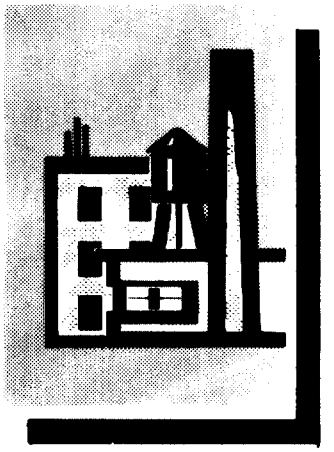
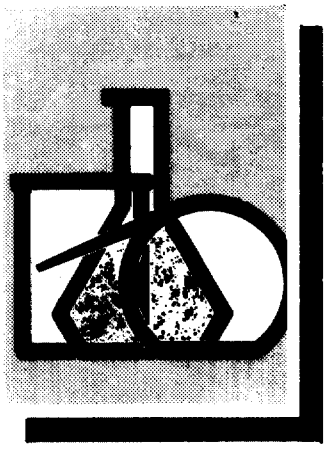
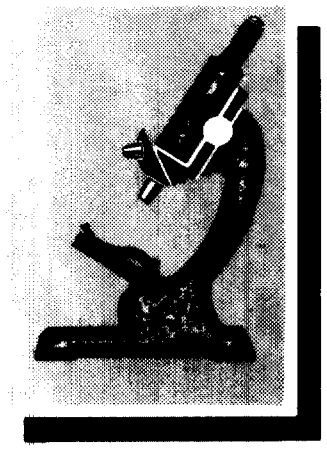
NIOSH

SPECIAL OCCUPATIONAL HAZARD REVIEW





DDT



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

SPECIAL OCCUPATIONAL HAZARD REVIEW

FOR

DDT

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Public Health Services
Center for Disease Control
National Institute for Occupational Safety and Health
Division of Criteria Documentation and Standards Development
Rockville, Maryland

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards in their workplace. Pursuant to the fulfillment of this need, the National Institute for Occupational Safety and Health (NIOSH) has developed a reporting strategy intended to assist employers in providing personal protection for employees from exposure to carcinogenic, mutagenic, and teratogenic substances. This strategy involves the development of Special Occupational Hazard Reviews which serve to support and complement the other major criteria documentation activities of the Institute. It is the intent of a Special Occupational Hazard Review to document, from a health standpoint, the problems associated with a given industrial chemical or process. While Special Occupational Hazard Reviews are not intended to supplant the more comprehensive NIOSH Criteria Documents nor the less comprehensive NIOSH Current Intelligence Bulletins, they are nevertheless prepared in such a way as to be amenable to full regulatory usage if so desired. Dissemination of Special Occupational Hazard Reviews may be accomplished through appropriate trade associations, unions, industries, and members of the scientific community.

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Acting Director, National Institute
for Occupational Safety and Health

CONTENTS

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

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

SUMMARY AND RECOMMENDATIONS

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

DDT is produced and marketed in the United States but its use is restricted to specified applications by the U.S. Public Health Service and Department of Agriculture and for controlling body lice (37 Federal Register 13369, July 7, 1972). More importantly, DDT is widely used in agriculture and for vector control outside the U.S., although resistance to DDT in agricultural pests has increased since its introduction. Total worldwide use of DDT for the decade 1971-81 is predicted to be 94,000 metric tons/year.

The acute toxicity of DDT is relatively low, the estimated oral LD50 in humans being 250 mg/kg. Documented chronic toxicity in humans, clearly related to DDT, is non-existent, and, therefore, the results of experiments with animals must be used to predict chronic effects that may occur in humans. Most notable of these chronic effects is DDT's potential for producing cancer in animals. DDT has produced an increased incidence of tumors in mice in at least eleven experiments. Most tumors involved the liver but tumors of the lungs and lymphatic system have also been reported. In one experiment with mice, DDT induced an increased incidence of tumors at dietary levels as low as 2 and 10 ppm. In two of three experiments involving rats, increased occurrences of liver tumors of varying degrees of malignancy have been reported.

Based on the demonstrated potential of DDT for inducing tumors in both rats and mice, NIOSH recommends that DDT be controlled and handled in the workplace as a suspected occupational carcinogen and that exposure to DDT be minimized to the greatest extent possible. With regard to airborne exposure, NIOSH recommends that the workplace environmental limit be no higher than 0.5 mg/cu m, which is the lowest concentration detectable by the current NIOSH validated sampling and analytical method (NIOSH method S274). Workers should also avoid skin contact with DDT, as the pesticide can be absorbed through the skin. Percutaneous absorption is substantially increased when DDT is dissolved in organic solvents.

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

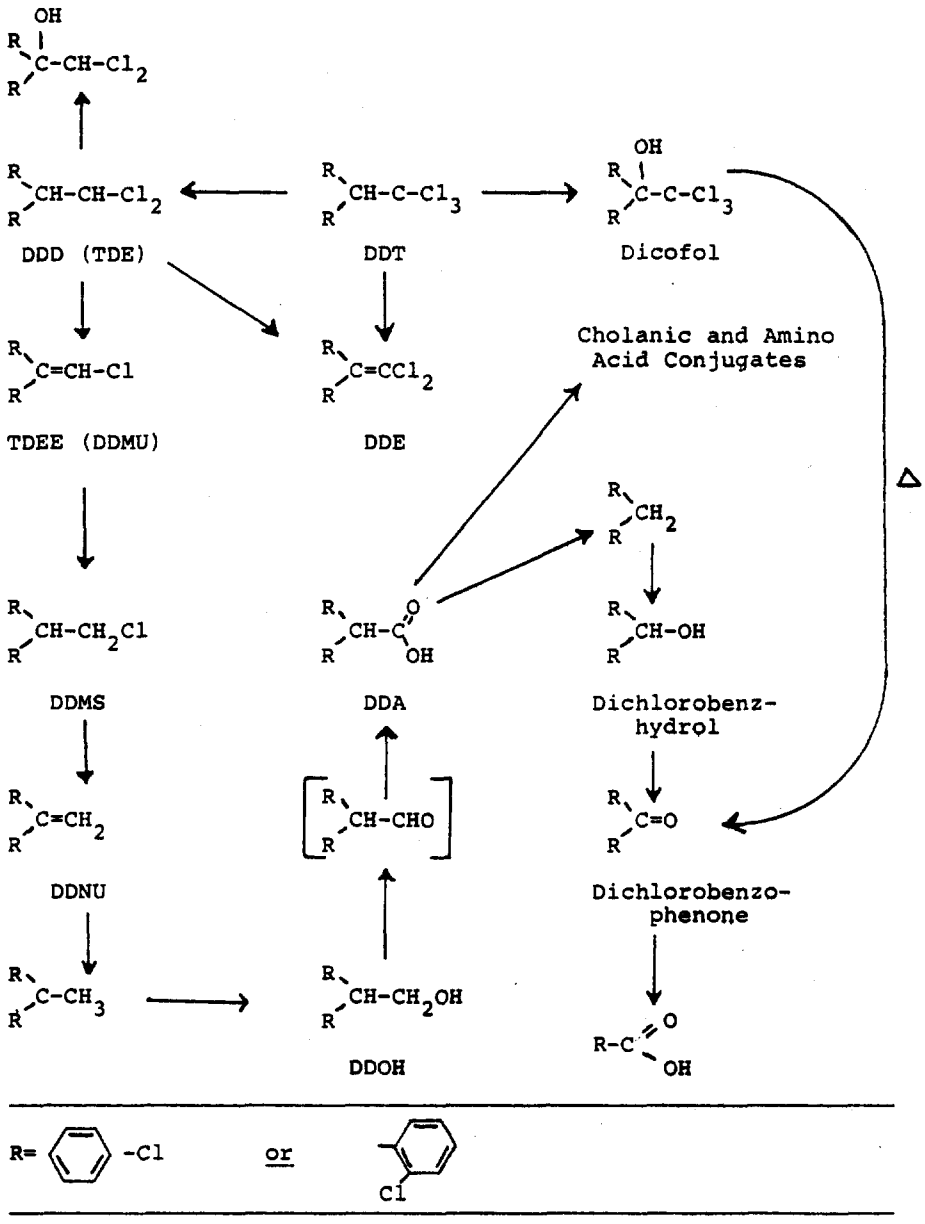
Compound	Activity	Exposure*			Reference
		Respiratory (mg/hr)	Dermal (mg/hr)	Total (% toxic dose/hr)	
DDT	Indoor house spraying		543	>0.31	Hayes 1959
DDT	Indoor house spraying	3.4**	1,755	1.02	Wolfe et al 1959
DDT	Outdoor house spraying		84	>0.05	Hayes 1959
DDT	Outdoor house spraying	0.11	243	0.14	Wolfe 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.

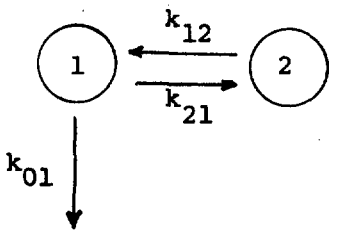
Data on the rate of uptake of DDT by mammals are very scanty. The only set of data sufficient for analysis is that of Laug et al (1950) for technical DDT in rats. When analyzed with a one-compartment model it yielded rate constants (λ) in the range 0.0066-0.013 for females and 0.025-0.026 for males, 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)

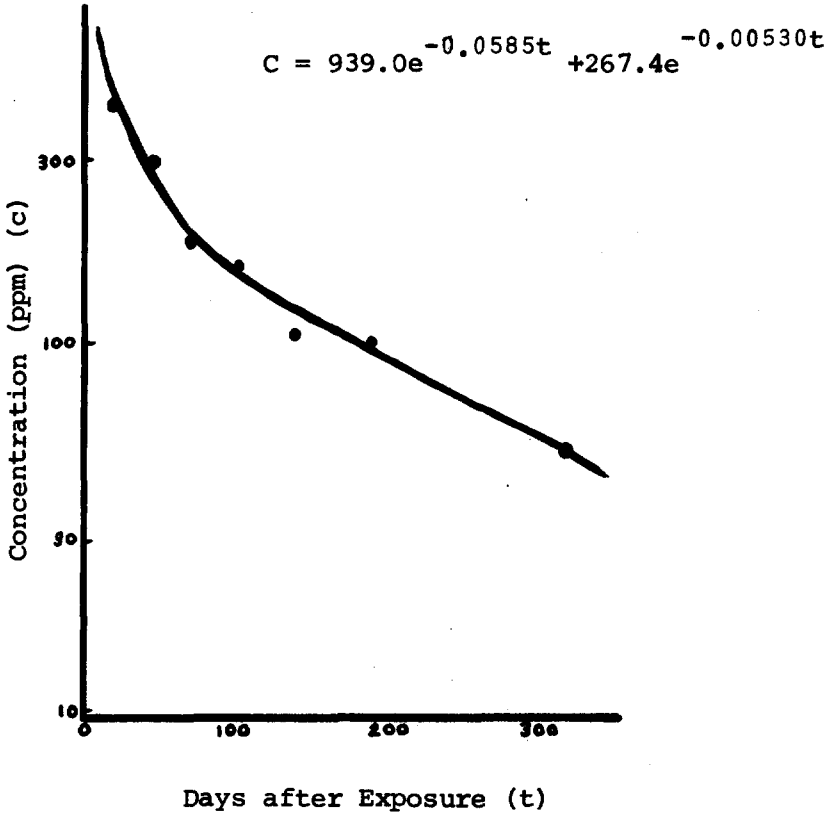


FIGURE 1.5.4 (Moriarty 1975)

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

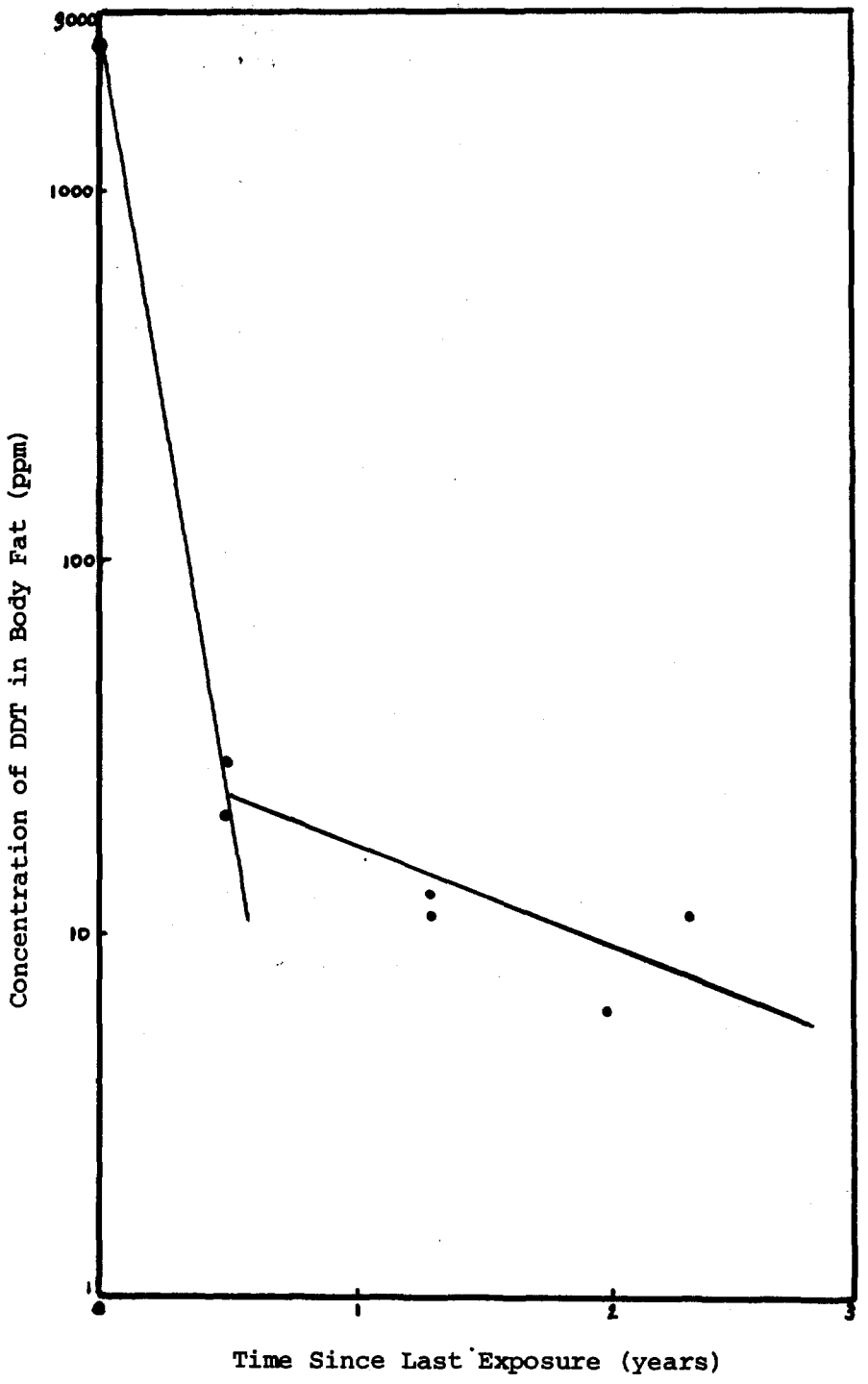


TABLE 1.5.3

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

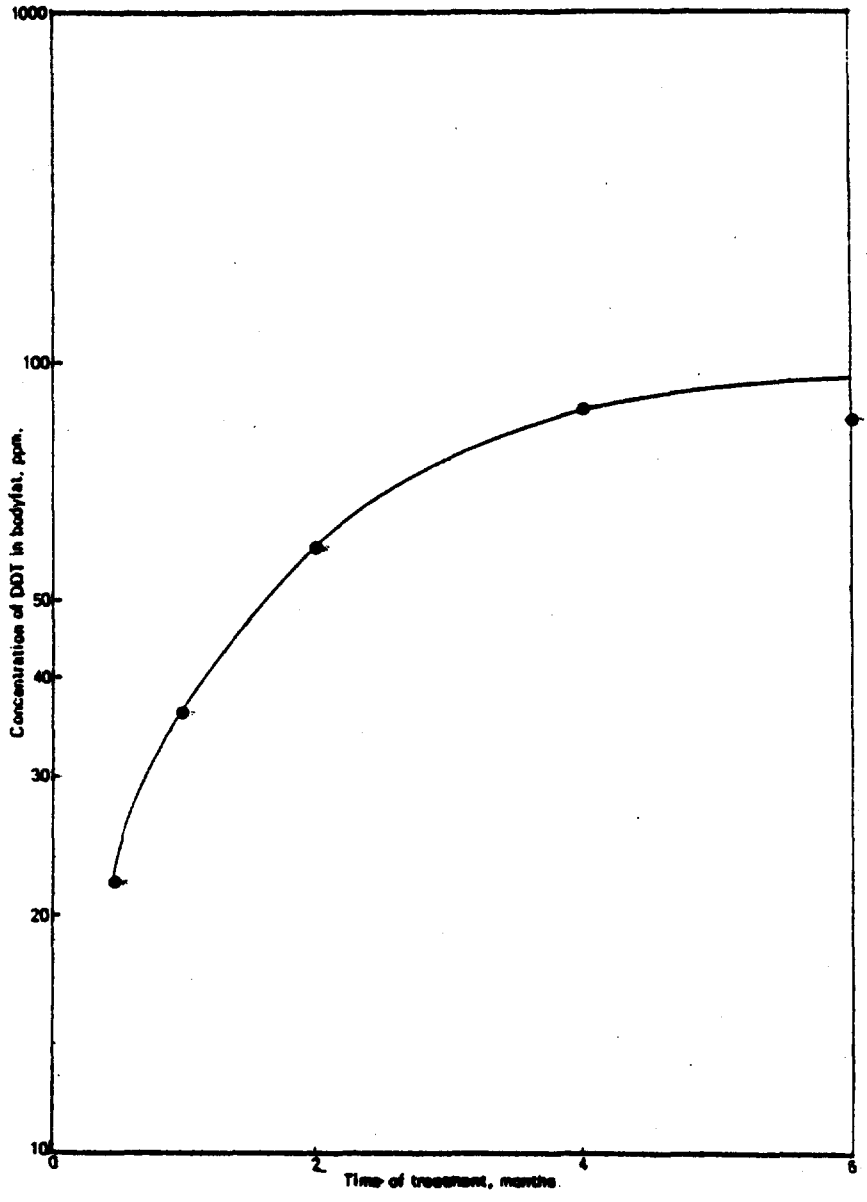


FIGURE 1.5.6 (USDHEW 1969)

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

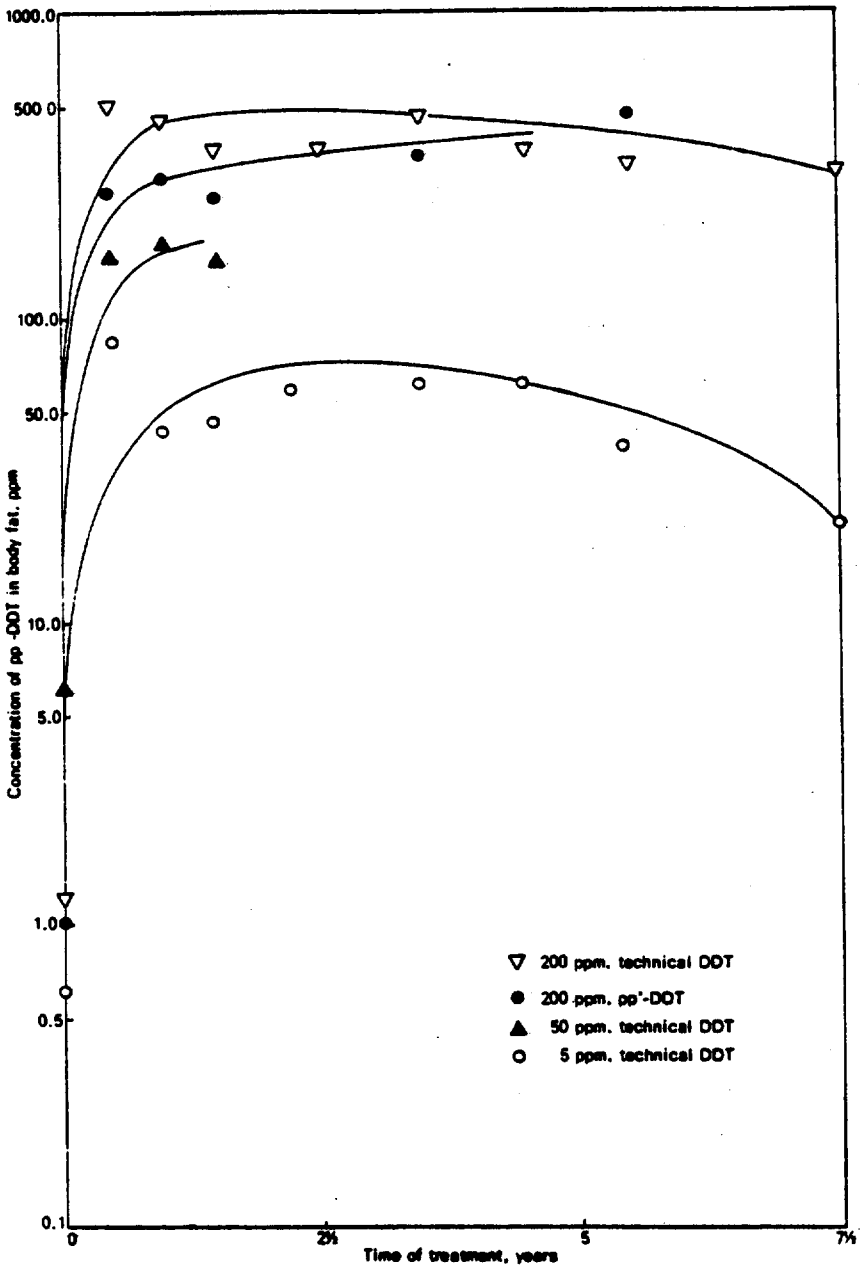


FIGURE 1.5.7 (USDHEW 1969).

