Table III. Distribution of Major Radioactive Compounds in 80% Ethyl Alcohol Extract of Bean Leaves

(After treatment with 50 γ of carbonyl-C^{14}–labeled CMU. Plants harvested after varying intervals)

Harvested, Days after Treatment	R_f 0.62–0.66, CMU Complex, %	R_f 0.84–0.87, Free CMU, %
1 hour	0	100
1	5	93
2	11	87
4	13	85
8	19	80
12	19	81

might result in a similar degradation. However, only two compounds containing carbon-14 in the acid hydrolyzate were revealed by the paper chromatographic technique when aqueous phenol or 1-butanol, propionic acid, and water were used as solvents. Therefore, it is believed that the cleavage of CMU-complex linkage must take place first during the hydrolysis, and subsequently the free carbonyl-C^{14}-CMU breakdown to form nonradioactive *p*-chloroaniline, dimethylamine, and radioactive carbon dioxide, which are not detected by paper chromatography. At the later stages of this experiment, the increase in concentration of CMU complex was small, indicating a general reduction and destruction of the metabolic activity. In a study with radioactive 2,4-D, Jaworski and Butts demonstrated that approximately 60% of carbon-14 was in the form of the 2,4-D complex 4 days after treatment (*2*). In the study with CMU, less than 20% of radioactive CMU has undergone a biochemical reaction. These results reveal the difference in rate of reaction between plant substrates and an exogenous chemical.

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PESTICIDE TOXICITY

Toxicity of Certain Chlorinated Hydrocarbon Insecticides for Laboratory Animals, with Special Reference to Aldrin and Dieldrin

JOSEPH F. TREON and FRANK P. CLEVELAND

Kettering Laboratory, Department of Preventive Medicine and Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio

The immediate toxicity of four polychlorinated dimethanonaphthalenes—aldrin, isodrin, dieldrin, and endrin—compared on the basis of oral administration to rats or rabbits or as applied and maintained upon the skin of rabbits, depends more directly upon their spatial configuration than their empirical composition. Repetitive applications of aldrin, dieldrin, or DDT upon the skin of rabbits exerted toxic effects decreasingly, according to the use or type of a vehicle, in the following order: in Ultrasene, in a vegetable oil (aldrin and DDT in olive oil and dieldrin in peanut oil), and as dry powders (no vehicle). When fed for 2 years to rats of either sex at levels of 2.5, 12.5, or 25.0 p.p.m., aldrin, dieldrin, and DDT do not appear to shorten the lives of the animals, the rate of mortality among the test groups being comparable statistically to that in corresponding control groups. The rates of growth of the test groups were equal to or in excess of that of the controls. The weights of the livers of the test rats, in relation to their body weights, were somewhat on the high side. Dogs are more susceptible than rats to the toxic effects of aldrin or dieldrin. In prolonged periods of feeding on diets containing aldrin or dieldrin at 1 or 3 p.p.m., dogs of either sex do not appear to be affected adversely. In the reproduction of rats, the feeding of a diet containing dieldrin in the concentration of 2.5 p.p.m. reduced the number of pregnancies, but had no effect upon the number of offspring per delivery and only a slight effect on the mortality of the suckling rats. At this level, aldrin had little or no effect.

THE IMMEDIATE TOXICITY of four polychlorinated dimethanonaphthalenes (aldrin, isodrin, dieldrin, and endrin), when given orally to rats or rabbits, is more closely related to the spatial configuration than to the empirical composition. Aldrin and isodrin have the same empirical composition and so do their respective epoxides, dieldrin and endrin, but in spatial configuration aldrin and dieldrin, and isodrin and endrin, form closely related pairs (Figure 1).

Aldrin (Compound 118 or Octalene) is the coined name for the insecticidal product containing not less than 95% of 1,2,3,-4,10,10 - hexachloro - 1,4,4a,5,8,8a - hexahydro - 1,4 - *endo,exo* - 5,8 - dimethanonaphthalene (commonly referred to as HHDN) and not more than 5% of related compounds.

