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REVIEW OF THE METABOLISM OF CHLORINATED HYDROCARBON INSECTICIDES ESPECIALLY IN MAMMALS[1]

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This review discusses the absorption, storage, biotransformation, and excretion of chlorinated hydrocarbon insecticides; thus, it emphasizes those aspects of physiology that can be studied by the methods of analytical organic chemistry. The broader aspects of toxicity, as they relate to the metabolism of these materials, were discussed by Winteringham & Barnes (1). This review emphasizes mammalian metabolism of the compounds, but contains some information on their metabolism by other organisms, a subject that has already been reviewed by Perry (2). In relation to mammals, greatest interest centers in numerous repeated doses that produce no obvious injury and that are so small that they might be encountered under practical conditions in the use of insecticides. For this reason, DDT and related residual insecticides are emphasized, but some information is given on the chlorinated hydrocarbon fumigants.

Compounds mentioned in this review are listed and identified in Table I.

Absorption

Methods of indirect measurement.—The fact that a particular insecticide is toxic when administered by a certain route proves that it has been absorbed, but the mere fact of toxicity gives little information on the amount or the rate of absorption.

It would appear that some idea of the efficiency of absorption from the skin or from the gastrointestinal tract of vertebrates could be gained by comparing the dermal or oral toxicity with the intravenous toxicity. This method has serious limitations. A water-insoluble material must usually be given intravenously, as an homogenized emulsion of an oily solution; under practical conditions, most of the oil droplets are blocked by the capillaries of the lung or taken up by the phagocytic cells of the liver and spleen. Thus, the fraction of the intravenously administered dose that is available immediately for distribution to critical tissues is unknown and probably small (3). After a single intravenous dose, as much DDT may be found stored in the tissue as after a single oral or intraperitoneal dose at rates as much as 10 times greater (4), and yet the intravenous toxicity is only 3 to 5 times greater than the toxicity by the other two routes. The explanation lies in the sequestering

[1] The survey of the literature pertaining to this review was concluded in July, 1964.

TABLE I

IDENTITY OF COMPOUNDS MENTIONED IN THIS REVIEW[a]

Common or Trade Name	Chemical Name	Reference
	DDT GROUP	
DBrDT	2,2-bis(*p*-bromophenyl) 1,1,1-trichloroethane	
DBrDA	2,2-bis(*p*-bromophenyl) acetic acid	(175)
DBrDE	2,2-bis(*p*-bromophenyl) 1,1-dichloroethylene	(176)
DDD	2,2-bis(*p*-chlorophenyl) 1,1-dichloroethane	
DDT	2,2-bis(*p*-chlorophenyl) 1,1,1-trichloroethane	
CO_2[b]	carbon dioxide	(102)
DBP[b]	4,4-dichlorobenzophenone	(177)
DDA	bis(*p*-chlorophenyl) acetic acid	(103)
DDD	see above	(23)
DDE	2,2-bis(*p*-chlorophenyl) 1,1-dichloroethylene	(135, 178)
DDMS	2,2-bis(*p*-chlorophenyl) 1-chloroethane	(134)
DDMU	2,2-bis(*p*-chlorophenyl) 1-chloroethylene	(134)
DDNU	unsym-bis(*p*-chlorophenyl) ethylene	(134)
DDOH	2,2-bis(*p*-chlorophenyl) ethanol	(134)
Kelthane[b]	see below	(179)
DIDT	2,2-bis(*p*-iodophenyl) 1,1,1-trichloroethane	
Kelthane	1,1-bis(*p*-chlorophenyl) 2,2,2-trichloroethanol	
methoxychlor	2,2-bis(*p*-methoxyphenyl) 1,1,1-trichloroethane	
Perthane	2,2-bis(*p*-ethylphenyl) 1,1-dichloroethane	
	CYCLODIENE GROUP	
aldrin	1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-*endo-exo*-5,8-dimethanonaphthalene	
dieldrin	see below	(118)
chlordane	1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane	
dieldrin	1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-*endo-exo*-5,8-dimethanonaphthalene	
endrin	1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-*endo-endo*-5,8-dimethanonaphthalene	
heptachlor	1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane	
heptachlor epoxide	1,4,5,6,7,8,8-heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-4,7-methanoindan	(115)

[a] Metabolites are shown indented under the parent compound, and one or more references to the discovery and proof of each metabolite are given. Note that certain metabolites are also insecticides that are produced commercially.

[b] In insects only.

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TABLE I (*Continued*)

Common or Trade Name	Chemical Name	Reference
isodrin	1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-*endo-endo*-5,8-dimethanonaphthalene	
trichloro 237	1,2,3,4,5,6,7,8,8-nonachloro-4,7-methane-3a,4,7,7a-tetrahydroindane	
	MISCELLANEOUS RESIDUAL COMPOUNDS	
BHC	1,2,3,4,5,6-hexachlorocyclohexane	
lindane	γ isomer of BHC	
pentachlorocyclohexene[b]	same	(136)
toxaphene	chlorinated camphene ($C_{10}H_{10}Cl_8$) contains 67–69% chlorine	
	FUMIGANTS	
carbon tetrachloride	same	
CO_2	carbon dioxide	(126)
carbonate	same	(126)
urea	carbonyldiamide	(126)
m-dichlorobenzene	same	
3,5-dichlorocatechol	same	(132)
2,4-dichlorophenol	same	(132)
3,5-dichlorophenol	same	(132)
2,4-dichlorophenyl mercapturic acid	same	(132)
o-dichlorobenzene	same	
3,4-dichlorocatechol	same	(138)
4,5-dichlorocatechol	same	(138)
2,3-dichlorophenol	same	(138)
3,4-dichlorophenol	same	(138)
3,4-dichlorophenyl mercapturic acid	same	(138)
p-dichlorobenzene	same	
2,5-dichlorophenol	same	(138)
2,5-dichloroquinol	same	(138)
methyl bromide	same	
trichloroethylene	same	
monochloroacetic acid	same	(180)
trichloroacetic acid	same	(181)
trichloroethanol	same	(181, 183)
chloroform	same	(181, 184)

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of the material injected intravenously. Finally, the chlorinated hydrocarbons have a relatively low toxicity so that it is difficult to use the method for measuring dermal absorption that Fredriksson (5) used for paraoxon. The slowness of absorption by other routes, as compared to the intravenous route, offers a certain protection to the organism so that apparent toxicity is determined by time as well as by the total absorbed dosage.

