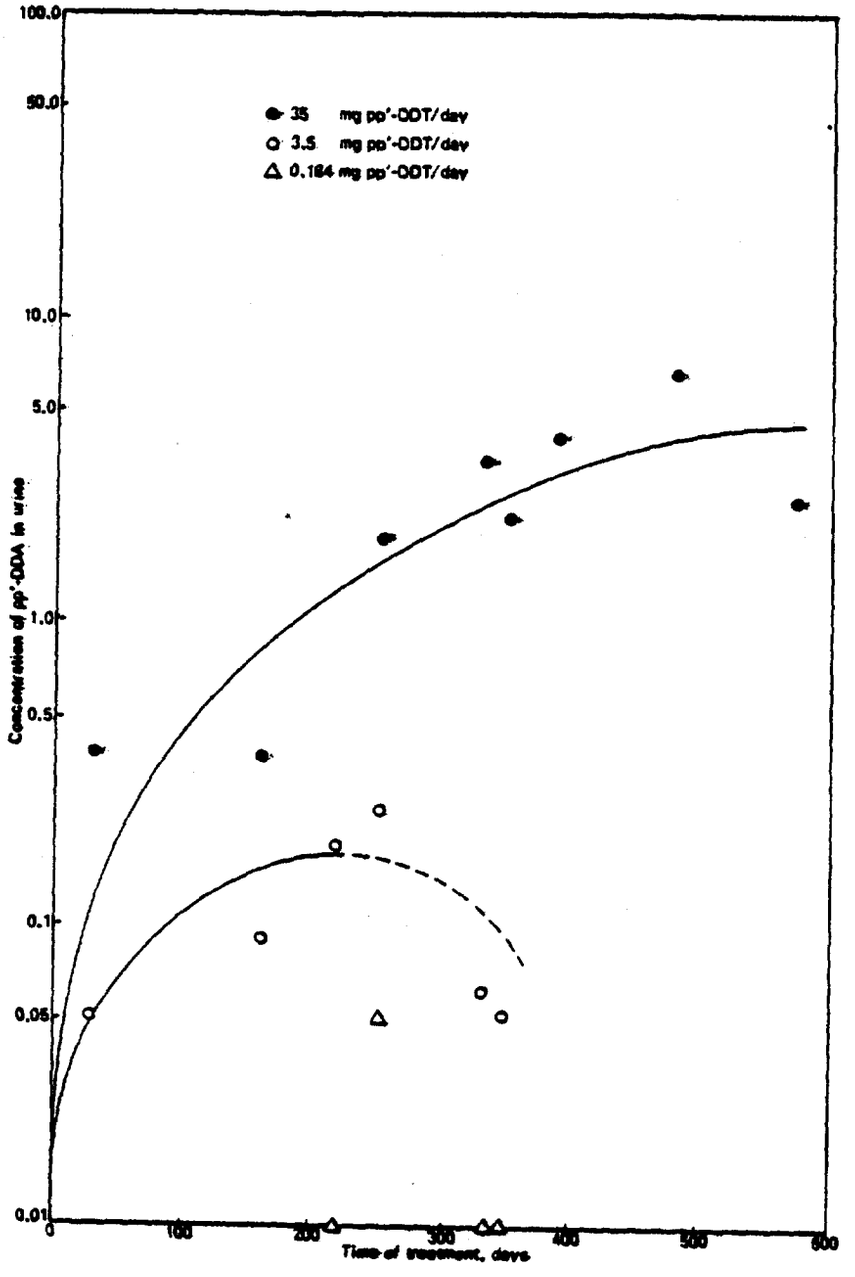


FIGURE 1.5.12 (USDHEW 1969)

RELATIONSHIP BETWEEN THE CONCENTRATION OF p,p'-DDA IN THE URINE OF MAN AND TIME OF TREATMENT WITH p,p'-DDT



was confirmed. The authors noted that p,p'-DDT was lost from storage in adipose tissue much more slowly in man than in the monkey, dog, or rat (Morgan and Roan 1972).