Isodrin (Compound 711) is the coined name for 1,2,3,4,10,10-hexachloro-1,4,4a,-5,8,8a - hexahydro - 1,4 - *endo,endo* - 5,8-dimethanonaphthalene.

Dieldrin (Compound 497 or Octalox) is the coined name for the insecticidal product containing not less than 85% of 1,2,3,-

4,10,10 - hexachloro - *exo* - 6,7 - epoxy-1,4,4a,5,6,7,8,8a - octahydro - 1,4 - *endo*,-*exo*-5,8-dimethanonaphthalene (commonly referred to as HEOD) and not more than 15% of related products.

Endrin (Compound 269) is the coined name for 1,2,3,4,10,10-hexachloro-*exo*-6,7-epoxy - 1,4,4a,5,6,7,8,8a-octahydro - 1,4-*endo*,*endo*-5,8-dimethanonaphthalene.

Values reported herein for aldrin and dieldrin are in terms of HHDN and HEOD, respectively.

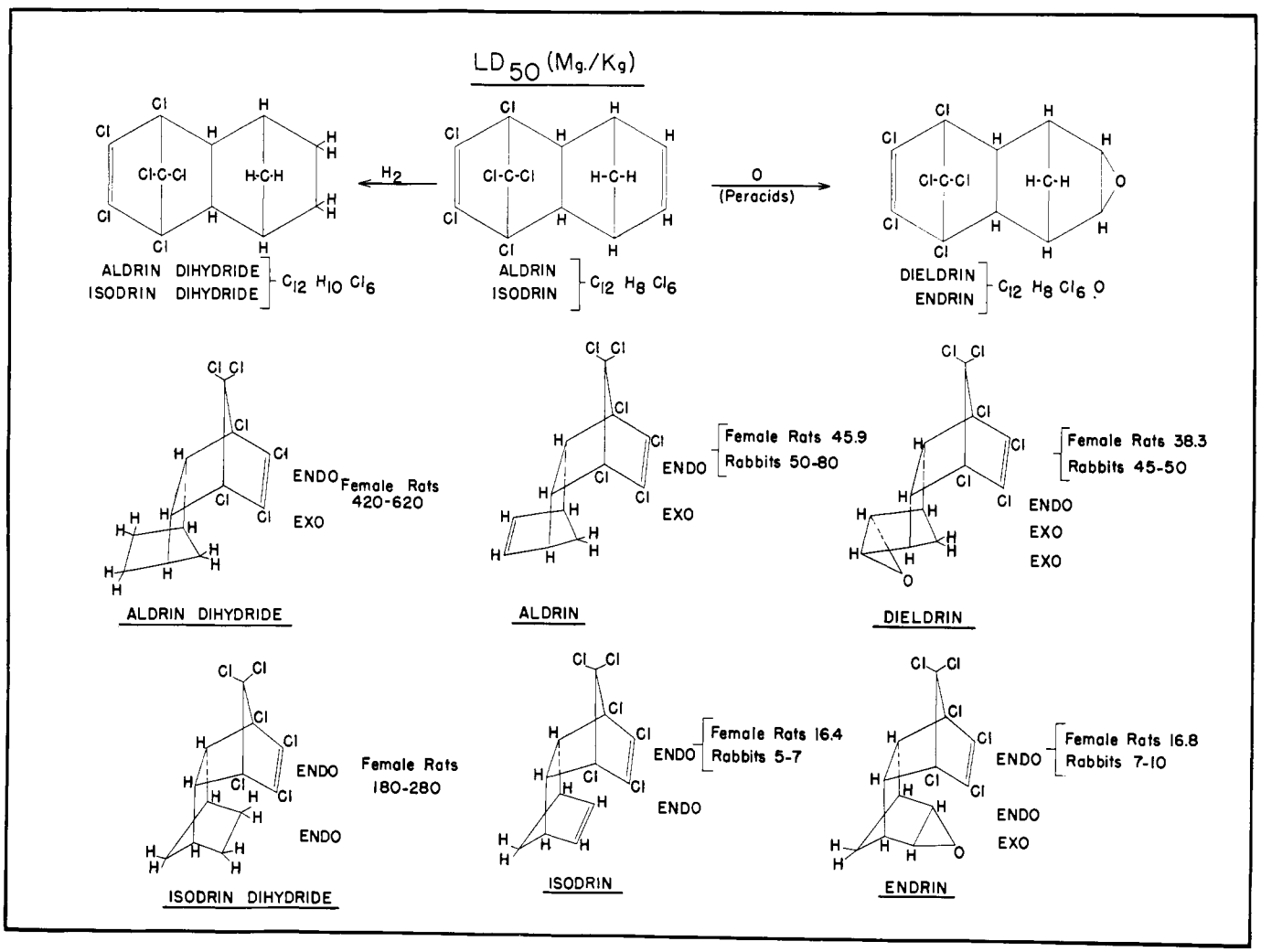
In aldrin and its epoxide, dieldrin, the upper six-membered ring is attached to the lower six-membered ring by replacing the *endo* hydrogens of the upper ring—that is, those hydrogens away from the bridge of the upper ring—whereas the lower six-membered ring is attached to the upper six-membered ring by replacing the *exo* hydrogens of the lower ring—i.e., those hydrogens of the lower ring which are on the same side of the lower ring as its methylene bridge. The *epo* oxygen of dieldrin is *exo* to this latter bridge. The lethal dosages (LD_{50}) of aldrin and dieldrin, as determined by the method of Bliss (*2*), for young female Carworth rats, each given a single oral dose of one of these compounds as a solution in peanut oil, are 45.9 and 38.3 mg. per kg. of body weight, respectively (Table I). The toxicity of the compounds with the *endo-endo* configuration, isodrin and endrin, when determined and expressed correspondingly, is considerably greater, the lethal dosages being 16.4 and 16.8 mg. per kg. (Table I).