Judah (4) showed that absorption of DDT from the alimentary tract is slow in the rat, for he could still recover from the gut contents 27 to 89 percent of the dose 3 hr after it was administered as an oil solution by stomach tube.

Methods of direct measurement.—Because of the problems mentioned, methods for the direct quantitative measurement of absorption in vertebrates are needed. Some direct studies have been made, but few were quantitative in the required sense.

In an unpublished study, it was found that dermal absorption of DIDT from xylene solution was irregular in rats but did occur within 5 min in 7 out of 17 animals. The technique was novel. It involved putting each rat through a hole in a lead shield. A Geiger counter, placed over the head of the rat, registered above background count only when radioactive DIDT which had been applied to the skin over the hips entered the circulation in sufficient concentration (3).

Of the radioactive DDT administered orally to three rats with their thoracic ducts cannulated, 47 to 65 percent was recovered from the lymph (6). Absorption reached a peak about 1.5 to 2.5 hr after administration in two of the rats, but tended to maintain a plateau for several hours in the third rat. DDT was absorbed at rates as high as 381 μg per hr in rats weighing 325 to 375 g. Fifty percent of the DDT-derived materials found in the lymph was absorbed in the first 2.5 to 7.0 hr, and 95 percent was absorbed in 18 hr. The total recovery of absorbed and unabsorbed DDT in this experiment varied from 89 to 118 percent. Although the possibility of some absorption of this compound from the intestine by the hepatic portal system is not ruled out, it appears unlikely. The absorption of dieldrin is reported to be different from that of DDT, but the reason for the difference is not apparent from the physical characteristics of the two compounds. Of radioactive dieldrin administered orally, only 8 percent was recovered in the lymph (7).

Obviously, any insecticide stored in the tissues must be considered to have been absorbed, provided exposure was by a natural route. So far, measurement of storage has usually demonstrated the absorption of a higher proportion of the administered dosage of chlorinated hydrocarbon insecticides than has been demonstrated in any other way. This method of measuring absorption is relatively efficient in connection with a small number of doses, but becomes progressively less efficient as a steady state of storage is approached and maintained. The fat and muscle of pigs that had been fed DDT residues for 36 days were found to contain 49 to 57 percent of the total dosage (8). However, the dosage was measured by analysis of the residue in the food, and

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if this analysis gave systematically low results, the apparent success of final recovery would be increased.

Absorption may also be inferred from the measurement of true excretion. Because storage tends to reach a steady state at any given tolerated dosage, it should be possible with modern techniques to account, on the average, for 100 percent of the daily intake in terms of elimination by mechanical passage of unabsorbed material plus true excretion by all routes. A comparison of fecal excretion following oral and intravenous dosage should permit recognition of excretory products resulting from previously absorbed material. (Following ingestion, there is at least a remote possibility that metabolites in the feces are the result of bacterial or enzyme action on unabsorbed compound or, conversely, that the original compound is absorbed but excreted unchanged or only conjugated.)

Relation of formulation to absorption.—It is consistent with available information to postulate that DDT has to be in solution in order to be absorbed by any portal; but, there may be enough fat in the diet or on the skin to dissolve a portion of any DDT present. DDT dissolved in a nonabsorbable solvent is poorly absorbed (9, 10); the same is true of toxaphene (11).

It has been shown by direct measurement that the absorption of dieldrin from the intestinal tract varies with the vehicle (7), but it is freely absorbed from the skin even without a solvent (12).

Absorption of fumigants.—Winteringham & Barnes (1) have called attention to the probability that dermal absorption of fumigants is less important in mammals than in insects. Von Oettingen (13) cited reports of instances in which gas masks protected soldiers from poisoning by methyl bromide under what appeared to be the most severe conditions of exposure and in spite of severe injuries of the skin. He also cited instances in which workers wearing gas masks were poisoned by methyl bromide, and he concluded that it is not established definitely whether or not the compound is absorbed through the intact skin. However, an instance in which the occurrence of cases of poisoning was stopped by substitution of effective canisters for ones shown to be ineffective (14), emphasizes the importance of ruling out any imperfection of masks or their use in connection with this compound.

Men and women exposed to 440 to 4,042 μg per l of trichloroethylene retained an average of 51 to 64 percent of the inhaled vapor (15, 16).

Storage

The factors that may influence storage and excretion include: compound, intensity and duration of dosage, efficiency of absorption, age, sex, species, tissue, and the integrity of organs, especially the liver and kidneys.

Storage in relation to compound.—The dynamics of storage vary according to compound and may even be different for the isomers, as well as for the metabolites of single compounds. The α, β, γ, and δ isomers of BHC are stored unaltered in the fat of rats and dogs (17). The differences in the rate of storage of the isomers in the rat are remarkable and explain, at least in large

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measure, the lack of parallelism in the toxicity of the isomers following single and repeated doses. The difference in storage does not parallel the solubility of the isomers in rat fat (18) nor does it depend on difference of absorption, but it must be explained by different rates of biotransformation. On the contrary, difference in storage does not seem to account for the greater susceptibility of the dog (as compared to the rat) to repeated doses of the γ isomer (17).

Although not necessarily related to storage, the interaction of the isomers of BHC must be taken into account in a consideration of their toxicity and metabolism. The partially antidotal effects of the β and δ isomers in regard to the γ isomer have been demonstrated (19, 20). The problem was approached in a different way by van Asperen (21), who showed that the antidotal effect of combinations of isomers given intravenously was absent in connection with 7-day mortality, following subcutaneous doses. Van Asperen preferred to explain the observed facts in terms of biological antagonism (a competition of the isomers for a site of action), rather than in terms of any inherent difference in their physiological effect. However, when given separately, the β and δ isomers do produce different and, in some respects, opposite symptomatology compared to the γ isomer (20). It appears that quantitative differences in storage and qualitative differences in physiological action are involved in the complex differences in the toxicity of the isomers given separately; these two factors, and perhaps competition for site of action, may be involved in the interaction of the isomers given in conjunction.