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

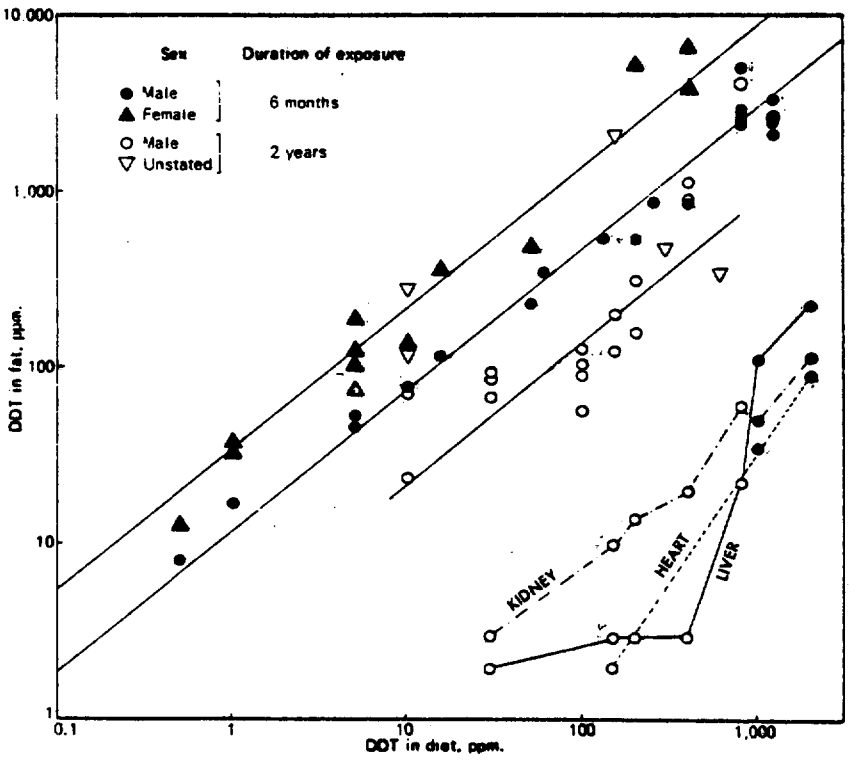


FIGURE 1.5.8 (USDHEW 1969)

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

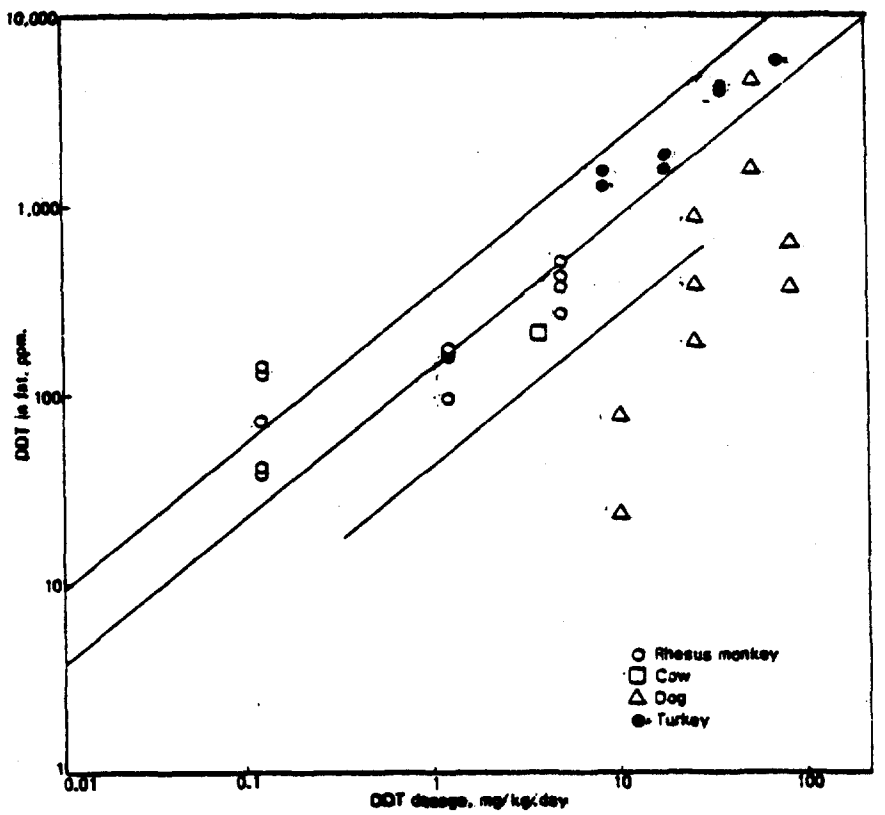


FIGURE 1.5.9 (USDHEW 1969)

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

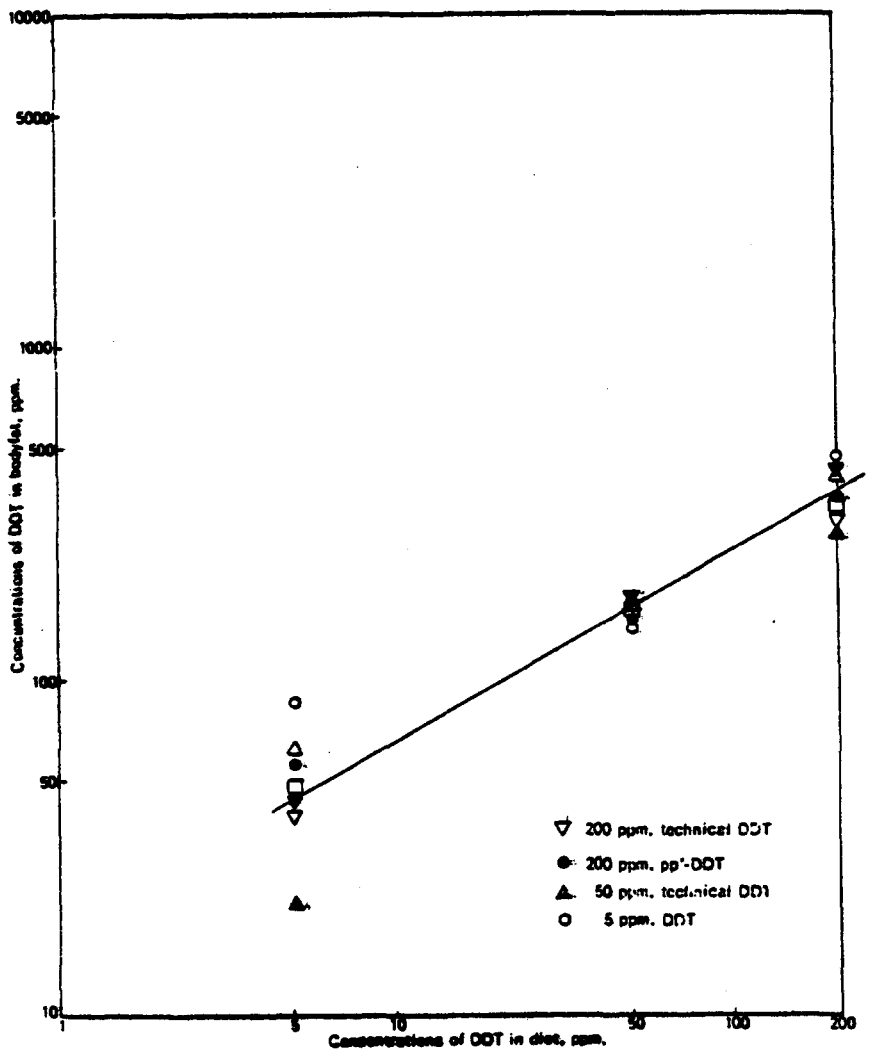


TABLE 1.5.4

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).

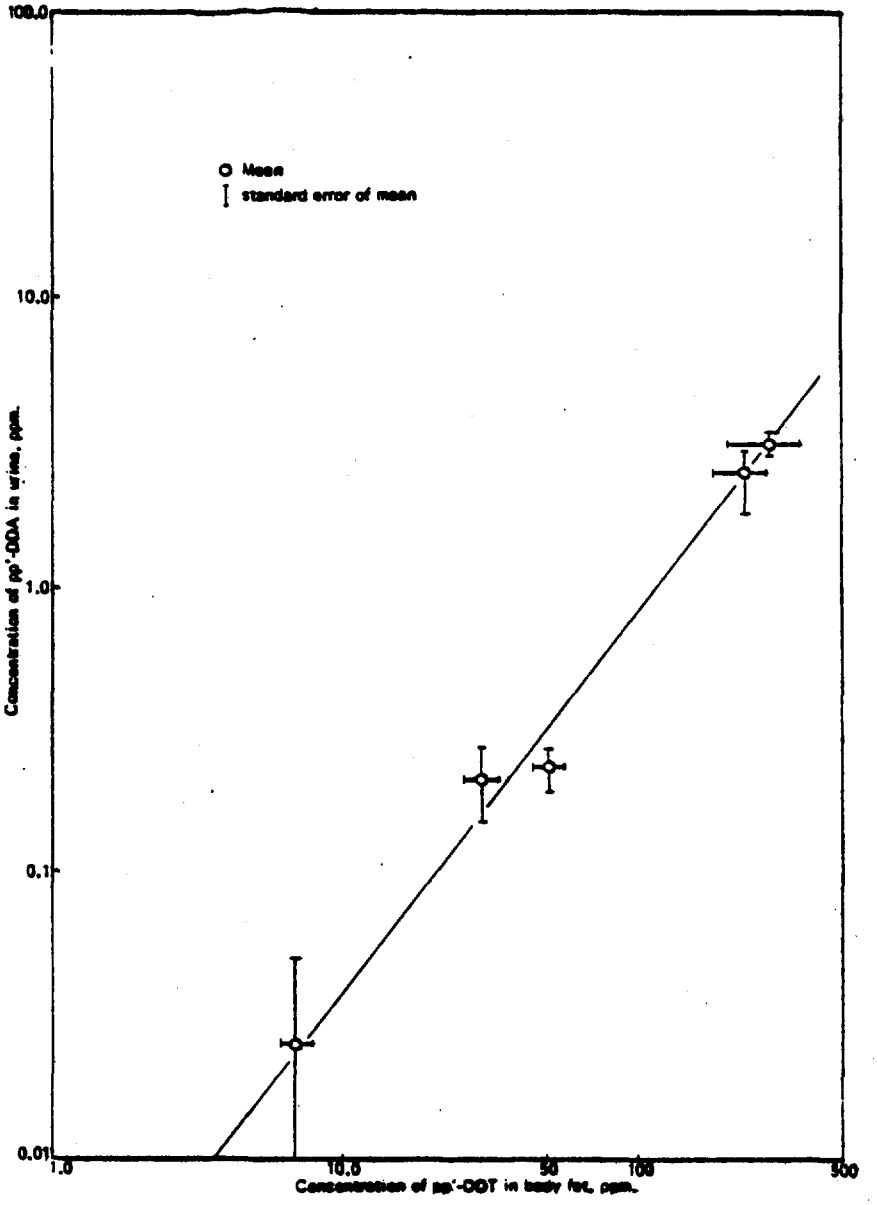
1.5.4 Pharmacokinetics in Humans

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

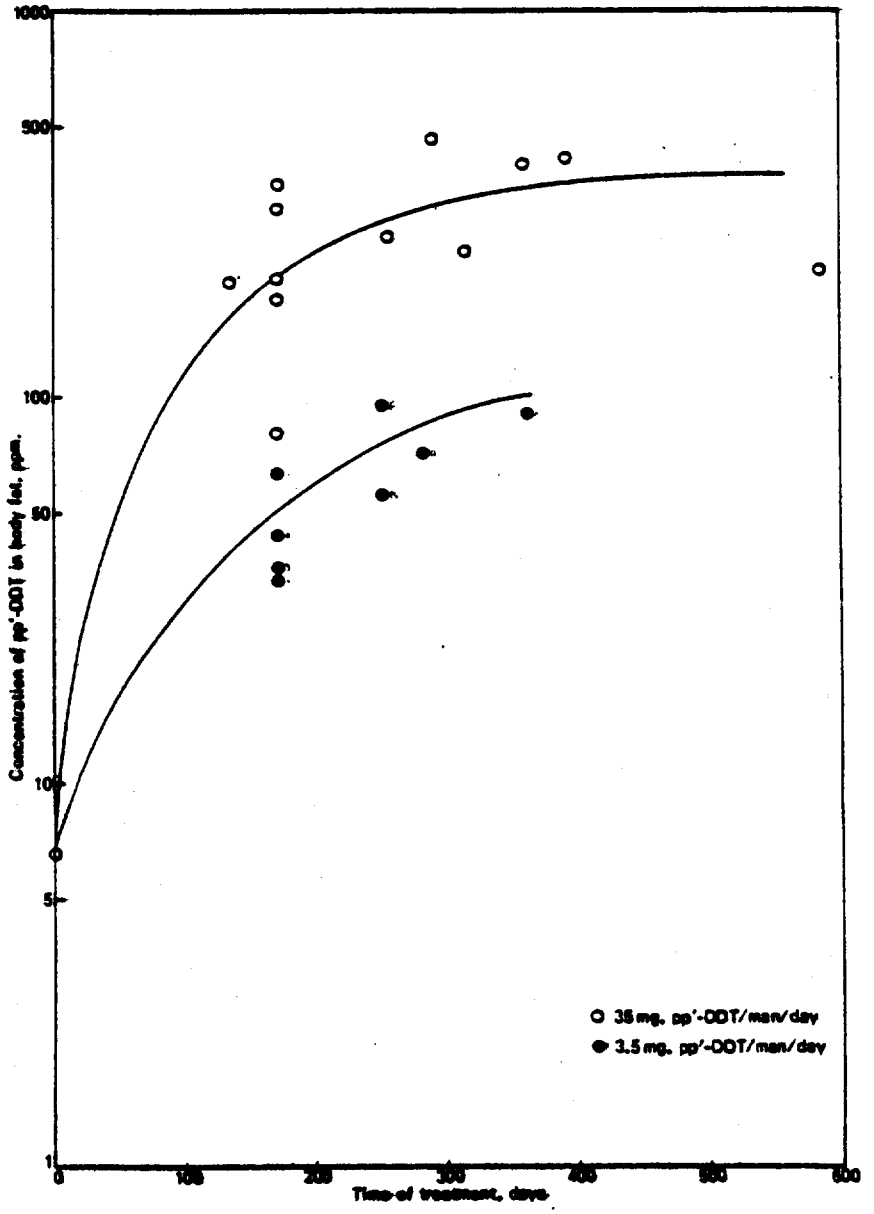
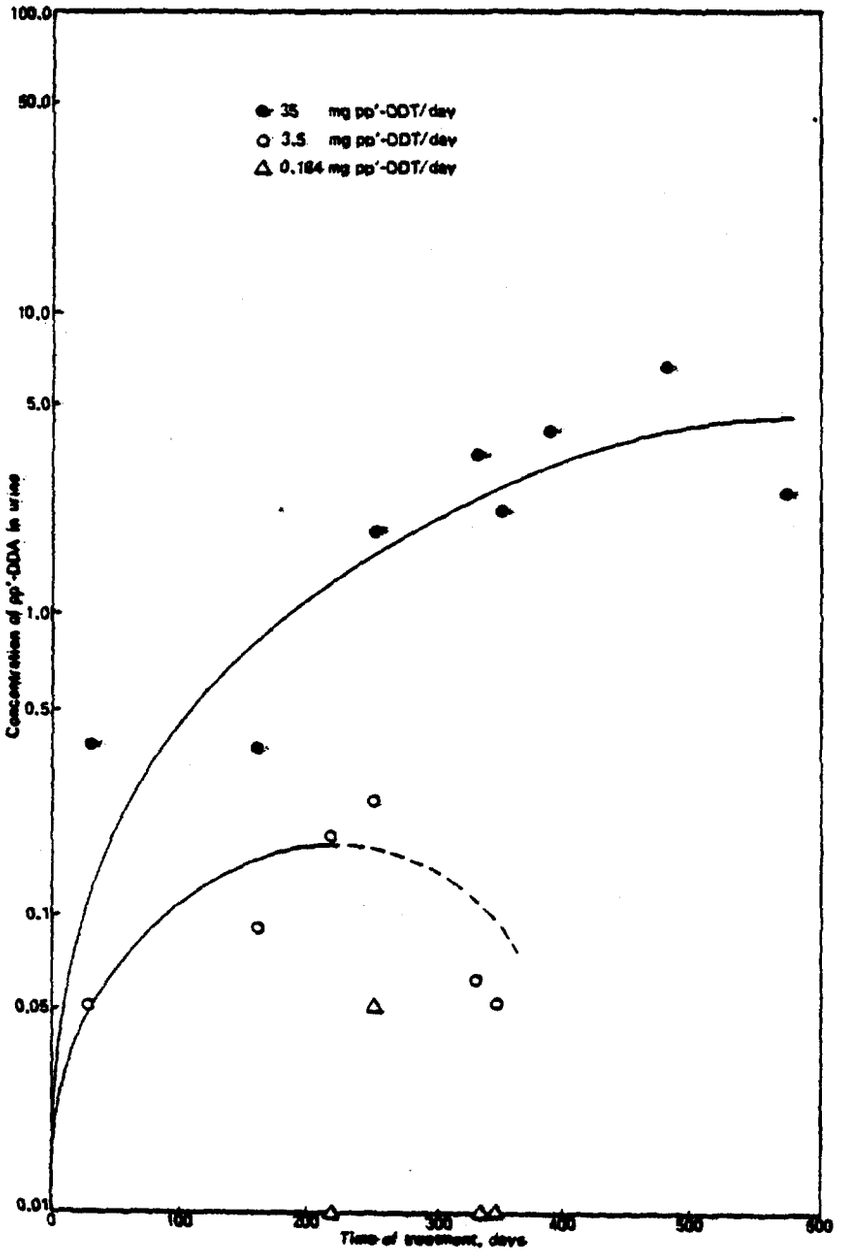


FIGURE 1.5.12 (USDHEW 1969)

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

2. TOXIC EEFECTS IN ANIMALS

2.1 Acute and Chronic Toxicity

2.1.1. Acute Toxicity

Tables 2.1.1 and 2.1.2 summarize the acute toxicity as detailed in earlier reviews (Hayes 1959). Table 2.1.3 summarizes the range of toxic doses in man and in male and female rats. Table 2.1.4 gives the oral LD50 values of some DDT metabolites.

The acute action of DDT is almost exclusively on the central nervous system (CNS). The first signs, which are generally similar in different species, are abnormally susceptible to alarm stimuli, motor unrest, and increased frequency of spontaneous movements. These are followed by tremors that become constant. As severity increases, attacks of epileptiform tonic-clonic convulsions occur. DDT poisoning may ultimately result in death from ventricular fibrillation. These symptoms may be caused by single large doses of DDT as well as repeated exposure to the pesticide (USDHEW 1969).

2.1.2 Factors Modifying Toxicity

Harbison (1975) found that newborn rats are less sensitive to the toxic effects of DDT than adults (Table 2.1.5). Pretreatment with phenobarbital increased the neonates' susceptibility to DDT poisoning. Harbison hypothesized that phenobarbital may stimulate production of a metabolite inherently more toxic than the parent compound in newborn rats.

TABLE 2.1.1

ACUTE ORAL AND DERMAL LD_{50} OF DDT IN ANIMALS

Species	Formulation	Oral (mg/kg)	Dermal (mg/kg)
Rat	Water Suspension or Powder	500-2,500	1,000,000
	Oil Solution	113-450	250-3,000
Mouse	Water Suspension or Powder	300-1,600	375,000
	Oil Solution	100-800	250-500
Guinea Pig	Water Suspension or Powder	2,000	1,500,000
	Oil Solution	250-560	1,000
Rabbit	Water Suspension or Powder	275	375,000
	Oil Solution	300-1,770	300-2,820
Cat	Water Suspension or Powder		
	Oil Solution	100-410	
Dog	Water Suspension or Powder		
	Oil Solution	> 300	

Adapted from Hayes 1959

TABLE 2.1.2

ACUTE SUBCUTANEOUS, INTRAVENOUS, AND INTRAPERITONEAL LD_{50} OF DDT IN COMMON LABORATORY ANIMALS

Species	Formulation	Subcutaneous (mg/kg)	IV (mg/kg)	IP (mg/kg)
Rat	Water Suspension or Powder	>2,000		
	Oil Solution	200- 1,500	47	80-200
Mouse	Water Suspension or Powder	1,000- 1,500		
	Oil Solution	300		
Guinea Pig	Water Suspension or Powder			
	Oil Solution	900		150
Rabbit	Water Suspension or Powder			
	Oil Solution	250->3,200	30-41	<2,100
Cat	Water Suspension or Powder			
	Oil Solution	<650	32	
Dog	Water Suspension or Powder			
	Oil Solution		68	
Monkey	Water Suspension or Powder			
	Oil Solution		55	

Adapted from Hayes 1959

TABLE 2.1.3

COMPARISON OF THE SUSCEPTIBILITY OF MAN AND OTHER ANIMALS TO DDT

	Dosage* (mg/kg)							
Species	Largest without Clinical Effect	Smallest with Clinical Effect	Median Clinical CD50	Smallest with Serious Effect	Largest Nonfatal	Smallest Fatal	LD50	Uniformly Fatal
Man	-	6	10	16**	285***	-	-	-
Rat, F	-	-	-	75	150	100	118	200
Rat, M	25	-	-	50	175	50	113	200

*Single oral dose unless otherwise noted
**Convulsions
***Part of dose vomited

Adapted from Hayes 1975

TABLE 2.1.4

ORAL LD50 VALUES FOR METABOLITES OF DDT

Compound	Species (sex)	LD50 (mg/kg)
DDE	Rat (M)	880
"	Rat (F)	1,240
"	Mouse	700
"	"	1,000
DDD	Rat (M)	>4,000
DDA	Rat	1,900
"	Rat (M)	740
"	Rat (F)	600
"	Mouse	720
"	"	590

Adapted from WHO 1977

TABLE 2.1.5

EFFECT OF AGE ON THE TOXICITY OF DDT TO RATS

Number of Doses	Age	LD50* (mg/kg)
1	Newborn	4,000
1	"	2,356
1	10 days	728
1	14-16 days	437.8
1	Weanling	355.2
1	2 months	250
1	3-4 months	194.5
1	Middle aged	235.8
1	Adult	225
4	Preweaning	279.2
4	Adult	285.6

*Total intake

Adapted from WHO 1977

Nutrition appears to affect DDT toxicity in that well-fed mammals, especially fat ones, are more resistant to DDT poisoning than are poorly fed animals. Increased dietary fat increases the toxicity of dietary DDT, while increased protein in the diet decreases it. These effects may be due to enhanced absorption and increased activity of degradative enzymes, respectively. In starvation tests, the mobilization of fat increases the concentration of DDT in the blood and, consequently, augments the chemical's toxic effects (USDHEW 1969). DDT has also been reported to be more toxic to rats at 36 C than at lower temperatures (4-8 C) (USDHEW 1969).

2.1.3 Mode of Action

The acute toxicity of DDT is believed to result from effects on the central and peripheral nervous system (Ecobichon 1970), but the precise mechanisms of action remain unknown. Narahashi and Yamasaki (1960) studied the effects of DDT on the giant axons of the cockroach. They found that DDT prolongs the recovery phase of the action potential indicating the pesticide's influence on potassium (K^+) efflux. They supported this finding with evidence that this effect is accentuated by a lower concentration of potassium ions in fluid surrounding the nerve. Narahashi and Haas (1967) showed that DDT also prolongs the flow of sodium ions into the giant axons of the lobster. Thus, DDT delays shutting of the Na^+ gate and prevents full opening of the K^+ gate.

In addition, it has been found that small concentrations of DDT inhibit Na^+-, K^+-, and Mg^{2+}--stimulated adenosine triphosphatase (ATPase) derived from a nerve ending fraction of the rabbit brain (Matsumara and Patil 1969). Schneider (1975) found that inhibition of ATPase by DDT

in the rat brain is not caused by the binding of the pesticide to a specific site on the enzyme. Rather, it is the result of indirect alterations of the membrane that interfere with allosteric transitions of the ATPases mediated by Na^+ and K^+.

Byczkowski (1976) examined the effects of single, sublethal doses of p,p'-DDT on liver and brain mitochondia of the rat and found a time- and dose-dependent decrease in oxidative phosphorylation efficiency. A time-dependent suppression of respiratory activity was noted, as well as a simulation of mitochondrial ATPase activity 24 hours after DDT activity. The author suggested that the uncoupling of oxidative phosphorylation in brain mitochondria may be responsible for some phenomena of DDT intoxication in mammals.

2.1.4 Long-Term Feeding Experiments

A number of experiments involving long-term dietary exposure of rats, mice, hamsters, dogs, and other mammals to DDT are summarized in Table 4.2.1. The most pronounced effects of exposure to DDT at high dietary levels are on the liver and the CNS. Dietary levels associated with reduced lifespan are 400 ppm in rats, 250 ppm in mice, and 1,000 ppm in hamsters. At these dietary levels, many animals suffered from tremors and convulsions, and most showed liver injury upon autopsy, although some survived for the normal lifespan (Fitzhugh and Nelson 1947, Tomatis et al 1972, Agthe et al 1970). At lower dietary exposure levels several adverse effects have been reported, including increased liver weight, histopathologic changes in the liver, impaired reproduction, and increased incidence of tumors of the liver, lungs, and lympathic system. These effects are summarized in the following sections.

2.2 Organ-Specific Toxicity

2.2.1 Liver and Kidney Effects

In addtion to the effects on the CNS and reproductive organs, chlorinated hydrocarbon insecticides have been shown to exert prominent pharmacologic and morphologic actions on hepatic and renal tissues. DDT treatment results in tubular degradation and vascular congestion in the kidney (Smith 1948). Histologic changes occur in the livers of rats with even low levels of DDT in their diet.

Nelson et al (1944) and Kunze et al (1949) reported that histopathology could be detected in the livers of rats maintained for 4-6 months on a diet containing DDT at 5 ppm. However, Cameron and Cheng (1951) were unable to demonstrate any pathology in rats killed after being exposed for more than a year at levels corresponding to food concentrations of up to approximately 350 ppm. Other investigators, including Treon and Cleveland (1955), reported liver changes induced by DDT at relatively low dosages (12.5 and 25 ppm). Ortega et al (1956a, b) reported that liver cell necrosis occurred with dosages in excess of 1,000 ppm but not at lower levels. Histologic changes restricted to the liver occurred at levels as low as 5 ppm, but liver function, as measured by bromsulphthalein excretion, was not affected in rats fed 400 ppm or less. The histologic changes in the parenchymal cells of the liver consisted of increased fat deposition, margination of cytoplasmic granules, and hypertrophy of the cells. The most characteristic change was the formation of complex, lipoid cytoplasmic inclusion bodies termed "liposphères." More recently, Ortega (1962) reported additional details

of these cytoplasmic alterations as noted in light and electron microscopy studies.

Monkeys develop liver histopathology only with exposure at relatively high dosage levels of DDT (Durham et al 1963). No liver histopathology occurred in monkeys fed DDT at dietary levels of 200 ppm or less for periods of up to 7.5 years. One of six monkeys fed DDT at 5,000 ppm did develop the cytoplasmic inclusions that have been characteristically associated with chlorinated hydrocarbon poisoning in the rat.

Kimbrough et al (1971) made detailed studies of changes in liver ultrastructure. Rats were exposed to technical DDT at 250 and 500 ppm and to DDT in combination with 50 ppm and 100 ppm, respectively, of technical grade dieldrin at 50 ppm and 100 ppm, respectively. After rats had been exposed for 8 weeks, their livers were examined by light and electron microscopy. Liver weights of all exposed groups were significantly higher than those of the controls, and the livers of rats fed the combination of DDT and dieldrin weighed significantly more than those of rats given DDT alone. Morphologic changes (outlined in Table 2.2.1), including an increase in SER and atypical mitochondria, were observed in all exposed groups and were more pronounced in rats given both DDT and dieldrin.