The data from these three studies were fitted to mathematical models by Moriarty (1975). Table 1.5.9 shows the resulting estimates of rate constants for loss of residues from the body. As Moriarty pointed out, these rate constants are lower than those reported for other species of mammals, with the possible exception of the minor component of residues in rhesus monkeys (see Table 1.5.3). The data in these studies are insufficient for estimating rate constants for uptake, but Figure 1.5.11 suggests a half-time for uptake in the range of 100-200 days, much shorter than the half-times for excretion.

Moriarty (1975) pointed out that residue concentrations of DDT in fat did not reach a true steady state in 21.5 months of exposure, despite the claim to the contrary by Hayes et al (1971) (see Figures 1.5.11, 1.5.12). Residue concentrations of DDE in fat did not even approach a steady state in this period (Hayes et al 1971, Morgan and Roan 1971). Assuming that in men ingesting 35 mg and 3.5 mg of DDT/day "quasi-steady" states for DDT levels in fat would have been reached at about 400 and 100 ppm, respectively, (Figure 1.5.11), and assuming that a man eats 1.5 kg of food/day, the corresponding storage factors (ppm in fat/ppm in diet) for DDT in humans are about 18 and 44. The second figure at least is higher than those recorded for other mammals (Table 1.5.5).

TABLE 1.5.9

LOSS OF RESIDUES OF DDT, DDE, AND DDD FROM HUMAN TISSUES AFTER CESSATION OF EXPOSURE

Compound	Tissue	Initial Level (ppm)	Period (days)	λ (d^{-1})	$t_{\frac{1}{2}}$ (days)	Reference
p,p'-DDT	Fat	325	1,150	0.0015	461	Hayes et al 1971
Technical DDT	"	281	1,150	0.0011	617	"
p,p'-DDT	Serum	0.383	320	0.0024	292	Morgan and Roan 1971
"	"	0.201	320	0.0012	568	"
"	Fat	118	320	0.0023	301	"
"	"	40	320	0.00058	1,204	"
p,p'-DDE	Serum	0.15	245	No significant loss		"
"	Fat	46	245	No significant loss		"
p,p'-DDD	Serum	0.01	120	0.014	50	"
"	Fat	6	120	0.015	50	"

Adapted from Moriarty 1975

No estimates of storage factors for DDE can be made from the experimental data, since no steady state was reached. However, in the general population, the average daily intake of DDE was estimated at about 30 µg/person (20 ppb in the diet) in 1966 (USEPA 1975), at a time when average residues in fat were constant at about 7 ppm (Hayes 1975). These data indicate a storage factor for DDE in man of roughly 35. By 1973, daily intake had fallen to about 5 µg/person, while residues in fat had fallen only to 4.8 ppm (USEPA 1975), but this represents a non-steady-state situation.

Storage of DDT in man may be affected by interactions with other chemicals, especially enzyme inducers. In a study by Davies et al (1971, Davis and Edmundson 1972a), volunteers given diphenylhydantoin at a rate of 300 mg/man/day for 9 months showed a 75% reduction in DDT storage and a 61% reduction in DDE storage. Epileptics on maintenance doses of diphenylhydantoin or phenobarbital stored little or no DDT or DDE in their fat or blood (Davies et al 1969; Table 1.5.10, Edmundson et al 1972d). The mean levels of p,p'-DDE in the blood of workers occupationally exposed to endrin were only 30-40% of those of controls, even 5 years after exposure to endrin had ceased (Jager 1970). However, occupational exposure to aldrin and dieldrin apparently did not modify DDT or DDE storage (Jager 1970).

Residue levels of DDT in blood serum were found to be associated with erythrocyte levels of glucose-6-phosphate dehydrogenase in a sample of 16 black children. Probably storage

TABLE 1.5.10

BLOOD DDE CONCENTRATIONS IN GENERAL POPULATION AND IN PATIENTS TAKING ANTICONVULSANTS

Group	No.	Concentration (ppb) of DDE		
		Mean	Range	Median
White				
General population	199	9.1	<1-55	8
Patients taking phenobarbital, phenytoin, or both	87	2.1	<1-10	1
Black				
General population	251	13.5	3-92	13
Patients taking phenobarbital, phenytoin, or both	34	2.3	<1-25	2

*At least 6 years old; on regular diet

Adapted from Edmundson et al 1972d

levels are associated with socioeconomic and cultural factors in addition to being associated with a genetic marker (Keil et al 1974).