There is some evidence that DDE (22) and DDD (23) reach a steady state of storage later than DDT. With the possible exception of males fed DDD at a rate of 1 ppm, rats store it at all dietary levels studied (24). The rat stores DDT in the fat at all accurately measurable or obtainable dietary levels (0.6 ppm or less) (25). Essentially the same is true for one or more species in relation to dieldrin (26) and endrin (27). On the contrary, the detectable storage of methoxychlor occurs only at dietary levels above a threshold (28, 29). Detectable storage of heptachlor epoxide requires a dietary level of heptachlor in excess of 0.3 ppm in the male rat and 0.1 ppm in the female (30). However, it may be that the apparent difference in the storage of very small doses depends more on analytical technique than upon a qualitative physiological difference.

Gannon, Link & Decker (31) reported that, at comparable dosages, more dieldrin was stored in fat and excreted in milk of cows when aldrin was fed, than when dieldrin itself was fed. The explanation for this curious finding is not apparent.

Storage in relation to dosage.—In several species, storage of DDT is less efficient at higher dosage levels (29, 32). Lehman (29) showed that, in varying degrees, the same is true of aldrin, dieldrin, endrin, and isodrin; on the contrary, lindane is stored with the same efficiency at all dosages studied, and

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methoxychlor, as already mentioned, shows a threshold and is stored only at higher dosage levels.

The apparent finding of DDT in freshwater fish (33) and various other wildlife from remote areas not thought to have been sprayed with the compound raises a question about the source of dosage. Sufficient work using analytical methods already available should establish the identity of the residues. However, determination of the source of dosage in different instances may not be so routine. Two possibilities have been suggested so far: transfer of DDT by food chain organisms and transfer of DDT by air currents.

The possibility of concentration of a chemical in the succeeding steps of a food chain is well established. A classical example concerns DDD in Clear Lake (34). It seems doubtful that the possibility of a food chain linking the apparently unexposed animal population to an obvious source of DDT has been excluded in most instances of unexplained storage of DDT.

It is common knowledge that in all spraying operations some insecticide misses the intended target. Although, as reviewed elsewhere (32), there have been numerous studies of the proportion of DDT that has been deposited on treated crops or other critical surfaces, there has been little effort to measure the proportion that escaped the treated area and its immediate vicinity. The mechanical dispersal of DDT by wind would seem to be limited, because most DDT is now used as water-wettable powder that cannot stay aloft long due to relatively large particle size. Furthermore, the vapor pressure of DDT does not seem adequate to account for the dispersal of appreciable amounts of the material to remote areas. However, Bowman et al. (35) showed that the small amount of DDT dispersed in water concentrates at interfaces and co-distills with the water. Whether this property of DDT can account quantitatively for the apparent presence of DDT in wildlife of remote areas remains to be determined.

Storage in relation to duration of dosage.—There is some evidence that, following a single large oral dose, DDT reaches a plateau in the blood within 2 hr with little increase thereafter (36). Lauger, Pulver & Montigel (37) reported that the concentration of DDT in several organs reached a maximum in 2 to 5 hr after a single large oral dose. In fact, soon after a single dose of any chlorinated hydrocarbon insecticide, its distribution is general and relatively equal. However, even after a single dose, there is a gradual redistribution leading to a higher concentration in fat than in other tissues (7, 38). This is true even when the concentration is actually lower in the lipids of adipose tissue than in the lipids of other tissues for several hours after dosage (38). The distribution in favor of fat is more marked following repeated doses than after a single dose.

At a constant daily dosage, the storage of DDT in fat increases steadily for a while, but eventually reaches a maximum or plateau in the rat (39–42), in the monkey (43), in cattle (44), and in man (22, 45). A steady state is also

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reached in the concentration of DDT in the milk of cows (46, 47) and in the eggs of chickens (48).

The time necessary for the rat to reach a steady state in the storage of DDT has been estimated at as little as 7 weeks (39, 40) and as much as 19 to 23 weeks (41, 42). The most likely value is considered to be 17 weeks (43). In the monkey, the time is unknown but it is less than 26 weeks (43). In man, the time is somewhat greater than 52 weeks (22).

Methoxychlor reaches a plateau in the fat of rats in 4 weeks (28); DDD requires more than 12 weeks in the rat (24). The α, γ, and δ isomers of BHC reach a steady state in the fat of rats after 4 to 6 weeks of feeding, but the β isomer apparently requires a longer time for equilibration (17). About half as much chlordane is stored in the fat of rats in only 5 days as after a little over 400 days (49), but there is no accurate information on the time at which a steady state is actually achieved. Heptachlor (stored as the epoxide) reaches a steady state of storage in the rat in 2 to 4 weeks (30) but reaches a steady rate of excretion in the milk of cattle in only about 12 days (50).

It has been claimed (51) that cattle and sheep achieve storage equilibrium for a wide range of insecticides in 4 to 8 weeks, although some values continued to increase through the sixteenth week of feeding. More recent work shows that a steady state is not achieved in cattle fed DDT even within 16 weeks (31). The same applies, though less definitely, to dieldrin in the milk of cows fed aldrin for 14 weeks (52). Cows fed endrin may attain a steady rate of endrin excretion in the milk in about 4 weeks (53).

It should be pointed out that there is great variation in the accuracy of the different estimates of the time necessary to reach a steady state of storage (or excretion) under any given conditions. There are few, if any, completely satisfactory measurements. Some authors found a steady state already achieved when their earliest measurements were made. Others more or less accepted the highest observed storage as being a steady state. This latter assumption can lead to two kinds of error depending on whether storage is really incomplete or whether a steady state has already been reached and the high value represents merely random variation about a somewhat lower mean, as eventually determined by really long-term study.

Finally, although achievement of a steady state of storage in response to a steady state of tolerated dosage is a general principle of pharmacology, secondary factors may modify the result in individual cases. For example, there is a suggestion in a graph presented by Laug et al. (42) that the storage of DDT in rats reaches a maximum and then falls off slightly. Although the original study was not designed to answer the question, there is a hint that the time at which the maximum is achieved depends on the age of the rat as well as on the duration of feeding and tends to occur when the rats are 21 to 27 weeks old. A much more distinct peak of storage of dieldrin, after the compound had been fed for 8 weeks, was reported by Coulson & McCarthy (54). Both results are consistent with unpublished results from the reviewer's laboratory. Particularly in the case of dieldrin, the reduction of storage in

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the face of continued intake is established, but its pharmacological basis is unknown. The phenomenon could be accounted for, in part, by the decrease in food intake which occurs when rats reach maturity at about 25 weeks of age. However, this factor is not adequate to account for the findings with dieldrin and may have little to do with the findings for DDT.