2.2.2 Liver Enzyme and Other Biochemical Effects

Numerous studies have been conducted in which DDT has been identified as an inducer of hepatic microsomal enzymes and hence as an effector of the metabolism of drugs, pesticides, and other foreign chemicals (Conney 1967; Hart and Fouts 1963, 1965; Balazs and Kupfer, 1966b). As discussed in Section 2.3.4, the induction of hepatic microsomal enzymes can lead to

TABLE 2.2.1

LIGHT AND ELECTRON MICROSOPIC FINDINGS IN THE LIVERS OF RATS EXPOSED TO DIELDRIN AND DDT IN THE DIET

Dietary Concentration	Light Microscopic Findings	Electron Microscopic Findings
DDT, 250 ppm	Cells around central veins sightly enlarged; smooth-looking cytoplasm; lipid inclusions, mild to moderate	Mild to moderate increase in SER, occasional large myelin figures; atypical mitochondria seen in 1 of 5 animals
DDT, 500 ppm	Enlarged cells except in the periphery of the lobules; moderate number of vacuolated cells with inclusions in 2 of 5 rats; margination; lipid inclusions, moderate in 2 of 5	Less glycogen in 2 of 5 livers; marked increase in SER, swollen in some areas; occasional myelin figures, occasional atypical mitochondria in 3 of 5 livers
Dieldrin, 50 ppm, plus DDT, 250 ppm	All cells enlarged, smooth cytoplasm, margination, inclusions moderate to many; lipid inclusions, mild to moderate	Moderate to marked increase in SER, swollen in some areas, less glycogen, slight to moderate number of atypical mitochondria
Dieldrin, 100 ppm, plus DDT, 500 ppm	All cells enlarged, many cells with exceptionally large nuclei; margination in cytoplasm and inclusions in almost all cells; lipid inclusions, not studied	Marked increase in SER, which was swollen; indistinct cell borders; atypical mitochondria; vacuolated areas in cytoplasm surrounded by layers of dense lamellated material
None	Liver cells normal; lipid inclusions, none to moderate	Occasional small myelin figures

Adapted from Kimbrough et al 1971

enhanced metabolism of steroid hormones, with consequent effects on reproduction.

The lowest reported dosage of DDT for induction of various microsomal enzymes in the rat has been estimated at about 0.05 mg/kg/day, ie, a dietary level of 1 ppm (Kinoshita et al 1966) or 0.5 mg/kg/day (Schwabe and Wendling 1967). Gillett et al (1966) estimated that the threshold dose for enzyme induction was 0.125 mg/kg/day. Street et al (1969) estimated the threshold at 0.05 mg/kg/day. The different estimates are not necessarily inconsistent, since they depend on different test systems. In any event, the lowest estimate (0.05 mg/kg/day) is only 0.2 times that known to be effective in man (Laws et al 1967, Poland et al 1970).

A 27 percent reduction in pentabarbital sleeping time occurred in rats injected intraperitoneally with a single dose of DDT at 1 mg/kgs, which was associated with an average concentration of DDT in the fat of only 9.5 ppm (Conney et al 1967).

Hoffman et al (1970) administered DDT to weanling male rats for 14 days. No increase in the rate of p-nitroanisole (p-NA) metabolism was observed at dietary concentrations of DDT of 0.5 or 2.0 ppm. Concentrations of 4-750 ppm in the diet for 14 days produced increases proportional to the log dose. Extrapolation of this portion of the dose-response curve to the abscissa indicated a no-effect concentration of DDT in the diet of 3.27 ppm.

In addition to having effects on microsomal hydroxylating enzymes, DDT has been shown to influence some enzymes of intermediary metabolism and other miscellaneous enzymes and biochemical functions in vitro and sometimes in vivo (Table 2.2.2). Hrdina et al (1975) have discussed

TABLE 2.2.2

SUMMARY OF BIOCHEMICAL PARAMETERS AFFECTED BY DDT IN MAMMALS IN VIVO

Insecticide	Parameter	Effect
DDT	Serum asparatate aminotransferase	Increase
	Serum alanine aminotransferase	"
DDT; Dieldrin	Blood lactic and pyruvic acid	"
	Plasma free fatty acids	"
	Plasma corticosterone	"
DDT	Hexose shunt pathway	Decrease
	Total liver protein	Increase
	Hepatic NAD, NADP, NADH, NADPH	Decrease
	Hepatic NAD hydrolase	Increase
	Hepatic choline esterase	"
DDT; Dieldrin	Hepatic RNA	"
	Incorporation of leucine ^{14}C into protein	"
	Hepatic triglycerides	"
	Hepatic succinic acid dehydrogenase	Decrease
	Hepatic gluconeogenic enzymes	Increase
	Hepatic mixed function oxidases	"
DDT	Uterine weight	"
	Uterine glycogen	"
	Uterine RNA	"
DDT	Brain cytochrome oxidase	Decrease
	Brain acetyl choline	"
	Brain 5-hydroxy indole-acetic acid	Increase
DDT	Brain glutamine	"

Adapted from Kohli 1975

the importance of glucose metabolism in the toxic effects of DDT on mammals and reviewed extensive data suggesting that the effects of DDT involve interactions with cyclic AMP. They proposed that the changes in carbohydrate metabolism induced by DDT might involve alterations in the cyclic AMP-adenyl cyclase system of kidney cortex and liver.

2.2.3 Effects on the Cardiovascular System

Most dogs killed by a single dose of DDT die of ventricular fibrillation, and the same is true of some cats, monkeys, and rabbits. Monkeys differ from dogs in that the DDT-sensitized heart is able to recover from fibrillation and resume a normal rhythm (Philips and Gilman 1946). DDT not only sensitizes the myocardium in a way similar to that of halogenated hydrocarbon solvents but, through its action on the central nervous system, produces the stimulus that increases the likelihood of fibrillation.

There is no evidence that repeated, tolerated doses of DDT sensitize the heart. Rats were fed DDT at a dietary level of 200 ppm (about 10 mg/kg/day) for 8 months, during which they received weekly, intraperitoneal doses of vasopressin, a compound that causes a temporary myocardial ischemia. Electrocardiograms showed no significant increase in cardiac arrhythmias in the DDT-fed rats as compared with controls. The same results were obtained in rabbits treated in essentially the same way (Jeyaratnam and Forshaw 1974). Male mice exposed to p,p'-DDE at dietary levels of 125 or 250 ppm throughout life suffered a high incidence of myocardial necrosis (Tomatis et al 1974a).

2.2.4 Adrenal Effects

DDD has been used as a drug to control different forms of adrenal overproduction of corticoids in man. This therapy originally was based on

the demonstration that DDD (Nelson and Woodard 1948), especially o,p-DDD (Cueto and Brown 1958), caused gross atrophy of the adrenals and degeneration of the cells of the inner adrenal cortex in dogs. However, a dosage of approximately 100 mg/kg/day for many weeks was necessary to produce any benefit in man (Bledsoe et al 1964, Southren et al 1966a, b). In contrast, only 4 mg/kg/day produced marked atrophy of the adrenal in the dog. Kupfer (1967) reviewed the extensive literature indicating that the effect in man and most other species, except the dog, is caused by stimulation of corticoid metabolism by massive doses of o,p'-DDD and not by any direct effect on the adrenal. Southren et al (1966a,b) agreed that the effect was predominantly extra-adrenal in man when the drug was first given but offered evidence that adrenal secretion of cortisol was eventually reduced.

2.2.5 Other Endocrine Effects

Besides the pronounced effects of DDT and some of its metabolites on the adrenal cortex in various species, the pesticide appears to influence other mammalian endocrine organs. Nelson et al (1944) were the first to report mild changes in the thyroids of mice, rats, guinea pigs, rabbits, and dogs fed sublethal doses of DDT. Fregly et al (1968) noted changes in indicators of metabolic rate, such as food intake and oxygen consumption, of the rats they dosed with o,p'-, p,p'-, and m,p'-DDD. At 1,000 ppm, although there was an increase in thyroid weight, there were no overt symptoms of either hyperthyroidism or hypothyroidism. At 3,000 ppm, on the other hand, the increased thyroid weight was accompanied by reduced food intake, body weight gain, and oxygen

consumption, and an increased rate of cooling upon exposure to cold air. These changes are indicative of a hypometabolic state, and the authors concluded that DDD resulted in hypothyroidism in the rat.

Bastomsky (1974) found that DDT did not affect the biliary excretion of thyroxine in rats but did increase bile flow and the biliary clearance rate of plasma thyroxine. It also caused a marginal elevation of bile: plasma ratios and slightly increased the proportion of biliary iodine present as glucuronide. DDT did not affect uptake of iodine by the thyroid.

In a study by Seidler et al (1976), administration of DDT at 30-75 mg/kg produced marked increases in the thyroid mass and levels of triiodothyronine and thyroxin in the thyroid of rats. Other simultaneous effects included a decrease in the thyroid iodine level, a reduction of serum iodine and protein-bound iodine, a slight increase in serum thyroxin, and a marked increase of serum triiodothyronine and the iodine fraction in the liver.

Jefferies (1975) reviewed the effects of DDT and other organochlorine compounds on the thyroid in birds and mammals and suggested that a number of sublethal effects of DDT may be associated with primary effects on the thyroid. These effects include changes in metabolic rate, body temperature, respiratory rate, behavior, reproduction, Vitamin A storage and circulation, lipid metabolism, carbohydrate metabolism, and calcium metabolism.

From examination of isolated pancreatic islets of DDT-exposed mice, Yau and Mennear (1977) determined that oral exposure to DDT at 50 mg/kg reduced insulin secretion to 32% of the control value. Similarly, islets from DDT-treated mice were significantly less responsive to tolbutamide, indicating that the pancreatic inhibitory effect of DDT is not specific for glucose stimulation.

2.2.6 Effects on the Immune System

Street and Sharma (1974) tested the immune response of rabbits fed graded concentrations of p,p'-DDT in their diets. The animals were challenged with sheep red blood cells and Freund's adjuvant after 4 weeks of feeding and then continued on the same diet during a subsequent 4-week evaluation of the status of their immune systems. DDT was found to reduce the count of plasma cells in popliteal lymph nodes, to reduce the number of germinal centers in the spleen, and to induce atrophy of the cortex of the thymus. These responses were generally scaled to increasing levels of the pesticide in the diet and were significant even at a dosage of 0.92 mg/kg/day for 28 days. Hemolysin and hemagglutinin titers were not significantly affected by treatment with DDT and no consistent trends observed. DDT decreased, though not significantly, the antigen-induced increase in serum gamma-globulin and significantly increased the preantigen gamma-globulin values. Skin sensitivity to tuberculin was decreased, but only at the high doses of DDT.

Hamid et al (1974) exposed rats to o,p'-DDD and found a decreased body weight, as well as decreases in the weights of the thymus, spleen, and adrenals. In well-nourished rats the numbers of plaque-forming cells (PFC) and rosette-forming cells (RFC) in the spleen and thymus were lowered by treatment with o,p'-DDD. Similarly treated rats on a protein-deficient diet had numbers of PFC and RFC in their spleen almost equal to those of controls. Atrophy of both the adrenal cortex and the thymolymphatic organs was found in the groups exposed to DDD, regardless of nutritional condition.

In another study, rats immunized with diptheria toxoid and fed diets containing DDT at 20 and 200 ppm levels for 31 days showed no effects on their serum antitoxin titers. However, the numbers of metachromatic, histamine-containing mast cells in mesenteries were reduced, by 46% in the 20 ppm group and by 61% in the 200 ppm group. The severity of anaphylactic shock was also reduced in the rats exposed to DDT (Gabliks et al 1975).

2.2.7 Central Nervous System Effects

The clinical signs and pathologic changes seen in mammals exposed to chlorinated hydrocarbon insecticides have led to attempts to establish whether any correlation exists between the observed neurotoxic effects of these compounds and changes in the function of the cerebral motor cortex and the cerebellum. Electroencephalographic (EEG) studies showed significant alterations in spontaneous electrical activity of the brain in cats, monkeys (Crescitelli and Gilman 1946), and rats (Woolley and Barron 1968, Henderson and Woolley 1970) after acute exposure to DDT. Administration of a single dose (50-75 mg/kg iv) of this insecticide to cats and monkeys caused the normal pattern of irregular bursts of waves to be shifted to a persistent type of rhythm in the cerebral motor cortex, whereas in the cerebellum there was a progressive increase in amplitude of waves followed by a constant peak at the time the tremors appeared (Crescitelli and Gilman 1946). Pollock and Wang (1953) showed that cats ingesting DDT in the diet manifested EEG changes associated with ataxia and tremors. These were observed initially in the cerebellum and, as the intensity of insecticide poisoning increased, seizure activity was noted

in the cerebral cortex. Dēsi et al (1966) and Farkas et al (1968) reported that when rats were given daily doses of DDT at 20 mg/kg, marked changes in the EEG pattern (increase in both frequency and amplitude) were observed after 4 weeks and slight ataxia was noted after 5 weeks. Woolley and Barron (1968) found that DDT-induced changes in cerebellar electrical activity occurred sooner and were greater in magnitude than those observed in other brain areas such as the motor cortex and the reticular formation. Further the changes in cerebellar activity occurred before signs of toxicity such as tremors became evident, suggesting that the cerebellum is particularly sensitive to the effects of DDT. Haymaker et al (1946) pointed out that the tremors and ataxia seen in acute DDT poisoning were similar to the signs of cerebellar dysfunction. The preceding EEG studies offered evidence to support the view that the cerebellum and the cerebral motor cortex may be two important target areas for the action of DDT on the central nervous system.

Scudder and Richardson (1970) found that chronic administration of technical DDT at low concentrations (0.1 or 1.0 µg/liter in drinking water) to pregnant mice and their offspring resulted in a significant decrease in the aggressiveness of male offspring. The mean latent period for attack behavior in paired encounters was 4-10 times greater in the exposed mice. No effects were observed in the offspring of mice exposed at 0.01 µg/liter.

Another effect of prenatal exposure to low levels of DDT was reported by Al-Hachim and Fink (1968). The offspring of female mice exposed to DDT at 2.5 mg/kg in the 2nd or 3rd week of pregnancy showed a delayed acquisition of conditioned avoidance responses when tested at age 32-37 days. Craig

and Ogilvie (1974) exposed female mice to technical DDT at 200 ppm in their diets throughout pregnancy and lactation. Their offspring subsequentl made significantly more errors and took significantly longer than controls in running a T-maze.

Peterle and Peterle (1971) studied the effects of feeding technical DDT at a dietary concentration of 7 ppm on the aggressive behavior of male mice. Treated mice "lost" more bouts, as determined by posturing and avoidance behavior, and controls made more biting attacks. Thus, the DDT-fed mice were significantly less agressive than control mice and were more likely to submit to territorial fights.

Medved et al (1968) reported that administration of DDT to cats (by an unspecified route) affected conditioned reflexes. A single dose of 100 mg/kg caused a total extinction of conditioned reflexes, which did not return to normal for 8-12 days. Doses of 50-75 mg/kg caused a small increase in latency of conditioned reflexes, which returned to normal after 3-4 days. No effects were observed after doses of 10 or 25 mg/kg.

Sobotka (1971) reported alterations in several behavioral and neurophysiologic parameters in mice given single low doses of DDT. The open-field exploratory activity was significantly enhanced 24 hours after a single oral dose of DDT at 25 mg/kg. At the same time, the ability of animals to adapt to the open-field situation was attenuated. In a multi-generation study with mice exposed to technical DDT at 2.8-3.0 ppm in the diet, no effects were observed on spontaneous or caffeine-induced motility (Tarján and Kemény 1969).

2.3 Effects on Reproduction

2.3.1 In Rats

Ottoboni (1969) reported that female rats reproduced normally when fed technical DDT at dietary concentrations as high as 200 ppm for two generations. At a dietary concentration of 20 ppm, female rats had a significantly longer reproductive lifespan (14.55 months) than littermate controls (8.91 months). The number of treated females conceiving and the number of successful pregnancies after the age of 17 months was significantly greater than in controls.

Jonsson et al (1975) administered technical DDT to female rats at concentrations of 75 and 150 ppm in the diet, for periods of 8 and 36 weeks. At the higher concentration of DDT, only one of seven females mated and no pups were born. At the lower concentration, the number of rats producing litters was reduced, but the size of litters was not altered significantly. Adverse effects on reproduction were noted at plasma DDT concentrations above 800 ppb, while concentrations below 500 ppb were associated with nearly normal reproduction.

Male and female Wistar rats given diets containing o,p'-DDT at 0, 20, 200, or 1,000 ppp or p,p'-DDT at 0, 20, 200, or 500 ppm were studied throughout a 6-month breeding period. Growth was severely depressed in pups nursing from dams fed p,p'-DDT at 200 or 500 ppm, and all pups in the 500 ppm group died within 10 days of birth. The growth of pups from the group fed o,p'-DDT at 1,000 ppm was reduced below that of controls, and surviving females from this group showed significantly reduced fertility

and fecundity when mated at age 80 days. Two sterile females from this group had polycystic ovaries. Offspring of rats fed o,p'-DDT at 200 ppm were reported to have reproduced normally (Clement and Okey 1974). In a study by Wrenn et al (1970), feeding o,p'-DDT at dietary concentrations of 1 or 2.5 ppm had no significant adverse effects on reproduction.

Treon and Cleveland (1955) reported the results of a three-generation reproductive study in Carworth Farms rats fed recrystallized DDT at 2.5, 12.5, and 25 ppm in the diet. The number of pregnancies and the size of litters were unaffected by DDT treatment, but all dose regimens caused a "slight" increase in mortality in offspring during the first 21 days of life.

Duby et al (1971) exposed rats to p,p'-DDT, o,p'-DDT, or technical DDT at dietary concentrations of 1 and 15 ppm through two generations. They found no effects by the three compounds on reproductive performance, as measured by litter size at birth, litter weight at day 21, growth patterns of offspring, time of vaginal opening, fertility, or fecundity.

Green (1969) exposed Sprague Dawley rats to DDT at a dietary concentration of 7 ppm and observed marked reductions in fertility and survival of offspring in the first generation of the exposed rats. No rats in the second generation exposed to DDT conceived. Simultaneous exposure to aldrin (5 ppm), endrin (5 ppm), or heptachlor (5 ppm) increased the adverse effects on conception rate and pup survival, but the effects appeared less than additive. Green (1969) also cited unpublished data by C. Agthe indicating impaired reproduction in rats exposed to DDT at 10 ppm.

2.3.2 In Dogs

Deichmann et al (1971) and Deichman and MacDonald (1971) reported a study in which four male and three female beagle dogs were exposed to p,p'-DDT at 12 mg/kg and four males and four females were exposed to a mixture of p,p'-DDT at 6 mg/kg and aldrin at 0.15 mg/kg. The dogs were exposed five times a week for 14 months, and attempts were made to breed them between the 2nd and 70th weeks after cessation of exposure. By then the concentrations of DDT and metabolites had fallen below 3 ppb in the blood and below 32 ppm in the fat in most of the dogs. Exposed dogs showed a moderate increase in serum alkaline phosphatase activity but no change in other measured biochemical parameters. Reproduction was severely affected, as evidenced by diminished libido in the males and delayed estrus in females. At the time of partuition, infertility, reduced mammary development and milk production, and increased infant and maternal mortality were apparent.

In contrast to these results of Deichmann et al (1971), Ottoboni et al (1977) reported little effect on reproduction in beagle dogs exposed to technical DDT at 1, 5, and 10 mg/kg/day for three generations. The only statistically significant effect they reported was an earlier occurence of first estrus (by 2-3 months) in treated females. They noted no adverse effects on gestation period, fertility, success of pregnancy, litter size, and lactation or on the viability, survival, sex ratio, or growth of pups. There was a consistent increase in liver weight in pups littered from exposed dogs.

2.3.3 In Mice

In a six-generation study in mice, DDT at 25 ppm was reported to have no effects on fertility, gestation, viability, lactation, and survival. At 100 ppm, lactation and survival were slightly reduced. Severe effects on reproduction were reported at 250 ppm (Keplinger et al 1968). Some adverse effects on reproduction, primarily decreased lactation indices and viability indices, were also reported in groups of mice fed combinations of pesticides, including aldrin at 10 ppm plus DDT at 100 ppm, chlordane at 100 ppm plus DDT at 100 ppm, and dieldrin at 10 ppm plus DDT at 100 ppm (Deichmann and Keplinger 1966, Keplinger et al 1968, Deichmann and MacDonald 1971).

Two large-scale feeding tests were conducted with BALB/c and CFW mice to investigate effects of techinical DDT on reproduction. In these studies DDT at 7 ppm in the diet did not affect adult mortality, fertility, or fecundity, and offspring were not adversely affected (Ware and Good 1967).

In a five-generation study, no effects were observed on the reproductive performance of BALB/c mice exposed to DDT at a dietary concentration of 2.8-3.0 ppm. Reproductive parameters studied included the numbers of pregnancies and births, litter size, survival to weaning, average weight at weaning, and average lifespan (Tárjan and Kemény 1969).

Lundberg and Kihlstrom (1973) investigated the effects on the number of implanted embryos in mice given injections of p,p'-DDT (containing "small amounts" of o,p'-DDT and p,p-DDD) at high doses (20, 50, and 100 mg/kg). Depending upon the dose regimen of DDT and the particular days injections were given during gestation, the number of implantation sites in the DDT-treated mice was decreased. Subsequent studies by Lundberg (1974) confirmed that DDT caused a decreased in the frequency of implanted embryos.

2.3.4 Interactions with Steroid Hormones

A number of investigators have shown that DDT and its metabolites are capable of inducing hepatic mixed function hydroxylating enzymes with consequent secondary effects on the circulating concentrations of steroid hormones. Kupfer (1975) and Kupfer and Bulger (1976a) have reviewed the literature on these effects, tracing the studies to the original discovery by Hart and Fouts (1963, 1965) that chlorinated hydrocarbons are potent inducers of mixed function oxidases (MFO). In the case of DDT, effects have been measured at dietary levels as low as 1 ppm (Hart and Fouts 1965, Kinoshita et al 1966).

Balazs and Kupfer (1966a,b) first established the link between induction of MFO by chlorinated hydrocarbons and enhanced steroid metabolism in vivo. Conney (1967), Conney et al (1967, 1973), and Welch et al (1971) demonstrated that exposing rats to chlorinated hydrocarbons and other inducers of MFO stimulates androgen and estrogen metabolism (measured in vitro) and diminishes the hormonal activity of administered steroids. Both o,p'-DDD and technical DDT have been shown to stimulate the hydroxylation of cortisol in vivo (Balazs and Kupfer 1966a, Kupfer et al 1964, Southren et al 1966a). The action of technical DDT is thought to be attributable to the o,p' isomer, because p,p'-DDT had little effect (Kupfer and Bulger 1976a).

Other interactions of DDT with steroid hormones and the male and female reproductive systems have been reviewed by Thomas (1975). DDT can interfere with male sex accessory gland metabolism as evidenced by a decrease in the affinity of the mouse prostate gland for radioactive

testosterone (Smith et al 1972). Doses of DDT that exerted this inhibitory effect on the assimilation of androgen by the mouse prostate gland failed to exert any uterotrophic effect in female mice. Such findings tend to exclude the possibility of inherent estrogenicity accounting for this inhibition of androgen uptake by the prostate gland. Studies by Wakeling and Visek (1973) revealed that o,p'-DDT can inhibit the binding of dihydrotestosterone to specific receptor proteins in the cytoplasmic fraction of the rat prostate gland.

Administration of DDT to male mice had no effect on testicular weights and produced no changes in sex accessory organ weights (Thomas and Lloyd 1973). Neither the seminal vesticles nor the prostate glands were affected by the oral administration of technical grade DDT. Prostate gland fructose, a chemical indicator of androgenic activity, was not altered by a 10-day administration of DDT in large doses.

Administration of a single oral dose of radiolabeled DDT resulted in the localization of considerable amounts of radioactivity in several organs of the male reproductive system (Smith et al 1972). The prostrate gland and gonads contained sizeable concentrations of radioactivity as early as 1 and 2 hours after ingestion of labeled DDT. Epididymal fat pads retained some DDT or its metabolites as long as 12 days after an oral dose. DDT or its metabolites were also detected in the seminal vesicles and in the seminal plasma of mice (Smith et al 1972). DDT has been reported to be present in high concentrations in the fat tissues and gonads of exposed female mice (Bäckström et al 1965). Tomatis et al (1971)

reported that, while fat tissues of exposed mice contained the highest amounts of DDT and its metabolites, appreciable levels were also found in the reproductive organs. In mice exposed to technical DDT at 50 ppm in the diet for 13-30 weeks mean concentrations were 48 ppm DDT, 16 ppm DDD, and 7.2 ppm DDE in ovaries and 15 ppm DDT, 1.7 ppm DDD, and 0.7 ppm DDE in testes.

Studies by Kuntzman et al (1966) showed that DDT exposure caused a marked increase in hepatic 16-alpha-androgen hydroxylase activity in immature male rats. Smaller increases reportedly occurred in the 6-beta and the 7-alpha hydroxylation of testosterone. These authors suggested that the 16-alpha hydroxylation of testosterone was catalyzed by a different enzyme system from that required for the 6-beta or the 7-alpha hydroxylations.