DDT, DDE, and DDD cross the placenta into the human fetus and are excreted into human milk (USDHEW 1969, Hayes 1975). Polishuk et al (1977b) showed that all six chemicals in this group are present in plasma lipids at higher levels than in milk lipids (Table 1.5.11). The same authors showed that all the chemicals in the group are present at higher levels in fetal lipids and in lipids of the placenta and amniotic fluid than in maternal lipids (Table 1.5.12). Bradt and Herrenkohl (1976) found that levels of DDT and metabolites in human milk decrease according to the number of children nursed. Lactating women apparently excrete more DDT and DDE than they ingest (Quinby et al 1965), presumably because they are depleting stores built up before giving birth. In the United States in 1973, mean levels of DDE in human adipose tissue lipids were about 4.8 ppm and those in human milk lipids were about 2.3 ppm (USEPA 1975, data from Human Moritoring Survey). Assuming excretion of about 25 g/day lipids in milk, compared to a current (1973) intake of about 5 μg (USEPA 1975). The corresponding intakes/unit of body weight are about 0.08 μg/kg/day in the mother and 12 μg/kg/day in the breast-fed infant--a difference of 150-fold. This probably represents a non-steady-state situation, since present-day DDE levels in humans probably reflect higher exposures in the past (USEPA 1975).

TABLE 1.5.11

CONCENTRATION OF DDT AND METABOLITES IN HUMAN MILK AND PLASMA

Compound	Mean Concentration (ppm) SD			
	In Extracted Plasma Lipids	In Extracted Milk Lipids	In Whole Plasma	In Whole Milk
p,p'-DDT	2.68±1.53	0.972±0.489	0.013±0.007	0.012±0.006
p,p'-DDD	1.78±0.922	0.805±0.459	0.009±0.004	0.010±0.004
p,p'-DDE	3.97±1.87	1.81 ±0.903	0.020±0.008	0.022±0.007
o,p'-DDT	2.23±1.35	0.614±0.390	0.011±0.006	0.007±0.004
o,p'-DDD	1.52±1.35	0.482±0.361	0.007±0.006	0.006±0.005
o,p'-DDE	2.23±0.884	0.763±0.439	0.011±0.004	0.010±0.004
$\sum$ DDT	15.1 ±7.21	5.77 ±2.82	0.074±0.029	0.072±0.025

Adapted from Polishuk et al 1977b

TABLE 1.5.12

CONCENTRATION OF DDT AND METABOLITES IN EXTRACTED LIPIDS FROM HUMAN TISSUES AND FLUIDS

Compound	Mean Concentration (ppm)					
	Adipose Tissue	Maternal Blood	Fetal Blood	Uterine Muscle	Placenta	Amniotic Fluid
p,p'-DDT	0.721±0.189	0.974±1.03	2.49 ±1.62	1.26 ±0.582	2.61 ±2.61	13.1 ±10.4
p,p'-DDD	0.262±0.161	0.333±0.387	0.937±1.01	0.422±0.330	0.441±0.450	9.18± 7.70
p,p'-DDE	1.92 ±0.901	1.87 ±1.50	3.84 ±2.27	5.60 ±2.67	3.95 ±1.65	26.7 ±19.8
o,p'-DDT	0.359±0.373	0.503±0.626	1.29 ±1.25	1.03 ±0.721	0.721±0.760	15.9 ±11.9
o,p'-DDD	0.074±0.177	0.333±1.08	0.401±0.723	0.506±0.508	0.437±0.801	4.08± 5.95
o,p'-DDE	0.424±0.214	0.348±0.437	1.03 ±0.914	2.09 ±0.470	0.788±0.794	16.9 ±11.0
Total p,p'	3.11 ±1.18	3.36 ±2.60	7.71 ±3.85	7.92 ±2.99	7.46 ±3.82	52.0 ±34.0
Total o,p'	0.902±0.544	1.21 ±1.71	2.84 ±1.80	3.87 ±1.25	2.04 ±1.67	38.9 ±28.8
Total DDT	4.01 ±1.61	4.58 ±4.03	10.5 ±5.22	11.8 ±3.06	9.50 ±5.20	90.9 ±57.7

Adapted from Polishuk et al 1977a