Storage in relation to age.—With the possible exception mentioned in the preceding paragraph, nothing is known about storage in relation to age that is not clearly, or at least potentially, explained by the intensity and duration of dosage. No age is immune: DDT is transferred to the fetus in dogs (55), rabbits (56), and man (57).

Storage in relation to sex.—At identical dosage levels of DDT in excess of about 0.05 mg per kg per day, the female rat, as compared with the male, stores more DDT and much more DDE (25, 58). At substantial dosage levels, the female rat stores more DDD (24), more Kelthane (59), more of each of the four common isomers of BHC (17), more chlordane (49, 60), more aldrin (61, 62), more endrin (62), more isodrin (62), and much more heptachlor epoxide (30). Female rats are reported not to store significantly more methoxychlor than males (28).

The greater storage of chlorinated hydrocarbon insecticides in the female, as compared with the male rat, is probably characteristic of most tissues and not of the fat only. This is documented by findings with DDT (63), aldrin, dieldrin, endrin, and isodrin (62).

The difference in the storage of DDT and DDE between male and female rats which had been fed DDT was reduced greatly but not reversed by hormones of the opposite sex, gonadectomy, or a combination of these treatments (58). The effect was somewhat greater on DDE storage so that the ratio of DDE to total DDT-derived material was actually reversed in hormone-treated animals, though not in those gonadectomized but not injected with hormone.

The difference in DDT storage between the sexes is small or absent in the dog (64), the hog (65), and the monkey (43).

Storage in relation to species.—The storage of DDT in man was first reported in 1948 by Howell (66). Storage in the general population of the United States was first studied in 1950 (67), and there has apparently been no progression in this storage since that time (22, 45, 68–71). Storage of DDT is lowest in primitive people whose food contains little DDT (72). In the United States generally, DDT storage is lowest in people who eat little or no meat and highest in those with the greatest occupational exposure (45). DDT storage in the general population of Hungary (58) is of the same magnitude as that in the United States. DDT storage in the people of Canada (73), England (74), France (75), and West Germany (76, 77) is somewhat lower than in the United States.

Dieldrin (68, 69, 71, 74), BHC (38, 69), and heptachlor epoxide (71) have been measured in the fat of the general population of one or more countries.

DDD (78), dieldrin [from both aldrin (79, 80) and dieldrin (81)], lindane

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(82), *p*-dichlorobenzene (83), trichloroethylene (84), methyl bromide (14), and carbon tetrachloride (85) have been recovered from various tissues of highly exposed individuals.

Storage of DDT has been reported in every species studied. Although there is some species difference in the storage of DDT at equivalent dosages (32), it is apparently much less than the species difference in the storage of dieldrin (26).

Storage in relation to tissue.—As already mentioned, all the compounds under discussion tend to be stored more extensively in adipose tissue than in other tissues. There is some indication that the occurrence of DDT (86, 87) and dieldrin (26) in other tissues is determined by their lipid content and especially by their neutral fat content. The high DDT content of yellow bone marrow (44) is almost certainly explained by the high fat content of the tissue. The rather high levels of DDT reported for the adrenal (37, 88) and the ovary (89) may reflect a high fat content of these organs. DDD is also extensively stored in the adrenal (24). One report (11) indicates that toxaphene or a derivative may be stored preferentially in the brain; the organic chloride content of acetone (but not ether) extracts of the brain was 20 times or more greater than that of controls. However, the distribution of DDT in the viscera before and after starvation suggests that the fat content of the tissue is not the only factor determining the relative concentration of DDT (63).

No difference was found in the concentration of DDT stored in the fat of different portions of the human body (45). On the other hand, slightly more endrin was found in fat from the body cavities of lambs than in fat from the outer surface of the same animals (90).

Although there is a recognized relationship between body fatness and susceptibility to chlorinated hydrocarbon insecticides (32), there is little or no quantitative information about the relationship between nutrition and the storage of these compouuds. An interesting exception is the finding by Gannon, Link & Decker (91) that, at equivalent dosages, dieldrin is secreted in the milk at a generally lower rate by fat cows than by thin ones. This difference presumably reflects more complete storage in the fat cows because there is no reason to suppose that their excretion of the compound was inherently less efficient by all routes.

Effect of liver injury on storage.—There is no evidence that liver injury predisposes to increased storage of most chlorinated hydrocarbon insecticides; but Laug & Kunze (92) showed that rats fed methoxychlor stored 10 to 100 times as much of the material in their fat and liver and suffered greater toxicity if given carbon tetrachloride concurrently, than did rats that got no carbon tetrachloride (92). Liver injury does not facilitate the storage of DDT in rats (3).

Storage in relation to toxicity.—The severity of poisoning in rats after a single dose of DDT is directly proportional to the concentration of the compound in their brains. The concentrations associated with death after one

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large dose are about the same as those associated with death after many smaller doses (38). A similar relationship was found for DDT in birds (93), although the concentrations associated with illness or death were slightly different in the different species. Rats dying from acute poisoning had DDT concentrations of 35 to 52 ppm in their brains (38). Rats dying of starvation, begun after the animals had eaten DDT for 3 months at an ordinarily harmless level, showed concentrations of 13 to 63 ppm (63). Rats dying as the result of nine relatively high doses of DDT had concentrations of 26 to 88 ppm in their brains (94). (These three ranges, based on the original data of the papers cited, are for tissue wet weight, thus to permit comparison with the values given below for birds.) Robins showing tremors had DDT concentrations greater than 50 ppm in their brains; and only 5 of 62 robins thought to have been killed by DDT had smaller concentrations, the majority falling in the range 50 to 120 ppm (93). The range for the majority of dead sparrows was 65 to 140 ppm (93).

Indirect evidence (7) indicates that the toxicity of dieldrin to rats is also related directly to the concentration of the compound present in the brain. No such relation of concentration of storage to toxicity was evident from the only relevant study made of DDT in fish (95).

Residues in food.—The storage of insecticides in the fat and meat of farm animals constitutes an important practical problem. Reviews of the subject (96–101) are available.