In the male mouse, DDT exposure can actually inhibit hepatic androgen hydroxylase activity (Thomas and Lloyd 1973). Both the 7-alpha- and 16-alpha-testosterone hydroxylases were profoundly inhibited by DDT in mouse hepatic microsomes. DDT exerted little effect on the 6-beta-testosterone hydroxylase enzyme.

It is noteworthy that o,p'-DDD exerts a remarkably consistent effect on the metabolism of androgens in humans (Hellman et al 1973). This compound can profoundly decrease the conversion of testosterone and androsteredione to androsterone and etiocholanolone. DDD can also increase the rate of conversion to uncharacterized polar metabolites. Thus the chemicals in the DDT complex can affect changes not only in the metabolism of steroids in the hepatic microsomes but also in the periphery (Thomas 1975).

Lloyd et al (1974) administered technical DDT at 25 or 50 mg/kg orally for 10 days to male mice. There was a significant reduction in the accumulation of testosterone and its principal metabolite 5-alpha-dihydrotestosterone by the anterior prostate gland. Hepatic formation of polar metabolites of testosterone was also reduced by DDT-pretreatment. No significant changes were observed in accessory sex organ weights or prostate gland fructose concentration. The authors suggested that DDT may alter the accumulation of prostatic androgens as a result of altered hepatic steroid hydroxylation.

2.3.5 Estrogenic Effects

In addition to DDT having the effects summarized above, o,p'-DDT has been reported by a number of authors to be estrogenically active and to have significant effects on development when administered to neonates. The estrogenic activity of o,p'-DDT (and of technical DDT which contains this isomer) was first reported by Bitman et al (1968) and Levin et al (1968). Singhal et al (1970) demonstrated that exposure to o,p'-DDT elevated certain uterine enzymes in female rats. Forster et al (1974) tested several homologs of DDT for their ability to inhibit specific binding of estradiol to uterine cytosol and nuclear fractions. Both o,p'-DDT and o,p'-DDE inhibited the in vitro binding of estrogen, but o,p'-DDD, m,p'-DDD, p,p'-DDE, p,p'-DDT, and DDA were inactive. Nelson et al (1976) found that o,p'-DDT required no metabolic activation to exert estrogenic effects, unlike analogs such as methoxychlor. The effects of various isomers and an analog are summarized in Table 2.3.1.

TABLE 2.3.1

ORDER OF ESTROGENIC POTENCIES OF VARIOUS DDT HOMOLOGS IN THE RAT

Uterotropic	Glycogen Elevation	Ornithine Decarboxylase Induction	Receptor Inhibition of E_2 Binding
o,p'-DDT	o,p'-DDT	o,p'-DDT	o,p'-DDT
Methoxychlor	o,p'-DDE (e)	o,p'-DDD	o,p'-DDD
p,p'-DDT	Methoxyclor (e)	p,p'-DDT	o,p'-DDE
o,p'-DDD	p,p'-DDT (e)	p,p'-DDE (e)	Methoxychlor
m,p'-DDD	o,p'-DDD (I)	p,p'-DDD (e)	p,p'-DDT
p,p'-DDE (I)	m,p'-DDD (I)		p,p'-DDD (I)
p,p'-DDD (I)	p,p'-DDD (I)		p,p'-DDE (I)
	p,p'-DDE (I)		

e = Equally active; I = Inactive

Adapted from Kupfer and Bulger 1976a

Duby et al (1971) reported that injection of o,p' - DDT into 21-day-old female rats (1,2,or 4 mg/rat) led to increased uterine weight at maturity. Similar exposure to p,p'-DDT had only slight effects, while treatment with technical DDT led to effects corresponding to the content of the o,p' isomer. Similar estrogenic effects were observed in mink exposed to o,p'-DDT at age 120-150 days.

Gellert et al (1974) found that neonatal rats exposed to o,p'-DDT had permanently altered neuroendocrine differentiation. Female rats given 0.1 mg of o,p'-DDT on the 2nd, 3rd, and 4th days of life showed precocious puberty, persistent vaginal estrus, and anovulation. Administration of o,p'-DDT to neonatal female rats also led to the development of polycystic ovaries and uterine histopathology, including patches of stratified squamous epithelium in the endometrium, after puberty. Male neonates were unaffected by similar treatment. However, Campbell (1976) reported precocious development of the adrenal cortex in male rats exposed to up to 400 µg of o,p'-DDT on days 1-5 after birth.

Wrenn et al (1970) found that o,p'-DDT innduced precacious puberty in rats fed doses as low as 50 µg daily on days 18-33. Lee and Visek (1975) reported that male rats injected with 3 mg of o,p'-DDT at 1-3 hours after birth subsequently showed an abnormal pattern of sexual brain differentiation. This was attributed to inhibition of normal action of testosterone on the developing brain.

Preweaning exposure of neonatal males to milk from dams injected with 50 mg o,p'-DDT daily during postnatal days 1-25 caused statistically significant alterations in body weight and in the weights of the testes and ventral prostate (Campbell and Mason 1975).

Krause et al (1975) reported that male rats exposed to technical DDT at 500 mg/kg on the 4th and 5th days of life or at 200 mg/kg/day on days 4-23 showed lower fertility than controls. This was associated with degeneration of spermatogenic cells and a decrease in the number of Leydig's cells. Damage to the seminiferous epithelium was attributed to reduction in testosterone.

Most of these studies indicating lasting effects of neonatal exposure to o,p'-DDT or technical DDT have involved direct administration of the compounds to the infant rats or mice. Kihlström et al (1975) found that the reproductive capacity of mice was also impaired by exposure to DDT in maternal milk, as a result of exposure of the mothers to four weekly doses of 50 mg/kg during lactation. Jonsson et al (1975) found that ingestion by female rats of diets containing technical DDT at 75 or 150 ppm, with consequent exposure of the embryos and neonates, did not lead to polycystic ovaries in the offspring. Wrenn et al (1970) observed that rats given o,p'-DDT at dietary levels of 1 and 2.5 ppm showed no measurable effects on reproduction, except an increase in the birth weight of pups in the 2.5 ppm group.

Kupfer and Bulger (1976a,b, 1977) have reported detailed studies of the mechanisms by which o,p'-DDT exerts estrogenic and other effects in mammals. They attributed at least some of the effects to the binding of o,p'-DDT to the estrogen binding receptor, a binding that has been demonstrated in rat and human tissues in vitro.

2.4 Teratogenesis

p,p'-DDT administered to pregnant mice at a rate of 1 mg/kg on days 10, 12, and 17 of gestation caused morphologic changes in the gonads and

reduced the fertility of offspring, especially females (McLachland and Dixon 1972).

Schmidt (1973) reported blastotoxic, embryotoxic, and fetotoxic effects of DDT given in single or repeated doses to pregnant mice. The minimum single embryotoxic dose was 25 mg/kg administered 10 days postcopulation; daily doses of 2.5 mg/kg were significantly embryotoxic. No teratogenic effects were reported.

In a study by Ottoboni (1969), the offspring of female rats exposed to technical DDT at dietary levels of 200 ppm throughout pregnancy and lactation showed a significant increase of "ringtail," a constriction of the tail followed by spontaneous amputation.

Hart et al (1971) reported that exposure of rabbits to DDT at 50 mg/kg on days 7,8, and 9 of gestation caused premature delivery, increased resorption, and decreased intrauterine growth, but no congenital defects were produced.

Green (1969) administered DDT at a dietary concentration of 7 ppm to Sprague-Dawley rats for 60 days before breeding and throughout pregnancy. There was a marked decrease in fertility and a small increase in the frequency of resorptions, but the incidence of abnormal embryos in the exposed rats (2/131) was no larger than that in the controls (9/396).

In other studies of reproduction of mammals exposed to DDT, congenital defects have been reported to be within the normal frequency range (Ottoboni 1969) or have not been mentioned. However, it is not clear that the offspring have been adequately examined in any study except those of Green (1969), Hart et al (1971), and Schmidt (1973).

2.5 Carcinogenesis

Data on the carcinogenicity of DDT and metabolites published through 1973 have been reviewed and summarized by the International Agency for Research on Cancer (IARC 1974). Extensive studies conducted by IARC, itself, have been reviewed by Tomatis and Turusov (1975).

2.5.1 In Mice

Innes et al (1969) reported the results of a study in which 18 male and 18 female (C57-BL/6 x C3H/Anf) F1 mice and a similar number of (C57BL/6 x AKR) F1 mice were given single doses of 46.4 mg/kg p,p'-DDT by stomach tube at 7 days of age, and the same absolute amount was then given daily until the animals were 28 days of age, when they were transferred to a diet containing p,p'-DDT at 140 ppm. Mice were killed at 81 weeks. In both strains, about 30% of the females died during treatment. Hepatomas were found in 11/18 male and 4/18 female exposed (C57BL/6 x C3H/Anf)F1 mice, compared with 8/79 in male and 0/87 in female controls, and in 7/18 male and 1/18 female exposed (C57BL/6 x AKR)F1 mice, compared with 5/90 in male and 1/82 in female controls. In addition, 6/18 exposed (C57BL/6 x AKR) F1 females died with malignant lymphomas, compared to 4/82 female controls. Both o,p'-DDD and p,p'-DDD were tested in parallel experiments in the same study, but results were not given in sufficient detail for evaluation.

A five-generation experiment, originally set up to investigate the effects of DDT on behavior, was used to provide animals for a carcinogenicity study. The tumor incidence in one test group and one control group of BALB/c mice from each of the five generations was studied. A total of 683 mice received a diet containing p,p'-DDT at 3 ppm, and 406 were given

the control diet. Lung carcinomas were observed in 16.9% of the treated mice and 1.2% of the controls. (The incidence of lung adenomas was not reported, although the authors noted an average incidence of 5% in their colony of mice.) The incidences of lymphomas were 4.8% in exposed mice and 1.0% in controls. Incidences of leukemias were 12.4% and 2.6% in exposed and control mice, respectively. Other tumors occurred in 5.8% and 1.0%, respectively (Tárjan and Kemény 1969). (Table 2.5.1).

Tomatis et al (1972) reported a two-generation dose-response study on the CF1 mice fed DDT. A total of 881 exposed and 224 control mice were included. Technical DDT at dietary concentrations of 2, 10, 50, and 250 ppm were administered for the animals' lifespans. In both the parent (P) and offspring (F1) generations there was an increased number of deaths from week 60 onwards in mice receiving DDT at 250 ppm. The only tumor incidence affected by exposure to DDT was that of liver-cell tumors, and in the two sexes, it ranged as follows:

Exposure Group	Male*	Female*
0 ppm	25/113	4/111
2 ppm	57/124	4/105
10 ppm	52/104	11/124
50 ppm	67/127	13/104
250 ppm	82/103	69/90

(*Number of animals surviving at the time the first tumor appeared at any site in each group)

The excess incidence of liver-cell tumors in mice of both sexes fed DDT at 250 ppm, relative to that of controls, was significant at the 1% level. The

TABLE 2.5.1

INCIDENCE OF TUMORS AND LEUKEMIAS IN THE F1-F5 GENERATIONS FED DDT AT 2.8-3.0 PPM IN THE DIET FOR 6 MONTHS

Group and Generation	No. of Mice	Tumors		Leukemia	
		Male	Female	Male	Female
DDT-Exposed					
F1	10	1	2	1	3
F2	35	9	8	2	-
F3	69	6	15	1	10
F4	264	30	34	7	28
F5	305	31	60	10	23
Total no.		77	119	21	64
Percentage		11.27	17.42	3.07	9.37
Control					
F1	3	-	1	1	1
F2	39	-	2	1	-
F3	51	1	3	-	-
F4	144	-	3	-	3
F5	169	1	2	1	3
Total no.		2	11	3	7
Percentage		0.49	2.71	0.74	1.72

Adapted from Tarján and Kemény 1969

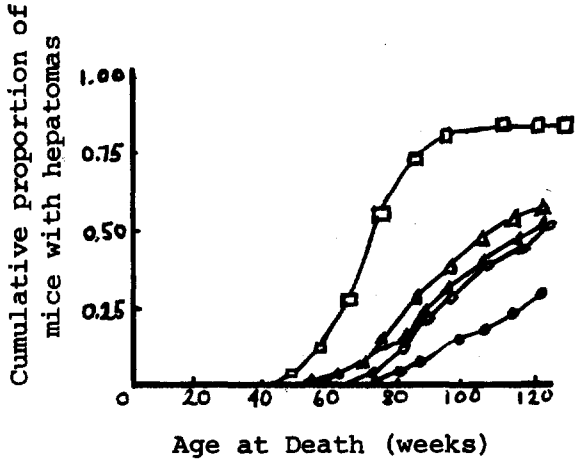
excess incidences of liver-cell tumors in males fed 2, 10, or 50 ppm were significant at the 1% level in animals surviving more than 60 weeks. In females, the excess incidence of liver-cell tumors was significant only at the 250 ppm level. In both sexes, liver-cell tumors was significant only at the 250 ppm level. In both sexes, liver-cell tumors appeared earlier in exposed mice than in controls (Figure 2.5.1). Four liver-cell tumors, all occurring in DDT-exposed mice, had metastasized. No remarkable differences between P and F1 mice were observed in this study.

These results were confirmed in a later study of the effects of technical DDT on six consecutive generations of CF1 mice (Turusov et al 1973). Terracini et al (1973a) reported a two-generation study in which 515 female and 431 male BALB/c mice were given technical DDT at dietary concentrations of 0, 2, 20, or 250 ppm for the animals' lifespans. The only tumors found in excess in the treated animals were liver-cell tumors. In females, the survival rates were comparable in all groups, and liver-cell tumors were found in 0/131 control mice, 0/135 mice fed DDT at 2 ppm, 1/128 mice at 20 ppm, and 71/121 mice at 250 ppm. In males, early deaths occurred in all groups as a consequence of fighting and in the group fed at 250 ppm because of the toxicity of DDT. In males that survived beyond 60 weeks of age, liver-cell tumors were found in 1/62 control mice, in 3/58 receiving DDT at 2 ppm, in 0/48 at 20 ppm, and in 15/31 at 250 ppm. The distribution of liver-cell tumors was unrelated to the litter of origin. No metastases were found. The tumors grew after transplantation into animals from the same strain (Terracini et al 1973a).

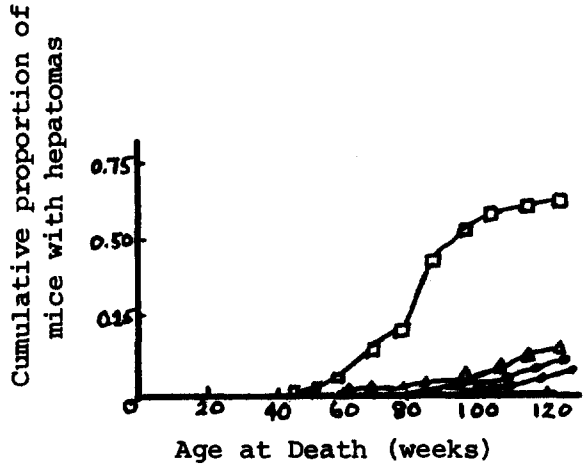
Confirmatory results were obtained in two subsequent generations of BALB/c mice fed technical DDT. In this experiment, however, F1-F3 mice,

FIGURE 2.5.1 (Tomatis and Turusov 1975)

LIVER CELL TUMORS IN MICE FED p,p'-DDT
AT VARIOUS DOSAGE LEVELS



a. Male Mice with Hepatomas
Dying at Different Time Periods



b. Female Mice with Hepatomas
Dying at Different Time Periods

• control; ▲ DDT 2 ppm; O 10 ppm; Δ 50 ppm; □ 250 ppm

which were exposed to DDT both in utero and throughout life, developed more liver tumors than did P mice, which were exposed to DDT only after weaning (Terracini et al 1973b).

Shabad et al (1973) reported a multigeneration study in A strain mice. DDT in sunflower-seed oil was administered to 234 mice at a concentration of 10 ppm. Data in the paper are ambiguous about the exact dose received by the mice. In two control groups, a total of 206 mice received either no treatment or sunflower-seed oil alone. Mice in the F0, F1, F2, F3, F4, and F5 generations were treated similarly. Thirty other mice were given 0.1 ml of a 50 ppm solution, ie, 5 mg of DDT, which adversely affected pregnancies, so no subsequent generations were obtained at this level. Approximately 30-50% of the animals in the exposed groups died before 6 months; all animals were killed after 12 months. The only tumors found were lung adenomas. The incidences of pulmonary adenomas in the F0-F5 generations exposed to DDT at 100 ppm were as follows:

F0, 8/42 (19%); F1, 4/26 (15%); F2, 6/25 (24%); F3, 19/41 (46%); F4, 16/37 (43%); F5, 8/63 (13%); controls (F0-F5), 15/206 (7%). Of the 30 mice receiving 50 ppm doses, 14 died before 6 months, and 3 of these (21.5%) had lung adenomas; of the 16 dying after this time, 8 (50%) had lung adenomas. The average number of lung nodules/mouse, about 7.2, was similar in both sexes, whereas there were 1.0-4.7 nodules/mouse in the six generations receiving 10 ppm doses and 1.0 nodule/mouse in controls. Because the animals were sacrificed after only 12 months of exposure, the absence of liver-cell tumors in the treated groups is of no significance.

Walker et al (1972) administered diets containing p,p'-DDT at 50 or 100 ppm to groups of 30-32 CF1 mice of each sex for 2 years.

The control groups included 47 mice of each sex. At 0,50, and 100 ppm, liver tumors occurred in 13%, 37%, and 53% of the males, respectively. In females, the corresponding incidences were 17%, 50%, and 76%. Liver tumors were characterized morphologically into two types. Type "a" tumors were characterized by simple nodular growths of solid cords of parenchymal cells. Type "b" tumors were those growing with papillary or adenoid growths, the cells proliferating in confluent sheets with necrosis and increased mitosis. The ratio of type "a" to type "b" tumors was greater than 3:1 in the treated group; no type "b" tumors occurred in controls. The incidences of other tumors were comparable in control and DDT-exposed mice. Metastases were found in one treated female.

In a subsequent study in which p,p'-DDT at 100 ppm was fed in the diet to 30 male and 30 female CF1 mice for 110 weeks, the animals were not sent for autopsy until the intra-abdominal masses were large enough to cause the animals to become anorexic or clinically affected. In this experiment, 79% of the males and 96% of the females developed liver tumors within 26 months, compared with 24% and 23% in the controls. The ratio of type "a" to type "b" tumors was about 1:1 in the DDT-treated mice (Thorpe and Walker 1973).

Subsequent to the original publications, additional information on the studies by Walker et al (1972) and Thorpe and Walker (1973) has been provided by Stevenson (1974), Thorpe (1974), Reuber (1974, 1976), Hunt (1974), and Epstein (1975). In the study by Walker et al (1972) 10 mice of each sex were fed p,p'-DDT at 200 ppm and 32 mice of each sex were fed

a mixture of p,p'-DDT at 50 ppm and HEOD (dieldrin) at 5 ppm. The incidence of liver tumors was significantly increased above that in controls in both of these exposure groups, as well as in the groups exposed to DDT at 50 ppm and 100 ppm, as reported in the original publication. Stained liver sections from six groups of animals in this study were evaluated by Reuber (1974), with the results shown in Table 2.5.2. According to Reuber (1974, 1976), type "b" tumors as defined by Walker et al (1972) consist primarily of hepatocellular carcinomas, whereas type "a" tumors include both hyperplastic nodules and well-differentiated hepatocellular carcinomas. Reuber's diagnoses of liver tumors as listed in Table 2.5.2 show a significant increase in hepatocellular carcinomas in females exposed to DDT at 50 ppm and a marked additive or synergistic effect of dieldrin. Metastases were found in one female exposed to DDT at 100 ppm and in one female exposed to DDT plus dieldrin (Walker et al 1972). The incidence of other tumors was comparable in control and DDT-exposed mice, but the age-adjusted incidence of lung tumors was increased in both sexes exposed to the DDT-dieldrin mixture (Hunt 1974).

Bennison and Mostofi (1950) reported a study in which 14 BALB/c mice of both sexes were exposed to DDT by skin painting with a 5% solution of DDT in kerosene once weekly for 52 weeks. Sixteen controls received no treatment. No skin tumors were found.

Gargus et al (1969) gave 42 neonatal Swiss mice single subcutaneous injections of DDT (composition unspecified) at 15,000 mg/kg within 72 hours after birth. The mice were killed after 6 months and examined for lung

TABLE 2.5.2

DIAGNOSES BY REUBER (1974) OF LIVER LESIONS IN MICE FED p,p'-DDT AT 50 PPM IN THE DIET

Exposure Group	Sex	Number Examined	Incidence of Liver Lesions* (%)					
			NH	H	N	SC	LC	TC
Control	M	45	62	29	9	0	0	0
"	F	32	47	44	9	0	0	0
DDT, 50 ppm	M	31	31	34	28	6	0	6
"	F	31	32	16	35	13	3	16
DDT, 50 ppm, plus HEOD**	M	33	3	18	21	15	42	58
"	F	31	0	0	6	29	65	94

*NH = no hyperplasia, H = hyperplasia, N = nodules, SC = small carcinomas (less than 5 mm), LC = large carcinomas, TC = total carcinomas
**Diets containing p,p'-DDT at 50 ppm and recrystallized dieldrin at 5 ppm

Adapted from Epstein 1975

tumors, which were not found in excess. The incidence of other tumors was not reported.

In a study reported by Tomatis et al (1974b), eight groups of CF1 mice, each containing about 60 males and 60 females, were exposed to technical DDT at 250 ppm in the diet. Four groups were exposed for 15 weeks; the other four groups were exposed for 30 weeks. Groups of mice from each exposure regimen were sacrificed after exposure and at 65, 95, and 120 weeks after the start of the experiment. Five additional groups of mice served as negative controls. The incidence of liver tumors was increased in both sexes in all six groups of mice exposed to DDT and killed at 65, 95, or 120 weeks. The size and multiplicity of liver tumors was also increased in all exposed groups. In mice exposed for 30 weeks, a similar proportion of males with liver tumors was observed when they were killed at 65, 95, and 120 weeks. In females, the incidence of liver tumors increased from the 65th to the 95th week. A similar pattern was observed in mice exposed for 15 weeks, but the incidence of liver tumors was much lower than that after 30 weeks of exposure. The authors concluded that DDT exposure, even for a limited period early in life, results in an increased incidence of liver tumors and in a shortening of latent period for their appearance. The results also show that the hepatocarcinogenicity of DDT is dose related and indicate that DDT-induced tumors do not regress but continue to grow after cessation of treatment (Tomatis et al 1974b).

Four groups of 30 male and 30 female inbred Swiss mice were exposed to technical grade DDT as follows: (a) in the diet at 100 ppm, (b) by oral

intubation at 10 mg/kg daily, (c) by subcutaneous injection in olive oil at 10 mg/kg twice/month; (d) by skin painting in olive oil at 10 mg/kg twice/week. A fifth group of 30 males ad 30 females were controls. Exposure started at 6-8 weeks of age and continued for 80 weeks. Tremors and convulsions were frequent in groups (b) and (c), but mortality was similar in all groups. Oral and subcutaneous DDT administration resulted in a significant increase in the incidence of malignant lymphomas, lung adenomas, and hepatocellular carcinomas. The highest tumor incidence was observed in the mice receiving DDT by subcutaneous injection. No significant increase in tumor incidence was observed in the skin-painted group (Kashyap et al 1977).

Kuwabara and Takayama (1974) compared liver tumors induced in mice by dietary DDT at 250 ppm, hexachlorocyclohexane (BHC) at 600 ppm, and 2-fluorenylacetamide (2-FAA) at 250 ppm. Mice exposed to DDT and BHC developed focal hepatic hyperplasia leading to hepatic cellular adenomas. Liver tumors induced by 2-FAA showed more strongly malignant characteristics and, only 2-FAA stimulated the production of alpha-fetoprotein.

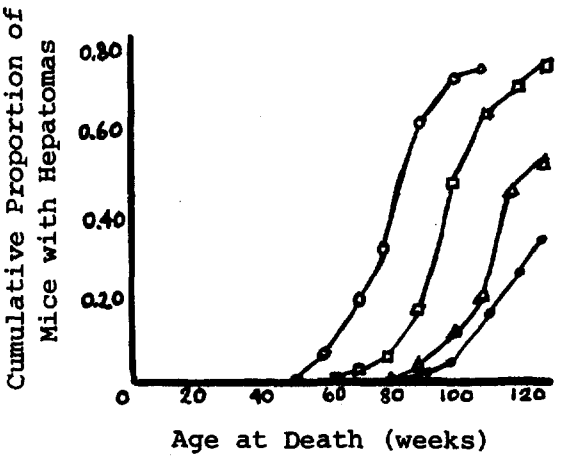
A group of 59 male and 59 female CF1 mice was fed a diet containing p,p'-DDD at 250 ppm for their lifespan, and tumor incidences were compared to those observed in a control group of 98 males and 90 females. Liver-cell tumors were found in 52% of the exposed males and 34% of the control males but only sporadically in females. Lung tumors were found in 86% of the males fed DDD, compared with 54% of male controls, and in 73% of the females given DDD, compared with 41% of female controls (Tomatis et al 1974a).