Female rabbits (1.9 to 2.5 kg.) were also more susceptible to isodrin and endrin than to aldrin and dieldrin, the approximate LD_{50}'s being: isodrin, between 5 and 7 mg. per kg.; endrin, between 7 and 10 mg. per kg.; aldrin, between 50 and 80 mg. per kg.; and dieldrin between 45 and 50 mg. per kg. The data on rabbits given aldrin and dieldrin were obtained by Borgmann (*3*), who also assisted in the work on the withdrawal of food.

The epoxide of aldrin or isodrin was found to have approximately the same toxicity as the parent chlorinated hydrocarbon. On the other hand, aldrin dihydride and isodrin dihydride, formed by the reduction of the double bond between chlorine-free carbons by hydrogen, were about $^1/_{10}$ to $^1/_{15}$ times as toxic as the parent substances, the approximate lethal dosages (LD_{50}) for rats falling between 420 and 620 mg. per kg. and 180 and 280 mg. per kg., respectively. A similar diminution in toxicity (for rabbits) had been found to attend the saturation of methyl and ethyl acrylate to the propionates.

Effect of Process of Manufacture. Aldrin has been prepared by two different procedures, one involving a "thermal" process, the other designated as the "Straus" process. The aldrin resulting from the Straus process, now obsolete, was several times more toxic than that obtained by the thermal process. When aldrin was given to young female Carworth rats as a 1 or 4% solution in Ultrasene, the LD_{50} in terms of aldrin, as determined by the method of Bliss, was 74.9 and 25.0 mg. per kg. for the thermal and Straus materials, respectively (Table II). The relatively high toxicity of the Straus product was attributed to the presence of impurities of greater toxicity than that of aldrin. Ball, Kay, and Sinclair (*1*) have found also that aldrin prepared by the Straus method is more toxic than that prepared by the thermal method.

Figure 1. Relationship between toxicity and spatial configuration of four polychlorinated dimethanonaphthalenes and certain derivatives



Effect of Solvent. Either recrystallized aldrin or technical crystalline thermal aldrin when given by mouth as a solution in Ultrasene to young female Carworth rats was less toxic than recrystallized aldrin given similarly in peanut oil. The LD_{50} (Bliss) values were 63.0, 67.7, and 45.9 mg. per kg., respectively (Table III). This relationship was not unique, a similar effect having been observed when rabbits were given toxaphene in peanut oil and in Ultrasene. The toxicity of aldrin was greater (LD_{50}, 18.8 mg. per kg.) when it was administered orally in an aromatic extract, TS-28-R (aromatic solvent marketed by Shell Chemical Corp.), but because fatalities resulted from the solvent alone the toxicity could not be attributed entirely to the aldrin.