BIOTRANSFORMATION

Identity of metabolites.—Chlorinated hydrocarbon insecticide metabolites that have been identified are listed in Table I. No attempt has been made to separate the metabolites according to the degree of certainty of their identification. As shown in the table, several metabolites have been detected in insects but not in mammals. If confirmed, the degradation of DDT to CO_2 by roaches (102) represents the most radical *in vivo* change of a residual hydrocarbon insecticide yet reported. However, even the fully confirmed biotransformations of chlorinated hydrocarbon insecticides accomplished by mammals are remarkable in view of the chemical stability of the compounds.

Many metabolites of chlorinated hydrocarbon insecticides have not been identified although they have been recognized clearly, for example, by solubility or chromatographic properties. Even when a new metabolite is identified, further study is usually required to determine whether one of the previously unidentified metabolites of the compound is or is not the same. Thus, there is a continuing interest and challenge in such metabolism studies.

White & Sweeney (103), who first identified DDA from rabbit urine, concluded on the basis of solubility that 15 to 20 percent of the DDT-derived material in the urine was neither DDT nor DDA. Positive evidence for the presence of one or more unidentified derivatives in urine was given by Ofner, Woodard & Calvery (104), Ofner & Calvery (105), and Neal et al. (106). Stohlman (107) demonstrated, in the urine of rabbits fed DDT, the presence

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of a neutral ether-soluble fraction in addition to the alkaline-water-soluble fraction (DDA) in the residue of acid ether extracts; he concluded on the basis of melting point, mixed melting point, and elementary analysis that the ether-soluble material was unchanged DDT. Smith (108) found evidence for the presence of DDT as well as DDA in human urine. Winteringham et al. (109) found that 35 percent of the radioactive material in the urine of a man who had ingested radioactive DBrDT behaved like the original compound. Even though the occurrence of any unchanged DDT in the urine of rabbits (104, 105, 110), rats (4), dogs (55), and man (106, 111, 112) has been denied, it would be advisable that the occurrence of DDT be re-evaluated at the same time that an effort is made to study the DDT-derived compound or compounds in urine for which the exact chemical identity remains unknown.

The identification of DDA in the feces of animals exposed to DDT was first reported by Judah (4) and was confirmed in connection with the bromine analog of DDT by Winteringham et al. (109). Jensen et al. (113) presented evidence that free DDA does not occur in the feces of rats dosed with DDT by different routes, but that at least five separate acidic metabolites are present in the ether-extractable portion. The metabolites are regarded as complexes or conjugates because they can be converted almost quantitatively by acid hydrolysis to material similar or identical to DDA. That the compounds are not esters is indicated by the very small effect of refluxing them for 6 hr with 10 percent sodium hydroxide. Jensen et al. (113) showed that most of the radioactive, ether-soluble material in the feces could be measured by the Schechter-Haller method if the nitration step is modified. However, it may be significant that the data presented in Table X of their paper show that a decreasing proportion of the metabolites in ether extracts was measured by the Schechter-Haller method as compared with radioassay of succeeding daily samples from a rat given a single intravenous injection of DDT. Furthermore, the concentration of water-soluble metabolites in the bile increased, especially between the third and fourth day, and may have been somewhat more sustained than the concentration of ether-soluble metabolites (113). Thus, there is a possibility that the proportion of different metabolites in the feces changes with time after a single dose. The DDT-derived material in the feces of rats dosed intravenously included 20 to 30 percent that was not extractable with acetone. This fraction was largely soluble in alkaline water but responded only very feebly to the Schechter-Haller method (113). Only a small amount of DDE and unchanged DDT was contributed by the bile to the feces.

Of DDT-derived, ether-soluble material in the bile, DDT constituted about 3 percent; DDE, 1 percent; free DDA, 25 to 35 percent; and the remainder consisted of complexes of DDA or closely related material. However, 17 percent of the metabolic products present in rat bile were not extractable by ether (113). Judah (4) found that the greater part of the DDT-derived material in the feces of rats was unaltered DDT even though the

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compound had been given intravenously. This result is entirely inconsistent with more recent findings, but cannot be disregarded completely.

According to the older literature, the major components of technical chlordane (heptachlor, trichloro 237, and α- and β-chlordane) are all stored in the fat of rats, rabbits, and dogs in the form of a metabolite that appears to be the same for the four compounds and for technical chlordane and also the same for the three species. This conclusion should be reinvestigated. Trichloro 237 and heptachlor (at higher dosage levels) were stored in fat as the original compound in addition to being stored as the metabolite. Heptachlor was found in the liver only as the metabolite (114), later identified as heptachlor epoxide (115).

Aldrin is converted largely or entirely to its epoxide, dieldrin (116–120). The conversion occurs rapidly and is independent of route of absorption (118). Dieldrin, whether converted from aldrin (118) or absorbed directly (26, 91, 118), is stored unchanged.

In man, dieldrin is eliminated in the urine in the form of at least two unidentified, neutral polar chlorinated metabolites; and microcoulometric gas chromatography gave evidence for the occurrence of at least five metabolites (121).

In rats treated with dieldrin, the urine contains at least three metabolites in addition to a compound indistinguishable from dieldrin. About half of the aqueous residue is in the form of chloride ion (7).

In 1963, Mörsdorf et al. (120) reported that both dieldrin and aldrin, which is converted to dieldrin, are metabolized to an identical hydrophilic metabolite which is found in relatively high concentration in the liver and is excreted in the bile. Using radioactive dieldrin, Heath & Vandekar (7) found that 78 percent of ^{36}Cl in the bile was a single compound, probably a glucuronide of a compound they designated "metabolite I". They also found a trace of dieldrin and evidence of several other metabolites. In the feces, about 65 percent of the ^{36}Cl was present as metabolite I; 6 percent was apparently another neutral but more polar compound; 12 percent was an acidic compound; about 3 percent was dieldrin; and the remaining 14 percent consisted of metabolites too polar to extract from aqueous acid with water. No chloride ions derived from dieldrin were present.

Metabolite I was characterized as neutral, somewhat more polar than dieldrin but, like dieldrin, quantitatively extractable from water by hydrocarbon solvents (7).