In the same experiment, 53 male and 55 female CF1 mice were fed a diet containing p,p'-DDE at 250 ppm for the animals' lifespans. Liver-cell tumors were found in 74% of the exposed males and in 98% of the exposed females, compared with 34% and 1% of the controls. The incidences of other tumors were not increased. In a third group fed a mixture of p,p'-DDE and p,p'-DDD, each at 125 ppm, the incidence of liver tumors was 76% in exposed males and 76% in exposed females. In the three exposed groups, tumors appeared earlier and in greater numbers than in the controls, both effects being greatest with p,p'-DDE and intermediate in the groups fed the mixture (Figure 2.5.2). In fact, this experiment shows that p,p'-DDE is more effective in inducing liver tumors than the parent compound p,p'-DDT (Tomatis and Turusov 1975).

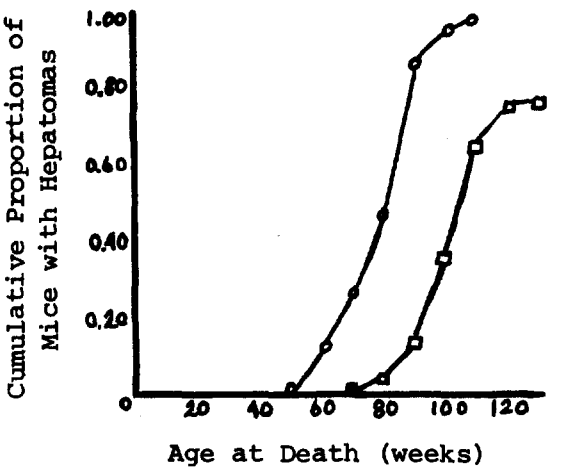
A bioassay of p,p'-DDT, p,p'-DDD, and p,p'-DDE for possible carcinogenicity in mice has recently been completed by Hazleton Laboratories America, Inc., for the National Cancer Institute, but the results are available only in preliminary form (NCI 1978). Groups of 50 male and 50 female B6C3F1 mice were exposed to p,p'-DDT, p,p'-DDD, or p,p'-DDE in the diet for 78 weeks, followed by 12 weeks on uncontaminated diets. The dietary concentrations used were as follows: DDT at 43 and 22 ppm for males and at 174 and 87 ppm for females, DDD at 822 and 411 ppm for males and females, and DDE at 253 and 147 ppm for males and females. The preliminary report indicated that DDT and DDD were not carcinogenic in the experiment, whereas DDE was carcinogenic, causing a statistically significant, dose-related increase in incidence of hepatocellular carcinomas in both sexes.

FIGURE 2.5.2 (Tomatis and Turusov 1975)

LIVER CELL TUMORS IN MICE FED p,p'-DDE, p,p'-DDD,
OR A MIXTURE OF THE TWO CHEMICALS



a. Male Mice with Hepatomas
Dying at Different Time Periods



b. Female Mice with Hepatomas
Dying at Different Time Periods

● control; △ DDD 250 ppm; ○ DDE 250 ppm; □ DDD 125 ppm plus DDE 125 ppm

2.5.2 In Rats

In two overlapping 2-year experiments, a total of 228 Osborne-Mendel rats received diets containing technical DDT (as a powder or as a solution in oil) at concentrations of 0 ppm (24 males and 12 females), 100 ppm (12 males), 200 ppm (24 males and 12 females), 400 ppm (24 males and 12 females), 600 ppm (24 males and 24 females), and 800 ppm (36 males and 24 females). Of the 192 rats exposed to DDT, 111 died before the 18 months of exposure when only 14 rats given 800 ppm, 23 rats given 600 ppm, 14 given 400 ppm, 24 given 200 ppm, 6 given 100 ppm, and 20 controls were alive. Tumor incidences for each dose level were not given. Of the 81 rats surviving for at least 18 months, 4 had "low-grade" hepatic-cell carcinomas (measuring 0.5-1.2 cm) and 11 had "nodular adenomatoid hyperplasia" (nodules measuring up to 0.3 cm). No liver lesions were found in the control rats. Hepatic-cell tumors were reported to occur spontaneously in 1% of the rats of this colony, and nodular adenomatous hyperplasia was reported to be rare (Fitzhugh and Nelson 1947).

Two experiments with Osborne-Mendel rats have been reported from the University of Miami. Groups of 30 males and 30 females were exposed for at least 2 years to recrystallized DDT at either 80 or 200 ppm and compared to 2 control groups of 30 animals of each sex. Undifferentiated bronchogenic carcinomas were seen in 8/60 rats fed DDT at 80 ppm, in 2/60 controls, and in none of the animals given DDT at 200 ppm. Two liver tumors were found in the two experiments; one occurred in a control female and the other in a female given DDT at 200 ppm. Incidences of other tumors were similar in control and treated rats (Deichmann et al 1967, Radomski et al 1965).

Fifteen male and 15 female Fischer rats were each given 15 mg of DDT (unspecified composition) by stomach tube, 5 times/week, starting at weaning. Exposure lasted 1 year, and survivors were observed for a further 6 months, the average survival being 14 months. No liver tumors were found, and no data were provided on the occurrence of other tumors (Weisburger and Weisburger 1968).

Rossi et al (1977) reported that DDT induced liver tumors in Wistar rats. Technical DDT was administered at 500 ppm in the diet to groups of 45 male and 45 female rats. Survival was similar in exposed and control rats. The incidence of liver tumors was 15/28 (56%) in females and 13/38 (35%) in males, versus zero in controls. The number of tumors per rat and the average size of the tumors increased with age, and both were greater in females than in males. Histologically, the liver tumors were nodular growths, which compressed surrounding parenchyma but did not infiltrate it. None of the tumors had metastasized. The tumors were classified as neoplastic nodules according to the terminology of the Rat Liver Workshop (Squire and Levitt 1975). The incidences of tumors at other sites were not significantly different in exposed and control rats except in the adrenals, in which the incidence of tumors was reduced from 6/38 in controls to 0/38 in DDT-exposed males (Rossi et al 1977).

Ten adult male Wistar rats were fed a low-protein, low-riboflavin diet containing o,p'-DDT at 600 ppm and killed at intervals from 24-469 days. Testicular damage was observed from the 2nd month onwards. Of the three rats killed after 348 or more days, one had microscopic adenomatous nodules and two had tumors of the interstitial cells of the testes. These

lesions were considered to be related to specific degenerative changes induced by o,p'-DDD on the adrenal cortex (Lacassagne and Hurst 1965).

A bioassay of p,p'-DDT, p,p'-DDD, and p,p'-DDE for possible carcinogenicity in rats has recently been completed by Hazleton Laboratories America, Inc., for the National Cancer Institute, but the results are available only in preliminary form (NCI 1978). Groups of 50 male and 50 female Osborne rats were exposed to p,p'-DDT, p,p'-DDD, or p,p'-DDE in the diet for 78 weeks, followed by 32 weeks on uncontaminated diets. The dietary concentrations used were as follows: DDT at 642 and 321 ppm for males and 420 and 210 ppm for females; DDD at 3,294 and 1,647 ppm for males and 1,700 and 850 ppm for females; and DDE at 839 and 437 ppm for males and 457 and 242 ppm for females. The preliminary report indicated that DDT and DDE were not carinogenic in the experiment, whereas DDD was carinogenic in male rats, causing a combination of follicular-cell carcinomas and follicular-cell adenomas of the thyroid.

2.5.3 In Hamsters

Groups of 25-30 Syrian golden hamsters of each sex were fed a diet containing p,p'-DDT at either 500 or 1,000 ppm in olive oil for 44 out of 48 weeks. Survival of the exposed hamsters at 50 weeks was 61% versus 75% of controls. All exposed animals and 62/79 (78%) controls were dead by the 90th week. Eleven exposed animals developed tumors at different sites, including one liver tumor, as did eight controls (Agthe et al 1970).

Groups of Syrian golden hamsters were exposed to p,p'-DDT in the diet at 100 ppm, 250 ppm, and 500 ppm for their lifespans. Growth and survival rates were similar in experimental and control animals. The experiments has been reported only in an abstract, which stated that exposure to DDT did not increase significantly the percentage of tumor-bearing animals in the exposed groups. The average number of tumors/exposed hamster and the percentage of hamsters with more than one tumor were not influenced by the exposure (Cabral and Shubik 1977).

Craillot et al (1975) administered technical DDT at dietary concentrations of 250, 500, or 1,000 ppm to groups of 30 male and 30 female hamsters for 18 months. Growth rates in the exposed hamsters were similar to those in the controls, but the control animals survived less well (average lifespan 13.0 months in control males and 14.9 months in control females, versus 15.3-17.3 months in exposed groups). The incidences of lymphosarcomas were markedly lower in hamsters exposed to DDT than in control hamsters, as follows:

Males: controls, 50%; DDT at 250 ppm, 23%; DDT at 500 ppm, 13%; DDT at 1,000 ppm, 0;

Females: controls, 41%; DDT at 250 ppm, 17%; DDT at 500 ppm,0; DDT at 1,000 ppm, 0.

The occurence of other types of tumors was not reported.

2.5.4. In Dogs

A total of 22 animals, approximately equally divided by sex, were fed diets containing DDT at 0 (2 dogs), 400 ppm (2 dogs), 2,000 ppm

(4 dogs), or 3,200 ppm (14 dogs). Only the control dogs, the two dogs given 400 ppm, and two of the dogs receiving 2,000 ppm survived to the time of sacrifice (39-49 months). Liver damage was reported (Lehman 1965, IARC 1974), but the study was too short to serve as an adequate carinogenicity test.

2.5.5 Carcinogenic Interactions

As noted in the preceding sections, the actions of DDT and dieldrin appear to be additive or synergistic inducing liver tumors in mice. Several additional experiments have demonstrated interactions between exposure to DDT and the effects of other carcinogens.

Female Sprague-Dawley rats, 36 days old, were fed a diet containing p,p'-DDT at 100 ppm for 2 weeks. Starting on day 50 of life, they were given, via stomach tube, 21 consecutive daily doses of 0.714 mg of DMBA (7,12-dimethylbenz[a]anthracene), a known carcinogen. Rats exposed to DDT and DMBA had a significantly lower incidence of mammary tumors than rats given DMBA alone; they also had fewer tumors/rat, and longer latent periods for the development of tumors. Leukemia incidence in rats surviving to day 280 was 2/29 in DDT-treated animals, versus 11/20 in animals given DMBA alone. DDT may inhibit the induction of mammary tumors and leukemia by DMBA, by stimulating hepatic metabolism and excretion of DMBA (Silinskas and Okey 1975). In agreement with this hypothesis, DDT and DDE reduced the toxic and adrenolytic effects of DMBA when they were administered at 1-100 mg/kg 0-10 days before exposure to DMBA (Turusov and Chemeris 1976). In contrast to these results showing

inhibitory effects of DDT on the carcinogenic effects of DMBA, dietary exposure to DDT at 100 ppm accelerated the development of cervical carcinoma induced in mice by topical application of methylcholanthrene (Uchiyama et al 1974).

In an experiment reported by Peraino et al (1975), DDT enhanced the hepatocarcinogenicity of 2-acetylaminofluouene (2-AAF). Male Sprague-Dawley rats, 22 days of age, were fed a diet containing 2-AAF at 200 ppm for 18 days, a control diet for 7 days, and then a diet containing technical DDT at 500 ppm for 389 days. Neither control rats nor rats exposed to DDT alone for 389 days developed liver tumors. Among rats fed 2-AAF alone, 28% (31/108) developed liver tumors, with an average multiplicity of 2.2 tumors/rat. Post-treatment with DDT increased the incidence of liver tumors to 75% (77/103), with an average multiciplity of 2.5 tumors/rat. The enhancing effect of DDT was associated with an increase in liver weight and an increase in liver DNA synthesis, as measured by the uptake of radiolabeled thymidine.

Weisburger and Wesiburger (1968) also found that DDT enhanced the hepatocarcinogenicity of 2-AAF. Groups of 15 male and 15 female Fischer rats were given daily doses of either 1 mg of 2-AAF or 1 mg of 2-AAF plus 10 mg of DDT, 5 days/week, for 52 weeks, followed by an average of 60 days without exposure. Hepatomas were observed in 90% of the males and 33% of the females in the DDT-exposed groups, versus 67% and 7%, respectively, in the groups exposed to 2-AAF alone.

2.6 Mutagenicity and Related Cytotoxic Effects

Kelly-Garvert and Legator (1973) described cytogenetic and mutagenic effects of purified (99%) DDT and DDE in a Chinese hamster cell line. The index of mutagenic activity was the shift from sensitivity to 8-azaguanine to resistance to it. DDE consistently induced a significant increase in the mutation frequency at nominal levels of 25-35 mg/ml. DDT induced a nonsignificant increase in two of five experiments at nominal levels of 35 mg/ml. The variability in cell survival may have been due to binding of the test chemicals to the medium, which reduced the effective concentrations. Cytogenetic studies indicated that DDE-treated cells displayed a significant increase in chromosome aberrations, primarily exchange figures and chromatid breaks. DDT produced no significant increase in chromosome abnormalities. The Chinese hamster cell cultures exposed to DDE also had more polyploid cells.

Palmer et al (1972) reported that p,p'-DDT, p,p'-DDE, and p,p'-DDD at concentrations of 10-50 µg/ml caused chromosome abnormalities in a cultured mammalian cell line (rat-kangaroo, Potorous tridactylis). The o,p'isomers were about one half as active as the p,p' isomers. All six compounds produced single and multiple chromatid breaks and p,p'-DDT and p,p'-DDE also produced exchange figures. p,p'-DDA was inactive even at 100 µg/ml. Legator et al (1973), in a collaborative study involving four laboratories, found no significant increase in cytogenetic abnormalities of bone marrow cells of rats (strain unspecified) exposed to p,p'-DDT at doses up to 100 mg/kg.

Palmer et al (1973) reported weakly positive effects of p,p'-DDT in a dominant lethal assay in rats. A statistically significant increase was found in the proportion of females having one or more dead implants after being mated during week 3 with males given a single oral dose of 100 mg/kg. No significant effects were found in females mated with males treated with DDT intraperitoneally at the same dose.

Mahr and Miltenburger (1976) studied the effects of p,p'-DDT at 12-81 ppm, p,p'-DDD at 11-75 ppm, p,p'-DDE at 44-88 ppm, and p,p'-DDA at 20-100 ppm on Chinese hamster cells in culture (B14 E28). All four compounds caused a dose-dependent reduction in the rate of cell proliferation, with DDD and DDT being the most toxic, DDE intermediate, and DDA the least toxic. Cytogenetic effects showed the same sequence of relative toxicity: DDD and DDT caused a marked increase in chromosome gaps and breaks, DDE was intermediate in activity, and DDA was the least active, causing a significant increase only in gaps. For all four compounds, the cytogenetic effects were dose-dependent and time-dependent up to a maximum time (4-24 hours) of exposure. No induction of configuration anomalies was found in any test. Chronic exposure of cells to DDT at 8 ppm for 3 months did not alter the proliferation rate or the incidence of cytogenetic abnormalities.

Lessa et al (1976) exposed human lymphocyte cultures to technical DDT at concentrations ranging from 0.06 to 15 µg/ml. The proportion of cells with structural aberrations, mostly chromatid gaps or breaks, was increased at all DDT concentrations, the increase being statistically significant at 0.20, 4.05, and 8.72 µg/ml but less marked at the

highest concentration.

Johnson and Jalal (1973) reported chromosomal aberrations induced by DDT in BALB/c mice exposed for 3 weeks to daily intraperitoneal injections of DDT in peanut oil at concentrations of 100-400 ppm. (The precise dose was not stated.) The frequency of chromosomal stickiness was significantly increased in the mice exposed at 100 ppm. Deletions (in the form of chromosomal fragments) were significantly increased at 200 ppm and above. Ring and metacentric chromosomes were infrequent.

Larsen and Jalal (1975) reported similar effects in BALB/c mice exposed to DDT at 25-250 mg/kg in single intraperitoneal injections. The mice were killed 48 hours later. Karyotypes from bone marrow cells of femurs were analyzed for gaps, deletions, and stickiness. Gaps, stickiness, and mitotic indices were not significantly increased in exposed mice, but deletions and gaps plus deletions were significantly higher in animals exposed to DDT at 50 mg/kg or higher.

Markaryan (1966) reported a significant increase in stickiness and chromosomal damage in mice given a single dose of DDT at 10 mg/kg. He suggested that the mutagenic effect of this dose (about one-sixteenth of the LD50) in mice was equivalent to that of 24 rads of radiation.

Clark (1974) tested technical DDT for mutagenicity in mice, Drosophila melanogaster, and Neurospora crassa. Two oral doses of DDT, each at 150 mg/kg, administered to male Swiss mice, induced dominant

lethal mutations in early spermatid and spermatocyte stages, reflected in a reduction in the number of implants per female and an increase in the number of dead implants; the difference was most marked 3-6 weeks after exposure. Chronic oral doses of DDT (100 mg/kg, twice a week, for 10 weeks) caused a persistent increase in the number of dominant lethal mutations. Histologic sections showed that chronic treatment with DDT caused changes in the morphology of the seminiferous tubules and degeneration of B-type spermatogonia. Acute treatment with DDT caused an increase in spermatocyte chromosome breakage, stickiness, and precocious separation of the X and Y bivalents.

Dietary exposure of male D melangoster (Canton-S) to DDT caused an increase in dominant lethal mutations in early spermatid and spermatocyte stages. DDT also caused nondisjunction of the X and Y chromosomes at the spermatocyte state and exposed males (strain y/R (1)2, vf/$B^{s}Y_{y}$+). A shift in sex ratio in the offspring of treated males was associated with breakage of the ring-X chromosome. Exposure of a population of D melanogaster (Canton-S) to DDT at low dietary levels for 8 months caused no significant increase in the frequency of second-chromosome recessive lethal mutants (Clark 1974).

Tests for the induction of recessive lethal mutations in the ad-3 region of a N crassa heterokaryon gave inconclusive results. However, in a host-mediated assay with N crassa in mice, technical DDT did not appear to be mutagenic (Clark 1974).

In contrast to the positive results obtained by Clark (1974) and Palmer et al (1973) in dominant lethal assays in Swiss mice and in

rats, Epstein and Shafner (1968) and Epstein et al (1972) found no significant effects of DDT in dominant lethal assays in ICR/Ha mice. Buselmaier et al (1972, 1973) reported that DDT and DDE gave "ambiguous" results in dominant lethal assays in NMRl mice. However, they reported that DDD was strongly mutagenic in a host-mediated assay with Serratia marcesscens in mice, whereas DDT, DDE, and DDA were inactive. None of the compounds was mutagenic in Salmonella typhimurium in a host-mediated assay in mice.

In other experiments with Drosophila, Lüers (1953) reported that DDT had no mutagenic effect. However, Vogel (1972) reported that p,p'-DDA was significantly mutagenic and p,p'-DDT was weakly active in Drosophila, inducing sex-liked recessive lethals; p,p'-DDE, p,p'-DDD, and p,p'-DDOM were not significantly active.

McCann et al (1975) and McCann and Ames (1976) reported that p,p'-DDE gave negative results for mutagenicity in the S typhimurium reversion bioassay (Ames Test), with and without activation by rat liver microsomal preparations (S-9). They used four strains of S typhimurium: TA 1535, a base-pair substitution mutant; TA 1537, a frameshift mutant; and the more sensitive strains TA 98 and TA 100. Van Dijck and Van de Voorde (1976) similarly reported that p,p'-DDT and p,p'-DDE were negative in this bioassay with activation by mouse liver microsomes. Marshall et al (1976) reported that DDT at 2,500 µg/plate and DDE at 1,000 µg/plate were not mutagenic in the S typhimurium bioassay, with or without rat liver homogenates. They used four strains of S typhimurium: TA 1535, TA 1536, TA 1537, and

TA 1538. The more sensitive strains TA 98 and TA 100 were not used. Shirasu et al (1976) also reported that p,p'-DDT was not mutagenic in these four strains of S typhimurium or in two tryptophaneless strains of E coli (B/r try WP2 and WP2 try hcr), but they did not attempt activation with microsomal enzymes. Shirasu et al (1976) classified p,p'-DDT as negative in recombination assays with B subtilis strains H17 REC^{+} and M45 Rec^{-}, but they did not provide specific data. Swenberg et al (1976) reported negative results for DDT at concentrations of 0.1-3.0 mM in an in vitro alkaline elution assay for DNA dammage in Chinese hamster (V79) cell culture with rat liver microsomal activation. Both McCann and Ames (1976) and Swenberg et al (1976) interpreted the results with DDE and DDT as "false negatives" because the systems utilized in their experiments otherwise usually give positive results with carcinogens.

Langenbach and Gingell (1975) tested p,p'-DDT, p,p'-DDD, p,p'-DDE, and p,p'-DDA in an in vitro mouse embryo cell culture susceptible to malignant transformation. All four compounds at concentrations of 2.8-43 μM caused transformations, with DDD being considerably more active than the other three compounds. However, none of the transformed foci had the typical malignantly transformed morphology produced by 7,12-dimethylbenz(a)anthracene (DMBA). None of 11 transformed cell foci from cultures exposed to DDT, DDE, DDD, or DDA caused tumors when innoculated into syngeneic mice, whereas 3/7 DMBA-transformed tumors did so.

Walker et al (1970a,b) reported that p,p'-DDT markedly inhibited the growth of Ehrlich ascites tumor cells in vivo. Technical DDT had similar but less marked effects. DDT also inhibited the incorporation of amino acid precursors of DNA, RNA, and protein into Ehrlich ascites tumor cells.

Chung et al (1967) reported that DDT at concentrations above 0.5 ug/ml reduced leucine incorporation by 20% in HeLa S cells in vitro. Uridine and thymidine incorporation were both decreased at low concentrations of DDT (0.5 µg/ml) but unaffected at higher concentrations (50 µg/ml). The small magnitude of the effect and its inconsistent relation to dose make its significance questionable.

Wyrobeck and Bruce (1975) reported that p,p'-DDT did not cause sperm abnormalities in mice after five daily intraperitoneal injections at 10 or 15 mg/kg. In the same experiment, many, but not all, mutagens and carcinogens caused sperm abnormalities.

Wallace et al (1976) conducted a multigeneration screening test for recessive mutations in the descendants of treated mice. Mice of an inbred strain (CF1, genotype aabbcc) were exposed to technical DDT at a dietary concentration of 250 ppm through five generations (Tomatis et al 1972) and were maintained under various degrees of inbreeding through the 12th generation, with appropriate controls. The stock did not suffer unduly from litter competition, and the breeding program used is stated to have provided a sensitive test. There was no evidence for a greater incidence of recessive invisible mutations in the exposed stock than in the controls. Two recessive visible mutations (black-and-tan and

exencephaly) were identified in the exposed stock, which had been derived from 60 females in the eighth generation. The authors concluded that, if DDT is mutagenic in this strain of mice, the effect is unlikely to have been a major one.

Grosch and Valcovic (1967) exposed the parthenogenetically reproducing wasp Habrobracon juglandis to DDT at nearly lethal levels. They reported no evidence of an increase in dominant or recessive lethal mutants, but the sensitivity of the system is doubtful.

3. Human Effects

3.1 Clinical and Case Reports

Human poisoning by DDT has been reported to have occured only through ingestion. The earliest symptom of poisoning is hyperesthesia of the mouth and lower part of the face. This is followed by paresthesia and tremor of the extremities, confusion, malaise, headache, fatigue, and delayed vomiting. The vomiting is probably of CNS origin and not due to local irritation. Convulsions occur only in severe poisoning (Hayes 1959, 1975; Gosselin et al 1976; WHO 1977).

Onset may be as soon as 30 minutes after ingestion of a large dose or as late as 6 hours after smaller but still toxic doses. Recovery from mild poisoning is essentially complete in 24 hours, but recovery from severe poisoning may require several days. In two instances, there was some residual weakness and ataxia of the hands 5 weeks after ingestion. The human acute oral LD_{50} has been estimated at about 250 mg/kg (Gosselin et al 1976). Table 2.1.3 gives a summary of information on human responses to various doses of DDT.

A few persons apparently have been killed by uncomplicated DDT poisoning, but none of these cases has been reported in detail. Death has been caused much more frequently by the ingestion of solutions of DDT, but in most instances the signs and symptoms were predominantly or exclusively those of poisoning by the solvent (Hayes 1959). This does not mean that the toxicity of the solvent always predominates. For example, the recurrent convulsions in a case reported by Cunningham and Hill (1952), though more characteristic of poisoning by one of the

cyclodiene insecticides, was certainly not typical of solvent poisoning. A 2-year-old child drank an unknown quantity of fly spray containing 5% DDT, but the nature of other active ingredients or the solvent was unknown. About 1 hour after drinking the material, the child became unconscious and had a generalized, sustained convulsion. Convulsions were present when the child was hospitalized 2 hours after taking the poison, but the convulsions were controlled by barbiturates and other sedatives. Convulsions recurred on the 4th day and again on the 21st day but were stopped each time by treatment with sedatives. On the 12th day, it was noted that the patient was deaf. Hearing began to improve about the 24th day and was normal as were other neurologic and psychologic findings when the patient was examined about 2.5 months after the accident (Cunningham and Hill 1952).