On the basis of its content of aldrin, formulated wettable powder containing 2.5% of thermal aldrin had about the same toxicity as recrystallized aldrin, when given in peanut oil to weanling female Carworth rats. The lethal dosages (LD_{50}), in terms of aldrin, were 39.7 and 45.9 mg. per kg., respectively. Ball and others (*1*) obtained the corresponding value of 44.8 mg. per kg. when this wettable powder was given in corn oil to female rats weighing 175 grams.

Effect of Sex and Age. Young female rats appear to be slightly more susceptible than young male rats to a single oral dose of any one of these four insecticides (Table IV). The greater susceptibility of female rats 6 months of age, over that of younger female rats, to the toxic effects of endrin and isodrin was unusual and does not lend itself to ready explanation. The reverse and more normal relationship between age and susceptibility was obtained in the case of males (Table IV).

Application upon Skin of Rabbits

Immediate Toxicity. When maintained for 24 hours in contact with the intact skin of female rabbits according to the sleeve technique of Draize, Woodard, and Calvery (*4*), the toxicity of the dry powders of recrystallized aldrin, dieldrin, isodrin, endrin, or DDT, ground to pass 100-mesh screen, appeared to be somewhat related to the structure of the compounds, the substances with the *endo-endo* configuration being the more toxic (Table V). The minimum lethal dosages lay between 0.60 and 1.25 grams per kg. for aldrin, 0.25 and 0.36 gram per kg. for dieldrin, and 0.060 and 0.094 gram per kg. for endrin; the lowest dosage of isodrin applied, 0.094 gram per kg., was lethal to two of three rabbits, whereas rabbits, without exception, tolerated DDT in the dosage of 2.5 grams per kg.

Repetitive Applications. The toxic effects resulting from repetitive contact of these materials with the skin of rabbits was enhanced in varying degree by the use of solvents. When maintained on the skin of rabbits for 2 hours on each of 5 days per week for 10 weeks (50 applications), the dry powders of aldrin, dieldrin, and DDT were severalfold less toxic than when applied in Ultrasene or in solution or suspension in a vegetable oil. The highest tolerable dosage and the lowest dosage that resulted fatally in some of the rabbits in groups of three or four are given in Table VI. When applied as dry powders, aldrin and dieldrin are more toxic than DDT, but less toxic than endrin. The high mortality resulting from repetitive applications of aldrin and dieldrin in Ultrasene occurred in association with alterations of the skin by the solvent, which may have promoted percutaneous absorption of both insecticide and solvent.

Prolonged Feeding

Rats In a preliminary experiment conducted over the period of 6 months, rats were fed on diets containing recrystallized aldrin, dieldrin, or DDT in concentrations of 2.5, 5.0, 25.0, 75.0, and 300.0 p.p.m., respectively. All of the rats of either sex fed on diets containing aldrin or dieldrin at 300.0 p.p.m. died within 2 weeks, but the incidence of mortality in all other groups was not significantly different than that encountered among corresponding control groups.

In another experiment, groups of 40 male and 40 female Carworth rats, 27 or 28 days of age, were given diets containing aldrin, dieldrin, or DDT in the concentrations of 2.5, 12.5, and 25.0 p.p.m., respectively. Since dieldrin and DDT were incorporated as alcoholic solutions into Purina Laboratory Chow Pellets, two groups of 40 (male and female) were fed on this type of pellet, to which alcohol, but no insecticide, had been added. As it was necessary to give aldrin in a ground diet, additional control groups of male and female rats were

Table I. Immediate Toxicity of Four Polychlorinated Dimethanonaphthalenes Given Orally to Rats

[Given to female Carworth rats, 25 to 31 days of age as 0.1 to 2.0% (w./v.) solution of insecticide in peanut oil]