Using radioactively tagged α and γ isomers of BHC, Koransky et al. (122) found that about 60 percent of the ^{36}Cl-labeled compounds excreted in the urine were inorganic and 40 percent were organic. Activation of the microsomal oxidizing enzymes of the liver by phenobarbital produced a marked increase in the rate of elimination of BHC. The overall increase in excretion was accompanied by a marked increase in the excretion of inorganic metabolites and a decrease in organic metabolites. On the other

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hand, a single 200 mg per kg dose of α-BHC, injected intraperitoneally in oil, accelerated the oxidation of hexobarbital by microsome preparations *in vitro* over a period of 4 weeks and reduced the narcotic effects of several barbiturates *in vivo* (122). DDT (123), chlordane (123, 124, 125), and endrin (123) also stimulate hepatic microsomal enzymes and shorten barbiturate sleeping time; aldrin, dieldrin, heptachlor, and heptachlor epoxide shorten sleeping time (125) undoubtedly through stimulation of the enzymes.

Although DDE and DDA are less toxic than DDT, it is not necessary that metabolic changes render a compound less toxic. The immediate toxicity of heptachlor epoxide is somewhat greater than that of heptachlor (30). This relation, of course, indicates that the epoxide is better tolerated during its relatively slow release from heptachlor than when given preformed as a single dose, or that only a fraction of absorbed heptachlor is metabolized to the epoxide.

In general, the biotransformation of the fumigants and other older compounds has been studied more thoroughly than that of the newer chlorinated hydrocarbon insecticides. Radioactive carbon tetrachloride inhaled by monkeys was metabolized to carbon dioxide that was recovered in the expired air (20 percent of total intake) and also as urinary urea and carbonate, but the chief metabolic product in the urine was an unidentified nonvolatile material that appeared to be a conjugate (126).

The decomposition of methyl bromide in mammalian tissues appears established (127, 128) although the decomposition may not be enzymatic as was supposed earlier (129). However, the toxicity of methyl chloride is essentially similar (13); and, as with methyl chloride (130), no methanol or mere traces of it can be detected in the blood of animals poisoned by methyl bromide (13, 131). It, therefore, appears that it is methyl bromide, rather than its derivatives, which is the toxicant (1).

The metabolic products of the three isomers of dichlorobenzene differ qualitatively (see Table I), quantitatively, or both in the rabbit (132); and the same isomer is excreted in different ways in different species. The implications of this fact for the toxicology of compounds in general, as well as dichlorobenzene, in particular, are evident.

Trichloroethylene is metabolized to trichloroethanol and trichloroacetic acid by the rabbit (133) and man (16). The sum of the two metabolites excreted per gram of trichloroethylene is about the same, and both excrete more trichloroethanol. However, the factor of difference is 1.7 in man and 120 in the rabbit.

Chemical nature of biotransformations.—Some identified metabolites of chlorinated hydrocarbon insecticides are not formed as one would expect. For example, when DDA was discovered, it was postulated on chemical grounds that DDE was a step in its formation (103). However, even rats, which produce both DDE and DDA from DDT, are incapable of forming DDA when fed preformed DDE (134). Monkeys excrete DDA when fed DDT, although they produce little or no DDE (43).

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That portion of the metabolism of DDT which leads to DDA has been elucidated beautifully by Peterson & Robison (134) who gave evidence for the following sequence: DDT → DDD → DDMU → hypothetical aldehyde → DDA.

The reactions that have been implicated in the biotransformation of chlorinated hydrocarbon insecticides are as described in the following. Dehydrochlorination is involved in the transformation of DDT to DDE (134, 135) and of lindane to pentachlorocyclohexene (136). Reductive dechlorination is involved in the formation of DDD from DDT by yeast (137) and rats (134). Incidentally, both yeast and rats fail to form DDD from DDE (134, 137). Hydrogenation is involved in the formation of DDMS from DDMU (134). Reductive hydroxylation converts DDNU to DDOH (134). Oxidation is exemplified by the conversion of DDOH to DDA (presumably with an intermediate aldehyde step) (134) and of *p*-dichlorobenzene to 2,5-dichloroquinol (138). Epoxidation is involved in the transformation of aldrin to dieldrin (118) and of heptachlor to its epoxide (115). Oxidative hydroxylation is exemplified by the formation of various phenols and catechols from the isomers of dichlorobenzene (see Table I). Both dechlorination and oxidation are involved in the breakdown of carbon tetrachloride to carbonate and carbon dioxide. The fact that urea is formed also indicates that the other two metabolites become part of the general metabolic pool.

Conjugates.—DDT and some other residual insecticides are converted to metabolites that are conjugated, but the character of most of the complexes remains to be demonstrated. DDT and DDD do not form mercapturic acids (as does dichlorobenzene) (139), nor is the DDT-derived material in bile conjugated with glucuronic or sulfuric acids (113).

In vitro studies.—Several insecticides are known to be degraded by mammalian tissue *in vitro*. DDT is broken down by the liver (4, 40), diaphragm, kidney, and brain (4) to form DDA. Lindane is degraded by the rat liver but not by intestinal contents (140). An enzyme that promotes the conversion of DDT to DDE has been demonstrated in insects (141, 142) but not in mammals.

Biotransformation in relation to species or strain.—It is a common observation that species vary in the way they metabolize drugs. Indeed, it seems possible that, if they were to be examined in sufficient detail, no two species would be found identical both quantitatively and qualitatively in their metabolism of a single drug. In any event, a number of species differences in metabolism are mentioned in this review.

There is considerable species variation in the metabolism of DDT. People in the general population of the United States store about 60 percent of DDT-derived material in the form of DDE (45). At about the same storage level, male rats store only about 22 percent as DDE, and females store only 29 percent (25). Monkeys convert little or no DDT to DDE although they are capable of storing DDE if it is fed preformed (43).

It is interesting to note that it is possible to develop resistance to DDT in

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mice through selection (143). It would be instructive to study the metabolic basis of this strain difference.

Excretion and Storage Loss

The elimination of unabsorbed pesticide is a protection from poisoning, and this elimination must be measured in any balance study. True excretion (elimination of previously absorbed material) of chlorinated hydrocarbon insecticides may occur by way of expired air, urine, feces, milk, dermal secretions (144), eggs, and even the fetus (55, 56, 57).