Other neurologic effects of DDT poisoning have been reported. Freemon (1975) stated that prolonged exposure resulted in neurologic dysfunction. Others have reported clinical manifestations, including polyneuropathy, paresthesias, tremors, and convulsions (Campbell 1946, Hsieh 1954). Peripheral neuropathy has been occasionally ascribed to DDT, usually as a result of occupational exposure. One syndrome consists of numbness and paraesthesias, hypotonia, and asymmetric weakness or paralysis, with a slow spontaneous recovery when exposure is terminated (Jenkins and Toole 1964, Mackerras and West 1946, Onifer and Whisnant 1957).

The signs of intoxication in a 10-year-old girl who died after exposure to DDT were reported by Jacobzinger and Raybin (1963). They

included red blotches on the skin, hands, and arms; petechiae, hemorrhagic bullae around the lips; cellulitis; lymphangitis; lymphadenitis; nosebleed; hematuria; and uncontrollable fever. Primary skin irritation is rarely if ever due to DDT, and allergic dermititis has been reported only infrequently (Higgins and Kindel 1949). Purpura with marked thrombocytopenia has occurred in exposed children (Karpinksi 1950). An isolated case of agranulocytosis (Wright et al 1946) and postmortem findings resembling periarteritis nodosa (Hill and Damiani 1946) suggest more serious allergic manifestations. Sánchez-Medal et al (1963) presented circumstantial evidence that implicated DDT as a cause of aplastic anemia and thrombocytopenia. However, the association of these conditions with BHC and other chlorinated hydrocarbons is on firmer ground (USDHEW 1969).

Causes of accidental and suicidal poisoning in which the effects were clearly caused by DDT are summarized in Table 3.1.1.

3.2. Volunteer Studies

A number of small-scale studies involving controlled exposure of volunteers to technical DDT were conducted in the 1940's (Hayes 1959, USDHEW 1969, WHO 1977). Table 3.2.1 summarizes the reported results of controlled oral exposures.

Two chronic exposure studies with penitentiary volunteers given DDT orally by capsule have been reported by Hayes et al (1956, 1971). The first study involved 51 men. Of these, three completed 1 year of dosage at 3.5 mg/man/day, and seven completed 1 year at 35 mg/man/day.

TABLE 3.1.1

SUMMARY OF THE EFFECTS OF THE ACCIDENTAL OR SUICIDAL INGESTION OF DDT

Individual Dose, Formulation, Number of Persons	Effects
300-4,500 mg, in food, 1 man	Onset in 1 hr; vomiting; restlessness; headache; heart weak and slow; recovery next day
Unknown dose, in tarts, 25 men	Onset in 2-2.5 hr; all weak and giddy; 4 vomited; 2 hospitalized; 1 confused, incoordinated, weak; 1 with palpitations and numbness of hands; recovery in 24-48 hr
5,000-6,000 mg, in pancakes, 3 men	Onset 2-3 hr; throbbing headache; dizziness; incoordination; paresthesias of extremities; urge to defecate; wide nonreacting pupils; reduced vision; dysarthria; facial weakness; tremor; ataxic gait; reduced sensitivity to touch; reduced reflexes; positive Romberg; slightly low blood pressure and persistent irregular heart action; partial recovery in 2-3 days, but slight jaundice appeared 4-5 days after ingestion and lasted 3-4 days; all normal 19 days after poisoning except irregular heart action in one
Up to 20,000 mg, in bread, 28 men	Onset in 30-60 min in those most severely affected; men first seen 2-3 hr after ingestion; in spite of severe early vomiting that reduced the effective dose, severity of illness and especially intensity of numbness and paralysis of extremities proportional to amount of DDT ingested; recovery in all but 8 men in 48 hr; 5 others fully recovered in 2 wk, but some weakness and ataxia of the hands in 3 5 weeks after ingestion

TABLE 3.1.1 (Continued)

SUMMARY OF THE EFFECTS OF THE ACCIDENTAL OR SUICIDAL INGESTION OF DDT

Individual Dose, Formulation, Number of Persons	Effects
Unknown dose, in flour, about 100 women	Onset about 3.5 hr after ingestion; total of about 85 cases of which 37 were hospitalized; symptoms mild and similar to those in earlier outbreaks except gastrointestinal disturbance in most severe cases included abdominal pain and diarrhea as well as nausea; most fully recovered in 24 hr
Unknown dose, 14 cases	Symptoms in established cases similar to those reported earlier
286-1,716 mg, in meatballs, 8 cases, 11 exposed	Except in one man who was already sick when he received a dosage of 6 mg/kg, no poisoning at dosages of 5.1-10.3 mg/kg (Doses calculated from known consumption of meatballs and estimated concentration of DDT in mixture--Hsieh 1954); excussive perspiration, nausea, vomiting, convulsions, headache, increased salivation, tremors, tachycardia, and cyanosis of the lips after ingestion of 16.3-120.5 mg/kg; onset in 2-6 hr depending on dosage; as much as 2 days for recovery
Unknown dose, 1 case	Death 13 hr after suicidal ingestion
Unknown dose, 22 unrelated cases	Twenty-two separate cases, including 15 attempted suicides; some complicated by solvents; 3 deaths

Adapted from WHO 1977, Hayes 1959, Committee on Pesticides 1951, USDHEW 1969

TABLE 3.2.1

SUMMARY OF THE EFFECTS OF ONE OR A FEW ORAL DOSES OF DDT ON VOLUNTEERS

Dose (mg)	Formulation	Result	Reference
1,500	Butter solution	No effect, but lice killed when fed 6 and 12 hr after dose	MacCormack 1945
500	Oil solution	No effect	Neal et al 1946
700	"	"	"
250	Suspension	None execpt slight distrubance of sensitivity of mouth	Velbinger 1947a,b
250	Oil solution	Variable hyperesthesia of mouth	"
500	"	"	"
750	"	Disturbance of sensitivity of lower part of face; uncertain gait; peak reaction (6 hr after ingestion) characterized by malaise, cold moist skin, and hypersensitivity to contact; reflexes normal	"
1,000	"	Same as above; no joint pains, fatigue, fear, or difficulty in seeing or hearing	"
1,500	"	Pricking of tongue and around mouth and nose beginning 2.5 hr after dose; disturbance of equilibrium; dizziness; confusion; tremor of extremities; peak reaction (10 hr after ingestion) characterized by great malaise, headache, and fatigue; delayed vomiting; almost complete recovery in 24 hr	"

The latter dosage was about 200 times the average daily rate of dietary exposure in the general population at that time. The second study involved 24 men, whose exposure to DDT lasted 21.5 months. Four men were controls, and daily oral doses of technical DDT were given at 3.5 mg/man to six men and at 35 mg/man to six others. Another eight men received p,p'-DDT at 35 mg/man/day. Twenty exposed men were kept under observation until 4 years after the beginning of the study, and 16 of these completed an additional year of observation. No volunteer in either study complained of any symptom or showed any sign of illness, in the tests used, that did not have recognizable cause unrelated to the exposure to DDT. At intervals, the men were given a systems review, physical examination, and a variety of laboratory tests. Particular attention was given to the neurologic examination and liver function tests. No adverse changes were detected, although two men were removed from the 1956 study because of illness. One had contracted hepatitis and the other suffered a myocardial infarction. However, their illnesses were not considered to be caused by exposure to DDT.

In another study which was reported by Morgan and Roan (1971), four volunteers were given oral doses of technical DDT at 10 or 20 mg/day, p,p'-DDE at 5 mg/day, or p,p'-DDD at 5 mg/day for 81-183 days. A battery of hematologic and clinical biochemical tests were conducted before, during, and after exposure. No abnormalities were detected in the four volunteers.

3.3 Studies of Occupationally Exposed Workers

Three studies have been reported of workers with prolonged heavy exposure to DDT. Ortelee (1958) carried out clinical and laboratory examinations of 40 workers, all of whom were exposed to DDT and some of whom were exposed to a number of other pesticides. The men had been employed at this work for up to 8 years, with "heavy" exposure in some cases for up to 6.5 years. Exposure was so intense that during working hours many of the men were coated with a heavy layer of DDT dust. By comparing their excretion of DDA with that of volunteers given known doses of DDT, it was possible to estimate that the average amounts of DDT absorbed by three groups of the workers with different degrees of occupational exposure were 14, 30, and 42 mg/man/day. With the exception of the excretion of DDA and the occurrence of a few cases of minor irritation of the skin and eyes, no correlation was found between any abnormality and exposure to the insecticide. Special attention was given to a complete neurologic examination and to laboratory tests for liver function. Although a few abnormalities, such as hypertension and hearing loss were revealed, the author considered them unrelated to DDT exposure. One worker with a previous history of malaria had a palpably enlarged liver, three had hyperactive deep tendon reflexes, and five had slight tremors of the outstretched hand at rest.

Laws et al (1967) studied 35 men employed for 11-19 years in a plant that had produced DDT continuously and exclusively since 1947 and, at the time of the study, produced 2,722 metric tons/month. Findings from medical histories, physical examinations, routine clinical

laboratory tests, and chest X-rays revealed no ill effects attributable to exposure to DDT. Storage levels of DDT and metabolites in the men's fat ranged from 38 to 647 ppm, versus an average of 8 ppm for the general population. Based on their storage of DDT in fat and excretion of DDA in urine, the average daily intake of DDT by the 20 men with high occupational exposure was estimated to be 17.5-18 mg/man.

Rabello et al (1975) studied lymphocytes from 42 workers who worked in direct contact with DDT in 3 insecticide plants. The frequency of chromatid aberrations was not significantly higher than that in controls from the same plants but not in direct contact with DDT. However, there was evidence that one of the control groups had high exposure to DDT, as evidenced by high residue levels in plasma. When this group was included with the directly exposed workers, there was a significant increase in chromatid aberrations in the exposed workers compared to the control groups. The frequency of chromatid aberrations was 12.0% in exposed workers, 8.8% in workers from the same plants not directly exposed to DDT, and 2.2% in a control group from the general population. The corresponding concentrations of DDT and metabolites in blood plasma were 0.993 ppm, 0.275 ppm, and 0.03 ppm, respectively. The authors suggested that exposure to DDT may cause chromatid lesions.

A number of other studies of occupationally exposed workers have been published, although in most cases no quantitative measures of exposure are available and the workers were exposed to other pesticides in addition to DDT. Studies by several investigators (Long et al 1969;

Morgan and Roan 1969, 1973, 1974; Warnick and Carter 1972; Sandifer et al 1972; Embry et al 1972;) have failed to reveal effects of clinical significance in workers with prolonged, moderate exposure to a wide variety of pesticides. The possibility of adaptive changes (other than enzyme induction) has been suggested (Tocci et al 1969), but the World Health Organization has dismissed these effects as unproven (WHO 1977).

Other reports give some evidence of toxic effects. The reports under discussion tend to fall into two sets, those involving general debility and those involving a single organ or system. Reported conditions representative of general debility include dermatitis, subtle blood changes, general weakness, palpitations, functional angiospasm, headache, dizziness, inappetence, vomiting, lower abdominal pain, chronic gastritis, benign chronic hepatitis, insomnia, a sympathetic "vascular/asthenic syndrome," "vegetative dystonia," and confusion (Kostyuk and Mukhtarova 1970, Bezuglyi et al 1973).

The largest number of heavily exposed workers whose health has been investigated are those associated with malaria control in Brazil and India (WHO 1973). In Brazil, periodic clinical examinations were made of 202 spraymen exposed to DDT for 6 or more years, 77 spraymen exposed for 13 years ending in 1959, and 406 controls. In the first examination, carried out in 1971, differences between exposed and unexposed groups were observed in some neurologic tests, but this result was not confirmed by the second examination in the same year or in subsequent examinations. During 3 years, a survey of illnesses

requiring medical care during the 6 months preceding each periodic medical examination failed to demonstrate any difference between exposed and control groups. A relatively small number of analyses indicated that the concentration of DDT in the blood of spraymen was about three times that of controls.

In India, the blood levels of 144 spraymen were 7.5-15 times those in controls and were at least as high as those reported for workers who make and formulate DDT elsewhere. When the spraymen were examined the following differences from controls were found: knee reflexes were brisker, slight tremor was more often present, and a timed Romberg test was more poorly performed by the spraymen. These apparently positive results led to the selection of 20 men for examination by a neurologist, who concluded that either the differences found initially were not real or that the men's conditions had returned to normal in the few months between the two examinations. The signs were apparently not dose-related, since they showed no correlation with serum levels of DDT (WHO 1973).

Persons have been reported to have experienced headache, dizziness, nausea, vomiting, pain and numbness of the limbs, and general weakness beginning 1-1.5 hours after entering a field treated with DDT (Kolyada and Mikhal'Chenkova 1973). This has been attributed to possible food poisoning or hysteria (WHO 1977). A small number of workers experienced mild narcotic effects (vergito and nausea) when working in confined spaces with DDT (Hayes 1959). Gil and Miron (1949) reported that some persons suffered temporary irritability, fatigue, and other

ill-defined symptoms after exposure in the dusty atmosphere of a delousing station, but the relation of these findings to DDT was not clear. The relationships of these reported symptoms to DDT, to solvents or carriers or to both, are not clear from the circumstances of the reports.

Effects on reproduction have also been reported. One study of the course of labor and puerperium in 390 vineyard workers exposed to DDT, sulfur, methyl parathion, and copper sulfate reported a higher frequency of miscarriage, toxicosis, and asthenia in women exposed to these pesticides than in women not so exposed. Histologic changes in placentas, CNS disturbances, and low birth weight in their children were also reported (Nikitina 1974). The mean concentration of DDT and metabolites in the exposed women were 0.12 ppm in milk and 0.19 ppm in placentas (4.8 and 5.4 times those in controls, respectively). Peck (1970) suggested that the interference with the synthesis of steriod hormones by DDT and other insecticides might be a cause of impotence reported in farmworkers.

Some cardiovascular effects have been reported. In a study of workers occupationally exposed to a combination of organochlorine and organophosphrous pesticides, the incidence of myocardial dystrophy was 56%, versus 9.3% in a control group, and abnormalities in EKG's and vascular effects were noted together with elevated levels of cholesterol and beta-lipoproteins in the blood and decreased phospholipid levels (Bezuglyi and Gorskaya 1976). Carlson and Kolmodin-Hedman (1977) reported that eight men exposed for 6 hours to a number of chlorinated

pesticides (mainly lindane, but including DDT) showed a fall in alpha-lipoprotein levels after their exposure had ceased. Kolmodin-Hedman (1973) had previously reported that these same workers had hyper-high-density alpha-lipoproteinemia.

Several investigators have reported toxic effects on the liver associated with exposure to DDT or other pesticides. Chronic liver damage (cirrhosis and chronic hepatitis) has been reported on the basis of liver biopsies from eight workers heavily exposed to BHC, DDT, or both for periods ranging from 5-13 years. Other factors such as alcoholism, were reportedly excluded as the cause of the cirrhosis (Schuttmann 1968). Bezuglyi et al (1976) reported a case of chronic toxic hepatitis progressing to liver cirrhosis in a pest control worker with 24 years of exposure to DDT, BHC, trichlorphon, ronnel, zinc phosphide, warfarin, and diphacinone. Elevated levels of C-reactive protein were found in workers with chronic exposure to organochlorine pesticides (Takahasi et al 1976). Morgan and Roan (1974) were unable to find a significant correlation between worker exposure to DDT (as determined by serum concentrations of DDT and DDE) and urinary glucaric acid excretion (a measure of microsomal enzyme activity). However, they found a small but significant increase in serum lactic dehydrogenase (LDH) activity and a more substantial and significant decrease in serum creatinine phosphokinase (CPK) in workers with higher levels of DDT and DDE in their serum (Table 3.3.1). Levels of other enzymes were unchanged.

Increased liver microsomal enzyme activity, as reflected by decreased plasma half-life of phenylbutazone, was found in 14 workers

TABLE 3.3.1

SERUM ENZYME ACTIVITIES AND URINARY GLUCARIC ACID EXCRETION IN RELATION TO SERUM CONCENTRATION OF p,p'-DDT IN 127 SUBJECTS

	Subject Quartiles, Based on Serum p,p'-DDT (ppb)				Analysis of Variance
	I	II	III	IX	Among Means
No. of subjects	32	32	32	31	
Mean serum p,p'-DDT (ppb)	2	4	9	52	
Ranges	0-3	3-5	5-16	16-167	
Urinary glucaric acid excretion, umoles/g urinary creatinine	23	18	20	17	NS
Serum GOT	29	26	23	25	NS
Serum GPT	33	35	35	39	NS
Serum LDH	172	174	183	194	P <0.05
Serum alkaline phosphatase	64	63	63	70	NS
Serum CPK	7	6	6	4	P <0.05

Adapted from Morgan and Roan 1974

exposed to DDT and lindane. However, the workers' exposure to lindane was the only one that was clearly significant, as indicated by its concentration in plasma (Kolmodin-Hedman 1973). In a previous study (Kolmodin et al 1969), workers exposed to DDT and lindane metabolized the drug antipyrine more rapidly than unexposed persons, a phenomenon which also was attributed to induction of liver microsomal enzymes.

Poland et al (1970) studied a group of workers in a DDT manufacturing plant. They found that the half-life of the drug phenylbutazone in the blood plasma of the workers was significantly reduced below that in unexposed controls. They also found that excretion of 6-beta-hydroxycortisol in urine was increased by 57% relative to that in controls. Both effects were considered to result from a DDT-induced increase in the activity of microsomal enzymes. The average level of p,p'-DDT in the blood of the exposed workers was 0.573 ppm, corresponding to an average daily intake of about 18 mg/man/day (Poland et al 1970).

Electroencephalograms were obtained from 73 workers exposed to DDT, BHC, and benzilan for periods ranging from 7 months to 20 years. Just over 78% of the records were normal and 21.9% were abnormal. The most severe changes were in persons exposed to the three compounds for 1-2 years; less severe changes were seen with either shorter or longer exposure. The changes were not correlated with age. Some of the EEG records showed bitemporal sharp waves with shifting lateralization combined with low voltage theta activity. Other records showed spike complexes, paroxysmal discharges composed of slow and sharp waves most pronounced anteriorly, and low-voltage rhythmic spikes posteriorly.

None of the persons examined showed abnormal clinical neurologic findings (Israeli and Mayersdorf 1973, Mayersdorf and Israeli 1974).

Extensive experience and numerous medical studies of groups of workers have been reviewed (Hayes 1959), with the finding that dermatitis was common in men who used DDT solutions. The rashes were apparently due primarily to the solvent, especially kerosene. As often happens with rashes caused by petroleum distillates, they were most severe in men when they first started work and cleared in a few days unless contamination was exceptionally severe. Ortelee (1958) also reported eye and skin irritations in his study of 40 workers with intense exposure to DDT.

3.4 Epidemiologic Studies in the General Population

A number of epidemiologic searches for health effects associated with general uses of DDT have been conducted in various parts of the United States, with generally negative results (USDHEW 1969). However, such studies are difficult to conduct in the general population, ie., in nonoccupationally exposed persons, because residues of DDT and its metabolites are widespread in the environment. Virtually everyone is exposed to traces of DDT in food, and residues of DDT and metabolites have been found in the tissues of almost every person examined (USEPA 1975). Accordingly it is impossible to identify unexposed groups for rigorous comparison with exposed groups.

However, since residues of DDT and its metabolites are retained in tissues for months or years after exposure, it is possible to use

these residues as indirect measures of the intensity of past exposure. In a number of published epidemiologic studies, correlations have been sought between various pathologic conditions and tissue levels of DDT and its metabolites.

Maier-Bode (1960) found no essential differences between the concentrations of DDT and DDE in 21 persons who died of cancer (unspecified sites) and those in persons who died of other diseases. Robinson et al (1965) detected no significant differences in levels of DDT and metabolites between 50 biopsy and 50 necropsy samples of fat. Among the necropsy samples, there were no differences between mean storage levels in groups classified by cause of death (neoplasm, cardiovascular disease, infection, or accident). Hoffman et al (1967) measured the concentrations of DDT and DDE in the lipids of abdominal wall tissue taken from 995 persons at autopsy and found no significant associations between residue levels and pathologic changes in any body tissues. For example, DDT and DDE at an average total concentration of 9.6 $\pm$ 6.5 ppm in abdominal wall fat was reported in 292 patients with cancer (unspecified sites). This did not differ significantly from an average of 9.4 $\pm$ 6.5 ppm in 396 patients with other diseases. Another study dealing with autopsy material from 38 persons over 36 years in age revealed that most of the patients with malignant tumors had above-average levels of DDT in their tissues. High concentrations of DDT were associated with the combination of emaciation, carcinoma, and extensive focal or generalized pathological conditions of the liver (Casarett et al 1968). In another investigation, the average concentrations of DDT

and metabolites in fat tissues at autopsy were 21.96 ppm in 40 cases of carcinoma, 21.37 ppm in five cases of leukemia, 13.66 ppm in 5 cases of Hodgkin's disease, and 9.75 ppm in 42 control cases. Each of the differences from controls was statistically significant. Samples of fat and brain from six patients with brain tumors contained DDT residues comparable to those of controls. Mean concentrations of DDE in tissues of patients with portal cirrhosis were 1.7 times higher than those in controls. Levels in patients with other liver diseases were difficult to analyze because of high variability. However, DDT levels were significantly higher (by a factor of 2.7) in tissues of patients with hypertension than in controls (Radomski et al 1968). (Table 3.4.1)

Oloffs et al (1974) found that liver specimens from cirrhotics contained significantly higher concentrations of DDT than specimens from controls. However, this effect was probably due to an increased concentration of lipid in the liver, as there were no differences between the concentrations of DDT in the adipose tissues or brains of cirrhotics and those in controls.

Wassermann et al (1976) reported that concentrations of DDT and metabolites in malignant tissues from patients with breast cancer were significantly higher than those in adjacent normal tissues in the same patients. In another study, significantly higher concentrations of DDT and metabolites were found in lung tissues from patients with lung cancer than in lung tissues from patients who died of other diseases (Dacre and Jennings 1970).

TABLE 3.4.1

PESTICIDE CONCENTRATIONS IN THE FAT TISSUE OF PATIENTS WITH VARIOUS TERMINAL CONDITIONS

Diagnosis	No. of Cases	Level of Pesticide (ppm SD)		
		p,p'-DDE	p,p'-DDD	p,p'-DDT
Normal	42	6.69 ± 4.07	0.28±0.38	2.77±1.42
Infectious diseases	20	8.89 ± 7.67	0.12±0.27	3.94±5.01
Atherosclerosis	54	12.01 ± 2.53	0.27±0.75	5.10±7.57
Hypertension	8	17.91 ± 6.28	0.40±0.42	6.54±3.64
Carcinoma	40	15.97 ± 3.78	0.34±0.51	5.65±5.61
Leukemia	5	16.10 ± 5.53	0.58±0.45	4.69±4.28
Chronic renal disease	8	8.11 ± 4.25	0.21±0.25	2.11±1.10
Pancreatitis	3	11.57±10.81	0.09	1.29±1.05
Hodgkin's disease	5	10.06 ± 4.43	0.38±0.27	3.22±1.20

Adapted from Radomski et al 1968

A statistical association between serum cholesterol and p,p'-DDE has been reported (Rashad et al 1976). This may have been due to stimulation of liver cholesterol synthesis by p,p'-DDE.

A study of six patients (five with pancytopenia and one with chronic lymphocytic leukemia) who had been exposed to pesticides revealed significant lymphocyte sensitization to DDT in two patients, as measured by the degree of inhibition of leukocyte migration (Traczyk et al 1976). As discussed in Section 3.3, cases of aplastic anemia and other blood dyscrasias have been associated circumstantially with exposure to DDT, but the association is stronger with BHC and other organochlorine pesticides (USDHEW 1969).

Appreciable serum levels of DDT and its residues have been reported in premature infants, although no other toxic effects were detected in these infants (D'Ercole et al 1976). In an independent study, DDE levels in whole blood were much higher in premature infants than in full-term infants. This difference was found independently in white and nonwhite ethnic groups (O'Leary et al 1972; Table 3.4.2).

In most of the studies in which elevated tissue levels of DDT have been associated with cancer or other diseases, levels of other chlorinated hydrocarbons, including dieldrin, heptachlor epoxide, and BHC) have also been elevated in the diseased patients (Casarett et al 1968, Radomski et al 1968, Wassermann et al 1976, Dacre and Jennings 1970).

TABLE 3.4.2

FETAL WHOLE BLOOD DDE VALUES (ppb) IN PREMATURE AND MATURE INFANTS

Race		Term	Premature
White	Mean	4.9	22.1
	Range	2-13	18.7-26.8
	Median	5	21
Negro	Mean	6.1	19.0
	Range	3-12	6.6-34.4
	Median	5	17
Total	Mean	5.8	19.5
	No.	44	23

Adapted from O'Leary et al 1972

4. CORRELATION OF EXPOSURE AND EFFECT

4.1 Effects on Humans

Cases of accidental and suicidal poisoning of humans by DDT are described in Section 3.1. All the reported cases of human poisoning involved ingestion. The earliest symptom of poisoning was hyperesthesia of the mouth and lower part of the face, which was followed by paresthesia of the same area and of the tongue, and an objective disturbance of equilibrium, paresthesia of the extremities, confusion, malaise, headache, fatigue, and delayed vomiting. Convulsions occurred only in severe poisoning.