Respiratory excretion.—Respiratory excretion may be important in connection with certain fumigants. McCollister et al. (126) found that, although monkeys eliminated 20 percent of absorbed radioactive carbon tetrachloride by exhalation during the first 18 hr following the end of exposure, ^{14}C continued to be measurable in samples of expired air for a period of 4 weeks. Material derived from carbon tetrachloride was found in the urine and feces also. Recent developments in gas liquid chromatography make it practical to measure fumigants and other solvents in the respired air of people for surprisingly long periods after occupational or accidental exposure.

Fecal, biliary, and urinary excretion.—For a wide range of compounds, urinary excretion has been studied more thoroughly than fecal excretion, yet fecal excretion is more important for certain compounds. True fecal excretion of DDT-derived material has been established (4, 145), and studies in this laboratory show that in the rat fecal excretion of DDT exceeds urinary excretion irrespective of the route of administration. The same is true of Perthane (146), methoxychlor (147), aldrin (148, 149), dieldrin (7, 148), and endrin (148). In fact, 90 percent of excretion of dieldrin-derived material is via the feces (7). It may be that most residual chlorinated hydrocarbon insecticides are excreted chiefly in the feces.

The fact of biliary excretion is proved for DDT (113, 150), Perthane (146), methoxychlor (147), aldrin (120), and dieldrin (7, 120). The rate of biliary excretion may be considerable. Thus, Weikel (147) recovered from rats as much as 40 percent of an intravenous dose of methoxychlor in 6 hr. The excretion reached a peak at about 30 min and then decreased rapidly for several hours; a slower excretion followed, and some activity still was present in the bile 48 hr after administration.

Burns, Dahm & Lindquist (151) found that there is an increase in urinary excretion of radioactive material following ligation of the bile duct in rats fed radioactive DDT. Because the chief metabolite of DDT in the urine is DDA, the result is indirect evidence that some of the material ordinarily excreted in the bile is related to DDA. Unfortunately, the authors did not identify the DDT-derived material in the urine.

The existence of an enterohepatic circulation of the metabolites of thes compounds appears certain. Bleiberg & Larson (146) collected bile from tw rats given radioactive Perthane intravenously and in an 8 hr period recover

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25 and 55 percent respectively of the ^{14}C. When the bile samples were combined and given orally to a third rat, about 70 percent of ^{14}C appeared in the feces and 13 percent in the urine over a 3-day period. This experiment also serves to illustrate the relatively rapid excretion of the metabolites as compared with the parent compound. Enterohepatic circulation of dieldrin itself was demonstrated by Heath & Vandekar (7) who found that the proportion of dieldrin excreted unchanged could be increased from 3 percent of the total excretion to 10 percent by cannulation of the bile duct.

The bile appears to be the principal source of DDT metabolites in the feces. In a rat in which the bile duct was cannulated before intravenous injection of radioactive DDT, 65 percent of the dose was recovered in the bile, 2 percent in the urine, and only 0.3 percent in the feces (113); and the possibility of some contamination of the feces by the urine could not be excluded.

The fact of biliary excretion of a metabolite suggests but does not prove that the liver is an important site for its production. In the case of aldrin and dieldrin, further evidence along this line is the high concentration of the parent compound and especially its hydrophilic metabolite in the liver (120).

A higher proportion of some other chlorinated hydrocarbon insecticides is excreted in the urine than is true for DDT. Thus, Stohlman, Thorpe & Smith (152) recovered from the urine of rabbits about 18 percent of the chlordane that the animals had received. Approximately 80 percent of radioactivity derived from both α- and γ-BHC was found in the urine and only about 20 percent in the feces (122).

Trichloroethylene is expired from the lungs for 2 days after exposure, and traces may be present on the third day. About 8 percent of the retained material is excreted as metabolites in the feces, but most is excreted in the urine (16). Suček & Vlachová (15) found that an average of 73 percent of the trichloroethylene retained by men and women after inhalation could be recovered in the urine as follows: monochloroacetic acid, 4 percent; trichloroacetic acid, 19 percent; and trichloroethanol, 50 percent. The excretion of metabolites of trichloroethylene could be increased by approximately 22 percent by giving glucose and insulin (15). The excretion of trichloroacetic acid drops almost to zero in animals given disulfiram (Antabuse) (153). In people treated with the same drug, urinary excretion of trichloroethanol was decreased 40 to 64 percent, and trichloroacetic acid 72 to 87 percent; there was a corresponding increase in the respiratory excretion of the unchanged trichloroethylene (154). The use of disulfiram offers some promise in the treatment of poisoning by trichloroethylene because trichloroethanol is more toxic than the parent compound (154).

The excretion of trichloroacetic acid in man is said to show a periodicity, reaching a maximum at 1300 hr (1:00 p.m.) each day. The other two metabolites show no such periodicity (15), and even the periodicity of trichloroacetic acid is denied by some (155). In man, excretion of the metabolites of trichloroethylene is fastest for monochloroacetic acid, intermediate

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for trichloroethanol, and slowest for trichloroacetic acid (15). Following the use of trichloroethylene as an anaesthetic, trichloroacetic acid may be detected in the urine for 5 to 12 days (155). Following accidental ingestion of trichloroethylene, trichloroacetic acid was found in the serum and urine for 27 days (156).

As with some other fumigants, the excretion of metabolites of the dichlorobenzenes is regarded as "slow" because excretion is still incomplete after 6 days (138). But the description is only relative. Following repeated high doses of DDT, urinary excretion may continue in man for more than 3 years after the last dose (3).

Excretion in milk.—The rate of excretion in the milk is proportional to dosage for DDT (31, 157), dieldrin (31, 91), aldrin, heptachlor, methoxychlor (31, 158), heptachlor epoxide (159, 160), and endrin (161). In fact, the slopes of the lines which relate concentration in milk to concentration in feed have been represented as identical for most of these compounds (31), although the data suggest that relatively less DDT is excreted in the milk at higher dosage levels.

The rate of excretion of bromide is also proportional to dosage regardless of the source. Cows generally secrete bromides in their milk in a concentration of 1 to 5 ppm, but may secrete somewhat more in areas such as tidewater Virginia where there is a relatively high natural concentration of bromides in the soil (162). Any addition of bromides to the diet, either in the form of inorganic bromide or bromide residues resulting from the fumigation of grain, produces increased concentrations of bromide in the blood and milk (163). When sodium bromide was fed, 18 percent of the dose was recovered from the milk; but, when residues from fumigation with methyl bromide were fed, 38 percent of the dose was secreted in the milk. Furthermore, there was a small but detectable difference in the relationship between the concentration of bromide in the blood and in the milk depending on the original source of bromide (163). The first difference could depend on incomplete analytical recovery of bromide from hay, but the second difference is more difficult to explain. Thus, although it is generally assumed that the bromide residues resulting from fumigation are inorganic (163, 164), there is some evidence that they are partly organic and are metabolized differently from inorganic bromide. In any event, when the dietary concentration of bromide was held constant, the concentration of bromide in the milk reached a steady state in 20 to 30 days (163).