In many cases of poisoning, quantitative information on exposure is not available, and the cases are often complicated by simultaneous ingestion of solvents (Hayes 1959). Poisoning incidents in which the effects were clearly caused by DDT are tabulated in Table 3.1.1. Table 3.2.1 summarizes the effects of one or a few oral doses of DDT on volunteers. These data form the primary basis for the following numerical estimates of toxic doses derived by Hayes (1975):

Largest nonfatal dose	285 mg/kg
Smallest dose with serious effect	16 mg/kg
Median clinical ED50	10 mg/kg
Smallest dose with clinical effect	6 mg/kg

The acute oral LD50 for DDT in humans has been estimated to be about 250 mg/kg (Gosselin et al 1976).

Three studies in which groups of volunteers were exposed to small oral doses of DDT, DDE, or DDE daily for long periods are described in

Section 3.2. In the two studies by Hayes (1956, 1971), 21 men were exposed to technical DDT or p,p'-DDT for up to 2 years at a dose level of 35 mg/day (about 0.5 mg/kg/day). No adverse effects were detected by a variety of tests, although two men were removed from one study because of illnesses (hepatitis and myocardial infarction), which the authors did not attribute to the effect of DDT. The third study involved only four men (Morgan and Roan 1971).

Table 4.1.1 summarizes studies of workers occupationally exposed to DDT, which are described more fully in Section 3.3. Although precise measures of the degree of exposure to DDT are rarely available, the concentrations of DDT and its metabolities in tissues were measured in several studies. The quantitative relationships between the intake of DDT, the storage of p,p'-DDT and p,p'-DDE in the tissues, and the excretion of p,p'-DDA in the urine are summarized in Section 1.5. These relationships are complicated by several factors including the slow conversion of p,p'-DDT to p,p'-DDE and the long retention of DDE in the body, the effects of intermittent exposure, and the effects of drugs and other pesticides in reducing storage of DDT and DDE. Nevertheless, measurements of tissue residues can be used to derive rough estimates of the exposure of persons during the preceding months. Where appropriate, these estimates are included in Table 4.1.1.

Only a few of the studies listed in Table 4.1.1 involved workers whose exposures were exclusively or primarily to DDT. Although some of these workers had tissue residue levels equivalent to mean intakes of DDT as high as 42 mg/day, no clinical effects were reported except for

skin and eye irritation and equivocal neurologic abnormalities (Ortelee 1958, Laws et al 1967, WHO 1973). The most pronounced effects were increased metabolism of drugs and steroids, indicative of induction of hepatic microsomal enzymes (Kolmodin-Hedmar 1973a,b; Poland et al 1970), and an increase in chromatid aberrations in lymphocytes of DDT workers relative to controls (Rabello et al 1975). These effects were found in workers with mean residues in blood of 1.0 ppm, equivalent to a daily intake of about 18 mg of DDT.

The other studies listed in Table 4.1.1 were complicated by the simultaneous exposure of the workers to other pesticides. In a few cases, measured changes were correlated with blood levels of DDT or DDE. These changes included increased levels of serum LDH and decreased serum creatinine phosphokinase (Morgan and Roan 1974), increased blood pressure and serum cholesterol (Sandifer et al 1972), and increased levels of SGOT (Warnick and Carter 1972). The last effect was observed in a group with mean residue level (DDT plus DDE) in serum of 61 ppb. This is the lowest tissue level statistically associated with a measured biologic effect in occupationally exposed workers in the reported studies.

In addition to the reported effects listed in Table 4.1.1, several other effects were reported in workers exposed simultaneously to DDT and to other pesticides (see Section 3.3). These effects include dermatitis, a variety of psychologic symptoms, gastritis, hepatitis, disorders of pregnancy and childbirth, myocardial dystrophy, abnormal EKG, vascular effects, hepatic cirrhosis, and abnormal EEG. However,

none of these or other effects can be ascribed unequivocally to exposure to DDT, and in most cases the degree of exposure was not reported.

Few data are available that can be used to assess the possibility that DDT has carcinogenic, teratogenic, or mutagenic effects in the human population or affects human reproduction. Seven studies have been reported in which levels of DDT and DDE in tissues taken at autopsy have been related to cause of death. In three of these studies, residue levels of DDT and DDE were significantly higher in cancer victims than in persons dying of other causes. No such association was found in the four other studies. Considered in toto, these findings fail to prove or disprove a cause-and-effect relationship.

Workers exposed for up to 19 years showed no indication of excess cancer incidence (Laws et al 1967), but the sample size (35) was too small to be the basis for definite conclusions. A significant increase in chromatid aberrations was reported in DDT workers with tissue residues equivalent to daily intakes of 6-27 mg (Rabello et al 1975). In one study, DDE levels in whole blood were much higher in premature infants than in full-term infants (O'Leary et al 1972). Nikitina (1974) reported an increased frequency of miscarriages and other abnormalities of pregnancy, together with reduced birth weight of infants, in female vineyard workers whose milk contained 0.12 ppm DDT (equivalent to daily intakes of 1-2 mg DDT). Although these workers were exposed to other pesticides in addition to DDT, this study commands attention as the only study found of occupationally exposed females.

4.2 Effects on Experimental Animals

Table 4.2.1 summarizes the reported effects of dietary exposure to DDT and its principal metabolites on animals. Teratogenic, carcinogenic, and mutagenic effects are listed in Tables 4.3.1., 4.3.2., and 4.3.3, respectively. In Table 4.2.1, primary emphasis is on studies involving repeated or long-term oral exposure. Some biochemical and functional effects resulting from short-term exposures to relatively high doses are not included in Table 4.2.1 but are discussed in Sections 2.2 and 2.3.4. No studies were found on the effects of DDT on animals exposed by the dermal or respiratory routes.

The most pronounced effects of exposure to DDT at high dietary levels were on the liver and the central nervous system. Dietary levels reported to be associated with reduced lifespan were 400 ppm in rats, 250 ppm in mice, and 1,000 ppm in hamsters. At these dietary levels, many animals suffered from tremors and convulsions, and most had lesions of the liver observed at autopsy, although some survived for the normal lifespan (Fitzhugh and Nelson 1947, Tomatis et al 1972, Agthe et al 1970).

In animals exposed to DDT at dietary concentrations between 25 and 250 ppm, the most consistent effects were increased liver weight, histopathologic changes in the liver (observable at autopsy), and reproduction, primarily due to preweaning mortality of offspring. Reproduction was reported to be normal in mice exposed at dietary levels of 25 ppm or less, but the data on rats are inconsistent. Although Ottoboni (1969) reported normal reproductive performance in rats exposed

at 200 ppm, several other investigators found adverse effects on reproduction at dietary levels of 50-100 ppm. Green (1969) reported severe effects, which were especially marked in the second generation, in animals exposed at a dietary concentration as low as 7 ppm.

Histopathologic changes were observed in the livers of rats exposed to DDT at dietary levels as low as 5 ppm (Ortega et al 1956a,b; Ortega 1962; Kunze et al 1949), and liver tumors occurred in mice exposed at 2 ppm (see Section 4.3). Immunosuppressive effects were detected in rabbits given DDT at 0.92 and 2.1 mg/kg/day (Street and Sharma 1974, 1975). Otherwise, the only reported significant effects at dietary levels below 10 ppm were the induction of hepatic microsomal enzymes and effects on behavior.

Several studies have shown increased microsomal enzyme activity in rats exposed to DDT at dietary levels between 0.9 and 4 ppm (Hoffmann et al 1969, Schwabe and Wendling 1967, Street et al 1969, Kinoshita et al 1966, Gillett 1968). No significant effects were evident after exposure at 0.5 or 0.2 ppm (Hoffmann et al 1969, Kinoshita et al 1966).

Exposure of male mice to DDT at 7 ppm in the diet for 10 days resulted in a reduction in aggressive behavior (Peterle and Peterle 1971). Exposure of pregnant mice to DDT in drinking water at concentrations of 1.0 or 0.1 ppb led to a significant reduction in the aggressiveness of their male offspring when tested at the age of 55 days; no effects were reported at 0.01 ppb (Scudder and Richardson 1970). These are by far the lowest exposure levels at which effects of DDT were reported to have been detected in experimental animals.

Only one report of an experiment involving long-term exposure of mammals to DDE was found. In this experiment, male mice exposed to DDE at 125 or 250 ppm throughout life suffered a high incidence of myocardial necrosis, in addition to the liver tumors discussed below (Tomatis et al 1974a).

4.1 Teratogenic, Carcinogenic, and Mutagenic Effects

Table 4.3.1 summarizes the experiments on teratogenesis, which are described in Section 2.4. There is no indication that DDT was teratogenic at doses tested (1-50 mg/kg).

Table 4.3.2 summarizes the experiments on carcinogenesis described in Section 2.5. DDT induced liver tumors in rats in two of the three experiments that were reported in sufficient detail for evaluation (Fitzhugh and Nelson 1947, Rossi et al 1977). In one experiment, 4 of 15 tumors in exposed rats were diagnosed as "low grade hepatic cell carcinomas" and the remainder as "nodular adenomatiod hyperplasia." In the other experiment, the tumors were classified as "neoplastic nodules".

DDT has been shown to be carcinogenic in mice in at least 11 experiments, many of which involved exposure for up to six generations, several dose levels or dosage regimens, or several routes of exposure (Table 4.3.2). The principal site of action was the liver, but an increased incidence of tumors of the lung and lymphatic system was reported in several experiments. The liver tumors showed a low degree of malignancy as judged by histopathologic characteristics, but were

readily transplantable and metatasized in a small fraction of cases (Tomatis and Turusov 1975).

Although dietary levels of 50-250 ppm were used in most experiments, DDT induced liver tumors in male CF1 mice at levels as low as 2 and 10 ppm (Tomatis et al 1972). At a dietary level of 250 ppm, DDT induced liver tumors in mice exposed for only 15 or 30 weeks early in life (Tomatis et al 1974b).

In one experiment, mice were exposed to DDD or DDE at 250 ppm or to both chemicals, each at 125 ppm. The mice exposed to DDD developed a high incidence of lung tumors, whereas those exposed to DDE developed a high incidence of liver tumors. In this experiment, DDE appeared to be more active in inducing liver tumors than DDT itself (Tomatis et al 1974a). Preliminary results of a more recent experiment indicate that DDE induced liver tumors in B6C3F1 mice, in circumstances in which technical DDT showed no significant effects (NCI 1978).

Table 4.3.3 summarizes the experiments on mutagenesis described in Section 2.5. DDT, DDE, and DDE have been reported to cause chromosome damage, primarily breaks and gaps, in a number of experiments, both in vivo and in vitro. These experiments have involved cells from several mammalian species, including man. On the other hand, DDT and DDE have given consistently negative results in bacterial mutagenesis bioassays involving systems sensitive to both base-pair substitutions and frame-shift mutations. In other mutagenicity tests, including dominant lethal assays in mice and Drosophila and host-mediated assays, DDT, DDD, and DDE have sometimes given positive results. Other tests

have provided inconclusive or negative results.

Most of the reported experiments on the mutagenicity of DDT involved short exposures at relatively high doses, and dose-response relations were not always clear. However, statistically significant increases in the frequency of chromosome damage in vitro have been reported at concentrations in the range 0.2-10 ppm (Lessa et al 1976, Palmer et al 1972). This range overlaps that of serum concentrations of DDT and DDE found in occupationally exposed workers (Table 4.1.1).

4.4 Summary

DDT is converted by mammals via DDD or DDE to a number of other metabolites and is excreted primarily as DDA in the urine. In most mammals, metabolism to DDE is only a minor pathway, but p,p'-DDE is retained in the tissues much more strongly than DDT or other metabolites. p,p'-DDE is also the most stable metabolite in the environment and may be found in small quantities in some samples of technical DDT.

After mammals are exposed to technical DDT, DDT, DDD, and DDE are circulated in their blood and are stored in their tissues, primarily in the fat. After ingestion, humans store DDT and DDE in their tissues at much higher concentrations than those measured in experimental animals exposed at comparable levels. Consequently, target tissues in humans are exposed at concentrations of DDT and DDE proportionately higher than in experimental animals that ingest comparable quantities.

Although several incidents of poisoning after accidental ingestion have been reported, DDT has relatively low toxicity for humans. The estimated LD50 is about 250 mg/kg and the median dose for clinical effects is about 10 mg/kg. Workers exposed for long periods to technical DDT and absorbing 18-42 mg/day, as reflected by residue concentrations up to 1.1 ppm in blood and 650 ppm in fat, showed only minor or equivocal clinical signs. However, tests on these workers showed elevated activity of hepatic microsomal enzymes. Other changes statistically associated with blood concentrations of DDT and DDE include increased levels of serum LDH and SGOT, decreased levels of serum CPK, and

increased blood pressure and serum cholesterol.

Although a few workers who were exposed to DDT for up to 19 years have been studied, the available reports are inadequate for determining whether DDT may have carcinogenic or teratogenic effects in humans. Workers with mean blood residues of 1.0 ppm (equivalent to a daily intake of about 18 mg of DDT) showed a significantly higher frequency of chromatid aberrations than less exposed controls. Female workers exposed to DDT and other pesticides are reported to have suffered a significantly higher frequency of miscarriages and prepartum and postpartum disorders than less exposed controls.

In experimental animals, exposure to DDT and its metabolites has caused a wide variety of toxic effects, especially on the liver and CNS, on several other organs and a number of enzyme systems. DDT and its metabolites also affect the levels of steriod hormones circulating in the blood and bound to hormone receptors, and adversely affect reproduction in exposed mammals. The o,p' isomers of DDT and DDE are estrogenic and have irreversible effects on the development of animals exposed early in life. DDT has been reported to be immunosuppressive in rabbits.

At exposure levels below 10 ppm in the diet, the principal reported effects of DDT and its metabolites have been induction of hepatic microsomal enzymes and effects on behavior. Microsomal enzyme activity was increased by exposure to DDT at 0.9-4 ppm in the diet, but not at 0.2 or 0.5 ppm. Three experiments have shown that prenatal or neonatal exposure of mice to DDT causes changes in their behavior later in life. One of these experiments involved exposure at concentrations as

low as 0.1 ppm in drinking water.

DDT is carcinogenic in mice, increasing the incidence of tumors primarily in the liver, but also in the lungs and lymphatic system in some experiments. In one experiment, DDT increased the incidence of liver tumors in mice exposed for their lifetime to only 2 ppm in the diet. Tissue levels of DDT in these mice were comparable to or lower than those reported in several studies of occupationally exposed workers. DDD and DDE are also carcinogenic in mice, causing liver and lung tumors; DDE is more effective than DDT itself. In two experiments with rats, DDT induced liver tumors (or "neoplastic nodules") with a low degree of malignancy. DDD has also been reported to be carcinogenic in rats. Three experiments involving exposure of hamsters to DDT have given negative results for carcinogenicity. DDT also interacts with other carcinogens in mice and rats, increasing the incidence of tumors in some experiments and decreasing it in others.

There is no reported evidence that DDT is teratogenic in mammals. Experiments investigating the mutagenicity of DDT and its metabolites have yielded a complex mixture of positive and negative results. DDT and DDE have given consistently negative results in bacterial mutagenesis bioassays. On the other hand, DDT, DDD, and DDE have been reported to cause chromosome damage in a number of experiments, both in vivo and in vitro. In two experiments, chromosome damage was reported to be evident after exposure to DDT at concentrations in the range of 0.2-10 ppm, a range which overlaps the serum concentrations of DDT and DDE found in occupationally exposed workers.

TABLE 4.1.1

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE OF DDT

Formulation	Duration and Route of Exposure	Tissue Levels of DDT, DDE, and DDA	Reported Effects	Reference
Mainly dust (manufacture and formulation)	0.4-8 yr dermal, respiratory, some oral	0.1-7.5 ppm DDA in urine (equivalent to DDT intake of 14-42 mg/d)	Skin and eye irritation, slight hand tremor in 5/40, enlarged liver in 1	Ortelee 1958
Chips, flakes, dust	Mean 14.4 yr dermal, respiratory	Mean 0.573 ppm p,p'-DDT and 0.506 ppm p,p'-DDE in serum (equivalent to DDT intake of 18 mg/d)	Serum half-life of phenylbutazone 19% less than in controls, urinary excretion of 6-beta-hydroxycortisol increased by 57%	Poland et al 1970
Not reported	2 mo - 10 yr unknown	0.16-3.25 ppm total residues in plasma (equivalent to DDT intake of 6-27 mg/d)	Chromatid aberrations in 12.2% of lymphocytes vs 8.8% in lower exposure group and 2.2% in unexposed controls (0.02-0.04 ppm total residues in plasma)	Rabello et al 1975
Chips, flakes, dust	11-19 yr dermal, respiratory	0.11-2.20 ppm total residues in serum, 38-646 ppm total residues in fat, 0-2.7 ppm DDA in urine (equivalent to DDT intake of 4-18 mg/d)	No effects attributable to exposure	Laws et al 1967

TABLE 4.1.1 (continued)

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE TO DDT

Forumlation	Duration and Route of Exposure	Tissue Levels of DDT, DDE, and DDA	Reported Effects	Reference
Spray	5-15 yr dermal, respiratory	Mean 1.11 ppm in blood (equivalent to DDT intake of 9 mg/d) vs 0.26 ppm in controls	Slight differences in knee reflex, tremor, performance of Romberg tests; not confirmed in a second examination	WHO 1973
Unknown (formulation and application)	5-22 yr unknown	0-167 ppb p,p'-DDT and 26-222 ppb DDE in serum	Increased serum LDH and decreased serum CPK in group with highest residues (104-222 ppb DDE)	Morgan and Roan 1974
Not reported	1-20 yr unknown (also exposed to BHC and "Benzilan")	-	Abnormal EEG in 21.9% of workers	Mayersdorf and Israeli 1974
Not stated (vineyard application)	Unknown (also exposed to sulfur, methyl parathion, and copper sulfate)	Mean 0.12 ppm in maternal milk and 0.19 ppm in placentas (4.8 and 5.4 times levels in controls, respectively)	Increased frequency of miscarriages, toxemia of pregnancy, uterine inertia, postpartum hemorrhage; reduced birth weight of infants; histopathologic changes in placentas	Nikitiana 1974

TABLE 4.1.1 (continued)

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE TO DDT

Formulation	Duration of Route of Exposure	Tissue Levels of DDT, DDE, and DDA	Reported Effects	Reference
Spray	Unknown (also exposed to lindane and other pesticides)	Mean 33 ppb DDE in plasma	Decreased half-life of antipyrine and phenylbutazone in plasma, hyper-alpha-HDL lipoproteinemia	Kolmodin et al 1969, Kolmodin and Hedman 1973a,b
-	Mean 12 yr Unknown (also exposed to organophosphate and carbamate pesticides	-	Increased levels of SGPT and cholesterol in groups exposed to organochlorine pesticides; correlation between blood pressure, serum cholesterol, and plasma DDT and DDE; no effects considered clinically significant	Sandifer et al 1972
-	"Chronically exposed" to DDT and various other pesticides	-	Elevated levels of several amino acids in plasma and elevated levels of SGOT, alkaline phosphatase, serum osmolality, and creatinine relative to controls	Tocci et al 1969

TABLE 4.1.1 (continued)

SUMMARY OF EFFECTS OF OCCUPATIONAL EXPOSURE OF DDT

Formulation	Duration and Route of Exposure	Tissue Levels of DDT, DDE, and DDA	Reported Effects	Reference
-	Not stated (occupationally exposed to various pesticides)	Mean 9.2 ppb p,p'-DDT and 29.3 ppb p,p'-DDE	Significant correlation between SGOT levels, number of band cells and serum DDE levels; other parameters not associated with DDE	Warnick and Carter 1972
Spray	6-13 yr dermal, respiratory	"Approximately 3 times that of controls" from general population	Minor differences in results of some neurologic tests; not confirmed in a second examination	WHO 1973

TABLE 4.2.1

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Rat	1,000 ppm o,p'-DDT 6 mo	-	Reduced growth, fertility; reduced fecundity of offspring	Clement and Okey 1974
"	800 ppm technical DDT 2 yr	-	Increased mortality, liver lesions	Fitzhugh and Nelson 1947, Fitzhugh 1948
"	600 ppm technical DDT 2 yr	-	Increased mortality, increased liver and kidney weights, liver lesions, reduction in preweaning survival of offspring, no survival of offspring in second generation	Fitzhugh and Nelson 1947, Fitzhugh 1948
"	500 ppm p,p'-DDT 6 mo	-	Death of all offspring within 10 d of birth	Clement and Okey 1974
"	400 ppm technical DDT 2 yr	1,000 ppm in fat	Increased mortality, increased liver weight, liver changes	Fitzhugh and Nelson 1947, Fitzhugh 1948
"	350 ppm 33-60 wk	-	No increase in histopathologic changes in liver relative to controls	Cameron and Cheng 1951
"	250 or 500 ppm technical DDT 8 wk	-	Increased liver weight, proliferation of smooth endoplasmic reticulum, atypical mitochondria	Kimbrough et al 1971

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Rat	20 mg/kg/d 4-5 wk	-	Changes in frequency and amplitude of EEG, slight ataxia	Farkas et al 1968
"	200 ppm technical DDT 2 yr	160-310 ppm in fat	Increased liver weight in females, liver lesions	Fitzhugh and Nelson 1947, Fitzhugh 1948
"	200 ppm p,p'-DDT 6 mo	-	Severe depression of growth in offspring	Clement and Okey 1974
"	200 ppm o,p'-DDT 6 mo	-	No effects on growth or subsequent reproductive performance of offspring	"
"	200 ppm technical DDT 2 generations	-	Normal reproduction, increase in liver weight, increase in incidence of ring-tail	Ottoboni 1969
"	150 ppm 8-36 wk	-	Reproductive failure	Jonsson et al 1975
"	100 ppm technical DDT 2 yr	100-130 ppm in fat	Mild liver lesions, reduction in pre-weaning survival of offspring	Fitzhugh and Nelson 1947, Fitzhugh 1948
"	75 ppm 8-36 wk	-	Reduction in number of females producing litters, no effect on litter size	Jonsson et al 1975

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Rat	50 ppm technical DDT 2 generations	-	Reduction in preweaning survival of offspring	Fitzhugh 1948
"	25 ppm 2 yr	-	Increased liver weight in males	Treon and Cleveland 1955
"	20 or 200 ppm technical DDT 31 d	-	Reduction in histamine-containing mast cells in mesenteries; reduction in severity of anaphylactic shock	Gabliks et al 1975
"	20 or 200 ppm o,p'-DDT 6 mo	-	No effects on reproductive performance of offspring	Clement and Okey 1974
"	20 ppm p,p'-DDT 6 mo	-	No effects on reproduction	"
"	20 ppm technical DDT 2 generations	-	Increased reproductive lifespan relative to controls, increase in incidence of ringtail	Ottoboni 1969
"	15 ppm p,p'-DDT, o,p'-DDT, or technical DDT 2 generations	-	No effects on reproductive performance	Duby et al 1971

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Rat	10 ppm technical DDT 2 yr	120-270 ppm in fat	Liver lesions, no effects on reproduction	Fitzhugh 1948
"	1 mg/kg single dose	9.4 ppm in fat	Increased activity of hepatic microsomal enzymes	Gerboth and Schwabe 1964
"	7 ppm 2 generations	-	Marked reduction in fertility and in survival of offspring from 1st generation; no conceptions in rats in 2nd generation	Green 1969
"	0.5 mg/kg/d 14 d	10.8 ppm in fat	Increase in hepatic microsomal enzyme activity	Schwabe and Wendling 1967
"	5 or 50 ppm 3 mo	-	Increased activity in hepatic microsomal enzymes	Hart and Fouts 1965
"	5 ppm 4-6 mo	-	"Liver injury"	Kunze et al 1949
"	5 or 15 ppm 2-18 mo	-	Histopathologic changes in liver in males, proliferation of SER, concentric membrane arrays	Ortega et al 1956, Ortega 1962
"	4, 8, 16, or 32 ppm technical DDT 14 d	-	Increased hepatic p-nitroanisole metabolism	Hoffmann et al 1969

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Rat	2.5, 12.5, or 25 ppm 3 generations	-	Slight increase in mortality of offspring at all three dose levels, no effects on number of pregnancies or size of litters	Treon and Cleveland 1955
"	0.2 mg/kg/d 14 d	2.56 ppm in fat	Nonsignificant increase in hepatic microsomal enzyme activity	Schwabe and Wendling 1967
"	1 or 2.5 ppm o,p'-DDT 168 d	-	No significant effects on reproduction	Wrenn et al 1970
"	1 ppm 175 d	-	No effects on reproductive performance	Duby et al 1971
"	1 ppm 14 d	-	Estimated dietary threshold for induction of hepatic microsomal enzyme activity	Street et al 1969
"	1, 5, 25, and 50 ppm 1 wk	-	Induction of hepatic microsomal enzymes; N-demethylase activity increased to 2.3 times control level after 1 wk at 1 ppm	Kinoshita et al 1966
"	1 or 2.5 ppm o,p'-DDT through pregnancy and lactation	-	No significant effects on reproductive performance	Wrenn et al 1970
"	0.9 ppm -	-	Estimated dietary threshold for induction of hepatic microsomal enzymes	Gillett et al 1968

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Rat	0.5 or 2 ppm technical DDT 14 d	-	No increase in liver weight or increase in p-nitroanisole metabolism	Hoffman et al 1967
"	0.2 ppm 1-13 wk	-	No significant increase in hepatic microsomal enzyme activity	Kinoshita et al 1968
Mouse	250 ppm p,p'-DDE lifespan	78-434 ppm DDE in fat	Reduced lifespan, high incidence of liver tumors, myocardial necrosis in 22/53 males	Tomatis et al 1974
"	125 ppm p,p'-DDE plus 125 ppm p,p'-DDD lifespan	17-222 ppm DDE, 0-5.4 ppm DDD in fat	Reduced lifespan, high incidence of liver tumors, mycardial necrosis in 11/56 males	"
"	250 ppm p,p'-DDD lifespan	0.5-5.6 ppm DDD in fat	Reduced lifespan, increased incidence of lung and liver tumors	"
"	250 ppm technical DDT 2 generations	271-629 ppm DDT, 6-37 ppm DDE in fat	Reduced lifespan, convulsions, tremors, increased incidence of liver tumors, increased preweaning mortality of offspring	Tomatis et al 1972
"	250 ppm 6 generations	-	Severe adverse effects on reproduction, primarily on lactation and survival of offspring	Keplinger et 1970

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Mouse	250 ppm technical DDT 4 generations	-	Reduced lifespan in females, convulsions, gastrointestional bleeding, increased incidence of liver tumors, no effect on reproductive performance	Terracini et al 1973a,b
"	25 or 50 mg/kg/d technical DDT 10 d	-	Reduction in accumulation of testosterone and 5-alpha-dihydrotestosterone by anterior prostate	Lloyd et al 1974
"	46 mg/kg/d p,p'-DDT until weaning, then 140 ppm 18 mo	-	Increased incidence of liver tumors	Innes et al 1969
"	100 ppm 6 generations	-	Slight reduction in lactation and survival of offspring	Keplinger et al 1970
"	100 ppm p,p'-DDT 2 yr	-	Increased incidence of liver tumors	Thorpe and Walker 1973, Walker et al 1973
"	10 or 20 mg/kg single dose	-	Changes in electroshock seizure patterns, increase in exploratory behavior, decrease in habituation	Sobotka 1971

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Mouse	10 mg/kg technical DDT daily by oral intubation or twice/mo sc 80 wk	-	Tremors and convulsions after 40 wk, no increase in mortality, increased incidence of corneal opacity, increased incidence of tumors	Kashyap et al 1977
"	50 ppm technical DDT 2 generations	-	Increased incidence of liver tumors	Tomatis et al 1972
"	50 ppm p,p'-DDT 2 yr	-	"	Walker et al 1973
"	25 ppm 6 generations	-	No effects on reproduction	Kelpinger et al 1970
"	2.5 mg/kg/d single dose during pregnancy	-	Delayed acquisition of conditioned avoidance responses by offspring at age 32-37 d	Al-Hachim and Fink 1967, 1968
"	20 ppm technical DDT 2 generations	-	No observed effects	Terracini et al 1973a
"	10 ppm technical DDT 2 generations	-	Increased incidence of liver tumors	Tomatis et al 1972

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Mouse	7 ppm technical DDT 120 d	-	No effects on reproduction	Ware and Good 1967
"	7 ppm technical DDT 10 d	-	Decrease in aggressive behavior and loss of dominance in males	Peterle and Peterle 1971
"	2.8-3.0 ppm technical DDT 5 generations	5-11 ppm in fat	Increase in incidence of lung and other tumors, leukemia; no effects on reproductive success or motility	Tarjan and Kemeny 1969
"	0.1 or 1.0 ppb in drinking water 8 wk during and after pregnancy	-	Significant decrease in aggressive behavior of male offspring at age 35 d	Scudder and Richardson 1970
"	0.01 ppb in drinking water 8 wk during and after pregnancy	-	No effects on agressive behavior of male offspring	"
Hamster	500 or 1,000 ppm p,p'-DDT 90 wk	-	Nervousness, convulsions, reduced lifespan	Agthe et al 1970
"	250 ppm p,p'-DDT 6 wk	60 ppm in fat	Decreased hexobarbital sleeping time, increased rate of metabolism of radiolabeled DDT	Gingell and Wallcave 1973

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Hamster	250, 500, or 1,000 ppm technical DDT 18 mo	-	Increased liver weight, increase activity of glucose-6-phosphate dehydrogenase, increased lifespan	Graillot et al 1975
"	125, 250, or 500 ppm lifespan	-	No effects on growth or survival rates	Cabral and Shubik 1977
Dog	3,200 ppm technical DDT 39-49 mo	-	Liver damage	Lehman 1952, 1965
"	2,000 ppm technical DDT 34-49 ppm	-	Minor liver damage	"
"	400 ppm technical DDT 39-49 mo	-	No observed effects	"
"	12 mg/kg/d p,p'-DDT 14 mo	3 ppb in blood, 32 ppm in fat at time of mating	Moderate increase in serum alkaline phosphatase, diminished libido in males, delayed estrus in females, reduction in mammary development and milk production, infertility, increased infant and maternal mortality	Deichmann et al 1971, Deichmann and MacDonald 1971

TABLE 4.2.1 (continued)

SUMMARY OF EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Tissue Levels	Reported Effects	Reference
Dog	1, 5, or 10 mg/kg/d technical DDT 3 generations	-	Earlier onset of estrus in exposed females than in controls; reproduction otherwise normal	Ottoboni et al 1977
Rabbit	0.92, 2.1, or 6.5 mg/kg/d p,p'-DDT 28 d	-	Increased spleen weight, decreased count of plasma cells in popliteal lymph nodes, reduction in germinal centers in spleen, atrophy of thymus cortex	Street and Sharma 1974
Rhesus monkey	200 ppm technical DDT or p,p'-DDT 3.5-7.5 yr	256-472 ppm DDT in fat	No observed effects attributable to exposure	Durham et al 1963
"	50 ppm technical DDT 1.6 yr	100-198 ppm DDT in fat	"	"
Sheep	250 ppm technical DDT 10-16 wk	-	Increased hepatic microsomal enzyme activity	Cecil et al 1975

TABLE 4.3.1

EXPERIMENTS INVOLVING ORAL ADMINISTRATION OF DDT TO ANIMALS IN WHICH TERATOGENIC EFFECTS WERE SOUGHT

Species	Dose and Time of Administration*	Reported Effects	Reference
Rabbit	50 mg/kg p,p'-DDT d 7, 8, and 9	Premature delivery, increase in resorptions, decreased intrauterine growth, no congenital abnormalities	Hart et al 1971
Mouse	1 mg/kg p,p'-DDT d 10, 12, and 17	Morphologic changes in gonads and reduction in fertility of offspring, especially females; no gross teratogenic effects	McLachlan and Dixon 1972
Rat	7 ppm in diet before and thoughout pregnancy	Marked decrease in fertility, small increase in resorption, no increase in frequency of congenital abnormalities	Green 1969

*Day of pregnancy

CARCINOGENIC EFFECTS

Species	Concentration and Duration
Rat, male (Osborne-Mendel)	1,647 or 3,294 ppm technical DDD 78 wk
Rat, female (Osborne-Mendel)	850 or 1,700 ppm technical DDD 78 wk
Rate, male (Osborne-Mendel)	839 or 437 ppm technical DDE 78 wk
"	100, 200, 400, 600, or 800 ppm technical DDT 2 yr
"	642 or 321 ppm technical DDT 78 wk
Rat	600 ppm o,p'-DDD 24-469 d
Rat (Wistar)	500 ppm technical DDT 2 yr

TABLE 4.3.2

OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Reported Effects	Reference
Combination follicular-cell carcinomas and follicular-cell adenomas	NCI 1978
No evidence of carcinogenicity	"
"	"
Reduced survival; 4 liver carcinomas and 11 liver nodules in 75 exposed rats vs 0 in controls	Fitzhugh and Nelson 1947
No evidence of carcinogenicity	NCI 1978
Interstitial cell testicular tumors in 2/3 rats surviving 348-469 d	Lacassagne and Hurst 1965
Increased incidence of liver tumors (neoplastic nodules) in both sexes	Rossi et al 1977

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Reported Effects	Reference
Rat, female (Osborne-Mendel)	242 or 457 ppm technical DDE 78 wk	No evidence of carcinogenicity	NCI 1978
"	210 or 420 ppm technical DDT 78 wk	"	"
Rat (Osborne-Mendel)	80 or 200 ppm recrystallized DDT up to 2 yr	Bronchogenic carcinomas in 8/60 rats at 80 ppm vs 2/60 in controls and 0 in rats at 200 ppm; not confirmed in other groups given DDT with other pesticides	Deichmann et al 1967, Radomski et al 1965
Mouse, male and female (B6C3F1)	411 or 822 ppm technical DDD 78 wk	No evidence of carcinogenicity	NCI 1978
"	147 or 253 ppm technical DDE 78 wk	Hepatocellular carcinomas	"
Mouse (CF1)	250 ppm technical DDT 6 generations lifespan	Increased incidence of liver cell tumors in both sexes	Turusov et al 1973
"	250 ppm p,p'-DDE 2 yr	Increased incidence of liver cell tumors in both sexes; tumor incidence greater and occurrence earlier than in animals exposed to DDT or p,p'-DDD at 250 ppm	Tomatis et al 1974a

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Reported Effects	Reference
Mouse (CF1)	250 ppm p,p'-DDD 2 yr	Increased incidence of liver cell tumors and lung adenomas in both sexes	Tomatis et al 1974a
"	125 ppm p,p'-DDE plus 125 ppm p,p'-DDD 2 yr	Increase in liver cell tumors in both sexes; incidence and time of occurrence of tumors intermediate between those of groups fed 250 ppm DDE and 250 ppm DDD	"
"	250 ppm technical DDT 2 yr	Decreased lifespan, increased incidence of liver cell tumors in both sexes, metastases from 2 tumors	Tomatis et al 1972
Mouse (BALB/c)	250 ppm technical DDT 4 generations lifespan	Reduced lifespan in females, increased incidence of liver cell tumors in both sexes, tumors successfully transplanted	Terracini et al 1973a,b
Mouse (CF1)	250 ppm technical DDT 15 or 30 wk followed by observation for 50-150 wk	Increase in liver cell tumors in all 6 exposed groups; tumor incidence dependent on length of exposure early in life; increase in size and multiplicity of tumors with age	Tomatis et al 1974b
Mouse (ICR)	250 ppm -	Focal hepatic hyperplasia developing into hepatic cellular adenoma, negative test for alpha-fetoprotein	Kuwabara and Takayama 1974

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Reported Effects	Reference
Mouse (CF1)	200 ppm p,p'-DDT 2 yr	Increase in liver tumors in both sexes	Stevenson 1974
Mouse, female (B6C3F1)	87 or 174 ppm technical DDT 78 wk	No evidence of carcinogenicity	
Mouse (2 hybrid strains)	46.4 mg/kg/d p,p'-DDT prior to weaning, then 140 ppm in diet 18 mo	Increased incidence of liver tumors in both strains and of lymphomas in females of one strain	Innes et al 1969
Mouse (Swiss)	100 ppm technical DDT in diet or 10 mg/kg/d by intubation 80 wk	Increase in malignant lymphomas, lung adenomas, and hepatocellular carcinomas	Kashyap et al 1977
Mouse (CF1)	100 ppm p,p'-DDT 110 wk	Increased incidence of liver tumors in both sexes	Thorpe and Walker 1973, Reuber 1974
"	50 or 100 ppm p,p'-DDT 2 yr	In both sexes, dose-related increases in liver tumors and increases in age-adjusted incidence of lung tumors	Walker et al 1972, Hunt 1974

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Reported Effects	Reference
Mouse (A)	50 ppm in oil (exact dose unspecified) 6-12 mo	Increase in pulmonary adenomas, increase in number of tumors per mouse	Shabad et al 1973
Mouse (CF1)	50 ppm p,p'-DDT with 5 ppm HEOD 2 yr	Increased incidence of liver tumors in both sexes, relative to controls and to mice fed 50 ppm DDT alone	Walker et al 1973, Epstein 1975
Mouse, male (B6C3F1)	22 or 43 ppm technical DDT 78 wk	No evidence of carcinogenicity	NCI 1978
Mouse (A)	10 ppm in oil (exact dose unspecified) 5 generations	Increase in pulmonary adenomas in parental mice and in all 5 subsequent generations, increased number of tumors per mouse	Shabad et al 1973
Mouse	2.8-3.0 ppm 5 generations	Increased incidence of leukemia and of lung carcinomas and other tumors, especially in 2nd-5th generations	Tarjan and Kemeny 1969
Mouse (BALB/c)	2 or 20 ppm technical DDT 4 generations	No significant increase in tumors in either sex	Terracini et al 1973a,b

TABLE 4.3.2 (continued)

CARCINOGENIC EFFECTS OF DIETARY ADMINISTRATION OF DDT TO ANIMALS

Species	Concentration and Duration	Reported Effects	Reference
Mouse (CF1)	2, 10, or 50 ppm technical DDT 6 generations	Increased incidence of liver cell tumors in males; nonsignificant increases in females	Turusov et al 1973
"	2, 10, or 50 ppm technical DDT 2 generations	Increased incidence of lung tumors in males; increased incidence of liver cell tumors in exposed males (67/127 at 50 ppm, 52/104 at 10 ppm, 57/124 at 2 ppm, 25/113 in controls); nonsignificant increases in females; metastases from 2 tumors in exposed mice	Tomatis et al 1972
Hamster	500 or 1,000 ppm p,p'-DDT 90 wk	No significant increase in tumors	Agthe et al 1970
"	250, 500, and 1,000 ppm 18 mo	Decreased incidence of lymphosarcomas; other tumors not listed	Graillot et al 1975
"	100, 250, or 500 ppm lifespan	No increase in tumors	Cabral and Shubik 1977

TABLE 4.3.3

SUMMARY OF MUTAGENIC EFFECTS OF DDT AND METABOLITES

Substance	Species or System	Strain	Dose	Reported Effects	Reference
Technical DDT	Salmonella typhimurium	TA 1535 TA 1536 TA 1537 TA 1538	20 µg/plate	No increase in revertants without rat liver microsomal preparations	Shirasu et al 1976
DDT	"	"	2,500 µg/plate	No increase in revertants with or without rat liver microsomal preparations	Marshall et al 1975
DDE	"	"	1,000 µg/plate	"	"
p,p'-DDT, p,p'-DDE	"	-	Not stated	No increase in revertants with mouse liver microsomal preparations	Van Dijck and Van de Voorde 1976
p,p'-DDE	"	TA 1535 TA 1537 TA 98 TA 100	5,000 µg/plate	No increase in revertants with or without rat liver microsomal preparations	McCann et al 1975
Technical DDT	Escherichia coli	B/r try WP2, WP2 try hcr	20 µg/plate	No increase in revertants without rat liver microsomal preparations	Shirasu et al 1976

TABLE 4.3.3 (continued)

SUMMARY OF MUTAGENIC EFFECTS OF DDT AND METABOLITES

Substance	Species or System	Strain	Dose	Reported Effects	Reference
Technical DDT	Bacillus subtilis	H17 Rec^+ M45 Rec^-	20 µg/plate	No increase in recombination mutants	Shirasu et al 1976
"	Neurospora crassa	Heterokaryon 12	750 mg/ 100 ml	Nonsignificant increase in recessive lethal mutants	Clark 1974
DDT, DDD, DDE, DDA	Salmonella typhimurium in NMRl mice (host-mediated assay)	-	500 mg/kg	No significant increase in mutation frequency	Buselmaier et al 1972
"	Serratia marcescens in NMRl Mice (host-mediated assay)	-	Not stated	DDD strongly mutagenic, DDT, DDE, and DDA inactive; DDD not mutagenic when applied directly to S. marcescens	"
Technical DDT	Neurospora crassa in Swiss mice (host-mediated assay)	Heterokaryon 12	150 mg/kg 2 oral doses	Nonsignificant increase in mutants	Clark 1974
p,p'-DDT p,p'-DDD, or p,p'-DDE	Rat-kangaroo cells	-	10 µg/ml	Chromosomal aberrations in 22.4, 15.5, and 13.7% of cells exposed to DDT, DDD, and DDE, respectively, vs 2.1% in controls	Palmer et al 1972

TABLE 4.3.3 (continued)

SUMMARY OF MUTAGENIC EFFECTS OF DDT AND METABOLITES

Substance	Species of System	Strain	Dose	Reported Effects	Reference
o,p'-DDT, o,p'-DDD, or o,p'-DDE	Rat-kangaroo cells	-	10 µg/ml	Chromosomal aberrations in 8.9, 8.3, and 5.9% of cells exposed to DDT, DDD, and DDE, respectively, vs 2.1% in controls	Palmer et al 1972
p,p'-DDT, p,p'-DDD, p,p'-DDE, p,p'-DDA	Mouse embryo cells	-	2.8-42.6 µM	Cell transformations (DDD most active); transformed cells not malignant	Langenbach and Gingell 1975
p,p'-DDT	Chinese hamster cells	V79	30-45 µg/ml	Nonsignificant increase in forward mutations, nonsignificant increase in cytogenetic abnormalities	Kelly-Garvert and Legator 1973
p,p'-DDE	"	"	25-40 µg/ml	Significant increase in forward mutations (to 8-azaguanine resistance), significant increase in cytogenetic abnormalities (exchanges)	"
p,p'-DDT, p,p'-DDD, p,p'-DDE, p,p'-DDA	"	B14 E28	12-100 µg/ml	Marked increase in chromosome gaps and breaks in cells exposed to DDT or DDD, increase in gaps in cells exposed to DDA, DDE intermediate in activity; dose-dependent effects for all 4 compounds	Mahr and Miltenburger 1976

TABLE 4.3.3 (continued)

SUMMARY OF MUTAGENIC EFFECTS OF DDT AND METABOLITES

Substance	Species or System	Strain	Dose	Reported Effects	Reference
DDT	Chinese hamster cells	V79	0.1-3.0 mM	Negative results in alkaline elution assay in vitro for DNA damage, with rat liver microsomal activation	Swenberg et al 1976
Technical DDT	Human lymphocytes	-	0.06-15.6 µg/ml	Significant increase in chromosome aberrations (chromatid gaps and breaks) at 0.2, 4.0, and 8.7 ug/ml DDT but not at higher concentrations	Lessa et al 1975
"	Drosophila melanogaster	Canton-S	1 µg on food medium	Dominant lethal mutations in early spermatid and spermatocte stages, nondisjunction of X and Y chromosomes, shift in sex ratio; no increase in recessive lethal mutations	Clark 1974
DDT	"	-	-	No increase in recessive lethal mutations	Luers 1953
p,p'-DDT, p,p'-DDD, p,p'-DDE, p,p'-DDA, p,p'-DDOM	"	Berlin wild K	0.2-3.7 mM	Significant increase in sex-linked recessive lethal mutants exposed to DDA or DDT, no effect with DDD, DDE, or DDOM	Vogel 1972
p,p'-DDT	Rat	Osborne-Meldel	50, 100, or 200 mg/kg single dose ip or 40, 80, or 100 mg/kg/d x 5 d ip	No significant increase in chromosomal aberrations in bone-marrow cells	Legator et al 1973

TABLE 4.3.3 (continued)

SUMMARY OF MUTAGENIC EFFECTS OF DDT AND METABOLITES

Substance	Species or System	Strain	Dose	Reported Effects	Reference
p,p'-DDT	Rat	-	25, 50, or 100 mg/kg single dose oral intubation or 20, 40, or 80 mg/kg/d x 5 d ip	Significant increase in dead implants in females mated to males exposed at 100 mg/kg (dominant lethal assay); no significant effects at lower doses	Palmer et al 1973
Technical DDT	Mouse	CF1	250 ppm 5 generations	No evidence of greater incidence of recessive invisible mutations in descendants of exposed mice relative to controls	Wallace et al 1976
"	"	Swiss	150 mg/kg x 2 oral doses, or 100 mg/kg 2x weekly for 10 wk	Dominant lethal mutations in early spermatid and spermatocyte stages, reduced number of implants/female and increased number of dead implants; chromosome breakage, stickiness, and nondisjunction in spermatocytes	Clark 1974
DDT, DDE, DDD, DDA	"	NMRI	1,200 mg/kg	Inconclusive results in dominant lethal assay	Buselmaier et al 1972
DDT	"	ICR/Ha	105-130 mg/kg ip or 10-100 mg/kg/d x 48 d	No significant increase in dead implants (dominant lethal assay)	Epstein et al 1972

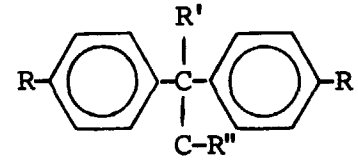
TABLE 4.3.3 (continued)

SUMMARY OF MUTAGENIC EFFECTS OF DDT AND METABOLITES

Substance	Species or System	Strain	Dose	Reported Effects	Reference
DDT	Mouse	BALB/c	- ip 3 wk	Significant dose-related increase in frequency of chromosomal stickiness and deletions	Johnson and Jalal 1973
"	"	"	25, 50, 100, or 250 mg/kg single dose ip	Significant dose-related increase in frequency of deletions in bone marrow cells, no increase in gaps or stickiness	Larsen and Jalal 1973, 1975
"	"	-	10 mg/kg	Significant increase in chromosomal aberrations (stickiness, rearrangements) in bone marrow cells	Markaryan 1966
"	"	C57B1 x C3H	10 or 25 mg/kg ip	No increase in sperm abnormalities	Wyrobeck and Bruce 1975

TABLE 5.1

STRUCTURE OF DDT AND ITS ANALOGS* OF THE FORM:



MANY OF THE COMPOUNDS ALSO EXIST AS o,p'-ISOMERS AND OTHER ISOMERS

Abbreviated Name	Chemical Name	R	R'	R"
DDT	1,1,1-trichloro-2,2-bis-(p-chlorophenyl) ethane	-Cl	-H	$-Cl_3$
DDE	1,1-dichloro-2,2-bis-(p-chlorophenyl) ethylene	-Cl	None	$-Cl_2$
DDD**	1,1-dichloro-2,2-bis-(p-chlorophenyl)ethane	-Cl	-H	$-HCl_2$
DDMU	1-chloro-2,2-bis-(p-chlorophenyl) ethylene	-Cl	None	-HCl
DDMS	1-chloro-2,2-bis-(p-chlorophenyl) ethane	-Cl	-H	$-H_2Cl$
DDNU	2,2-bis(p-chlorophenyl) ethylene	-Cl	None	$-H_2$
DDOH	2,2-bis(p-chlorophenyl) ethanol	-Cl	-H	$-H_2OH$
DDA	2,2-bis(p-chlorophenyl) acetic acid	-Cl	-H	-OOH

* Each is a recognized metabolite of DDT in the rat.

**As an insecticide, this compound has the approved name of TDE, and it has been sold under the name Rothane; as a drug, it is called mitotane.

Adapted from WHO 1977

TABLE 5.2

PHYSICAL AND CHEMICAL PROPERTIES OF DDT

Appearance	Colorless crystals or white to slightly off-white powder
Empirical formula	$C_{14}H_9Cl_5$
Formula weight	354.49
Melting point	108.5-109 C
Boiling point	260 C
Vapor pressure	1.5×10^{-7} mm Hg at 20 C
Octanol/water partition coefficient	4.96
Solubility	Practically insoluble in water Solubility in 100 ml of: acetone = 58 g benzene = 78 g benzyl benzoate = 42 g carbon tetrachloride = 45 g chlorobenzene = 74 g cyclohexanone = 116 g 95% alc. = 2 g ethyl ether = 28 g gasoline = 10 g isopropanol = 3 g kerosene = 8-10 g morpholine = 75 g peanut oil = 11 g pine oil = 10-16 g tetralin = 61 g tributyl phosphate = 50 g freely soluble in pyridine, dioxane Solubility in organic solvents increases with a rise in temperature
Stability	Stable to light and oxidation

From Condensed Chemical Directory 1977, Merck Index 1976, Handbook of Chemistry and Physics 1976

TABLE 5.3

SYNONYMS AND TRADE NAMES FOR DDT

Dichlorodiphenyltrichloroethane
Dicophane
Chlorophenothane
1,1,1-Trichloro-2,2-bis(p-chlorophenyl) ethane)
1,1'-(2,2,2-Trichloroethylidene)bis(4-chlorobenzene)
alpha,alpha-bis(p-Chlorophenyl),beta,beta,beta-trichloroethane
Pentachlorin
p,p'-DDT
Gesarol
Neocid

From Condensed Chemical Dictionary 1977, Merck 1976

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