It has been indicated by several authors (46, 47, 165) that 10 percent or more of DDT derived from residues on forage is excreted subsequently in the milk. On some days certain cows secreted up to 32.5 percent of their daily DDT intake in their milk (46). However, these results must be viewed with caution, for they depend not only on analysis of DDT in milk, but also on analysis of DDT residues in hay. Any systematic failure to detect all of the residue in the hay would lead to an overestimate of the proportion of the dose

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recovered in the milk. It may be significant that Ely et al. (166, 167, 168) were able to recover in the milk of cows only 1.8 to 7.0 percent of the DDT administered as an oil solution.

Huber & Bishop (160) reported that cows fed heptachlor and heptachlor epoxide residues on hay secreted 20 to 29 percent in their milk in the form of heptachlor epoxide. Again, much depends on the accuracy of the analysis of the residues in hay. Incidentally, the residues in the hay presumably resulted from translocation, because heptachlor was applied to the soil very early in the season and not to the maturing crop. Methoxychlor appears in the milk of cows following large doses (31, 158); but, according to Biddulph et al. (169), the compound cannot be detected in the milk, blood, fat, kidney, liver, or muscle, under practical conditions of forage treatment with methoxychlor. Direct treatment of cows with methoxychlor leads to an increase of the compound in the milk, but an undetermined proportion of it may reach the milk by extraneous contamination rather than secretion (170). Incidentally, a comparison of ratios of concentrations of insecticides in fat to concentrations in milk is meaningless unless it is made under standardized conditions—preferably a steady state of intake and storage.

Cows fed heptachlor reached a steady state of secretion of heptachlor epoxide in the milk in only 10 days (160). Cows fed on high doses of dieldrin continued to excrete the compound in their milk for more than 47 days after dosage was stopped (171). The concentration of heptachlor epoxide returned to pretreatment levels in 15 to 45 days depending on the intensity of treatment (160). Lindane required less than 20 days to reach very low levels (172).

Relation of excretion to storage and storage loss.—Undoubtedly, excretion accounts for the fact that equilibrium of storage is reached and that stores are reduced when dosage is discontinued. However, our knowledge of excretion is adequate to account quantitatively for known equilibrium values or known rates of storage loss in only a few instances. A notable exception is dieldrin (149). Of course, high storage is generally correlated with slow excretion as in the β isomer of BHC as compared with the α, γ, and δ isomers (17, 173). Thus, when excretion is relatively inefficient, storage tends to be high and storage loss slow.

Some of the earliest studies of chlorinated residual insecticides indicated that the rate of storage loss is not constant after dosage is discontinued. In 1949, Kunze et al. (41) reported that following small doses of DDT about half remained in storage a month after dosage was discontinued and a quarter after 3 months. Male rats, which had stored chlordane in their fat at a concentration of about 40 ppm, reduced the store by about a quarter in only 5 days and by about a half in 20 days (49). If these values for storage of DDT and chlordane are plotted on semilog paper, they do not fit straight lines but instead they yield curves that fall more rapidly at first and then more gradually. Similar curves were published by Gannon & Decker (174) in connection with the concentration of dieldrin in milk following reduction or ter-

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mination of dosage. We have found similar curves for the storage of DDT and the excretion of DDA in man after dosage is stopped (3). Although Ware & Gilmore (172) showed that a plot of the log of lindane concentration in milk against time following spraying of the cows fell reasonably well on a straight line, the values actually fall even more closely on a curve such as those under discussion.

Greater efficiency of excretion at higher storage levels accounts, at least in part, for the observed fact (29, 32) that relatively less DDT is stored at high dosage levels than at low dosage levels. In a similar way, the greater efficiency of male rats in excreting DDT-derived material accounts, at least in part, for the lesser storage of DDT and DDE in males as compared to females of that species.

Although the term "half-life" is frequently used in connection with storage loss, the term "percent per day" is preferable for both storage loss and excretion. The latter term is far more appropriate for describing changes in rates produced by starvation or some other temporary factor. Furthermore, as just pointed out, the rate of loss of some chlorinated residual insecticides decreases as the storage decreases. The term half-life is completely valid only insofar as storage loss follows a straight line when the log of storage is plotted against time after dosage. As an example of the rapid change that may occur, Heath & Vandekar (7) found that about 5 percent of the dose of dieldrin was excreted in the bile daily following a single intravenous infusion of tagged material, but the rate increased to more than 10 percent per day in rats that had been starved a few days.

Storage loss.—Storage loss of the residual chlorinated insecticides is intermediate in speed between that of most drugs and that of lead and other bone seekers. Storage loss may be slow even for the fumigants. Thus, Spain & Frey (85) report the recovery of carbon tetrachloride-derived material from postmortem tissues of people dying as much as 17 days after exposure to the chemical.

Discussion

Investigators have given somewhat more attention to the identity of metabolites than to the quantitative aspects of the metabolism of foreign chemicals. When measurements are made, they often involve only one tissue or only one route of excretion. Even when a balance study is attempted, it is frequently impossible to account for all of the dosage. The record is particularly poor for long-term studies; but, as already pointed out, it is these studies that are of greatest interest in connection with residual insecticides. The use of radioisotopes or chromatography may make it easier to complete a balance study successsfully and may simultaneously make it possible to recognize metabolites. However, the use of these methods merely to demonstrate the existence of previously unrecognized metabolites is not a substitute for a balance study. The factor unaccounted for qualitatively or quantitatively may be the biologically significant one.

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In conclusion, knowledge of the metabolism of DDT is incomplete, and knowledge of the metabolism of other residual chlorinated hydrocarbon insecticides is fragmentary in comparison. The economic importance, public health applications, and broad biological significance of this class of chemicals demand continuing study of their distribution and fate in the animal organism.

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