Recrystallized Insecticide	Spatial Configuration of Hydrocarbon	LD_{50}, Mg./Kg.	Fiducial Limits 0.05, Mg./Kg.	Slope
Aldrin	*endo-exo*	45.9[a]	35.8–54.2	5.01
Dieldrin	*endo-exo*	38.3[b]	32.7–44.8	6.985
Isodrin	*endo-endo*	16.4	12.6–21.5	3.952
Endrin	*endo-endo*	16.8	13.0–21.7	3.391

[a] Expressed in terms of 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-*endo*,*exo*-5,8-dimethanonaphthalene.
[b] Expressed in terms of 1,2,3,4,10,10-hexachloro-*exo*-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-*endo*,*exo*-5,8-dimethanonaphthalene.

Table II. Immediate Toxicity of Impure Aldrin Obtained from Different Processes of Manufacturing

[Given to female Carworth rats, 25 to 27 days of age. 60% (w./v.) solutions of thermal or Straus aldrin as obtained in manufacturing, without purification, were diluted with Ultrasene to contain 1 or 4% of aldrin]

Material	LD_{50}, Mg./Kg.	Fiducial Limits 0.05, Mg./Kg.	Slope
Thermal aldrin	74.9[a]	63.9–87.7	5.79
Straus aldrin	25.0[a]	21.8–28.8	5.87
Impurity in Straus aldrin	0.71	0.63–0.80	7.27

[a] Expressed in terms of 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-*endo*,*exo*-5,8-dimethanonaphthalene.

Table III. Effect of Solvent on Immediate Toxicity of Aldrin

(Given to female Carworth rats, 25 to 29 days of age)

Grade of Aldrin	Solvent	LD_{50}, Mg./Kg.[a]	Fiducial Limits 0.05, Mg./Kg.	Slope
Recrystallized	Ultrasene	63.0	51.8–70.5	5.78
Tech. cryst. thermal	Ultrasene	67.7	59.1–80.3	5.95
Recrystallized	Peanut oil	45.9	35.8–54.2	5.01
Tech. cryst. thermal	TS-28-R[b]	18.8[c]	14.3–25.5	3.51

[a] Expressed in terms of 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-*endo*,*exo*-5,8-dimethanonaphthalene.
[b] Aromatic solvent (Shell Chemical Corp.).
[c] Toxicity due in part to toxicity of solvent, an aromatic extract obtained from petroleum, boiling range 310° to 400° F.

Table IV. Influence of Sex and Age of Rats on Susceptibility to Toxic Effects of Recrystallized Aldrin, Dieldrin, Isodrin, or Endrin

Sex	Age	LD_{50}, Mg./Kg. Aldrin	Dieldrin	Isodrin	Endrin
Female	25–31 days	45.9[a]	38.3	16.4	16.8
Male	25–31 days	49[b,c]	47[b,c]	27.8	28.8
Female	6.0 months	...	...	11.7	7.3
Male	6.0 months	...	...	42.1	43.4

[a] Expressed in terms of 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-*endo,exo*-5,8-dimethanonaphthalene.
[b] Expressed in terms of 1,2,3,4,10,10-hexachloro-*exo*-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-*endo,exo*-5,8-dimethanonaphthalene.
[c] Rats approximately 2 months of age (*3*).

Table V. Immediate Toxicity of Aldrin, Dieldrin, Isodrin, Endrin or DDT Maintained in Contact with Intact Skin of Female Rabbits by Method of Draize, Woodard, and Calvery

(Applied as recrystallized dry powder that passed 100-mesh screen. Maintained under rubber sleeve for 24 hours)

Insecticide	Spatial Configuration	Minimum Lethal Dosage, G./Kg.
DDT	...	>2.5
Aldrin	*endo-exo*	0.60–1.25
Dieldrin	*endo-exo*	0.25–0.36
Isodrin	*endo-endo*	<0.094
Endrin	*endo-endo*	0.060–0.094

given the ground basic diet (without aldrin).

When fed over a period of 2 years to rats of either sex at levels of 2.5, 12.5, and 25.0 p.p.m., respectively, neither dieldrin nor DDT caused a significant increase in mortality over that encountered in a group of corresponding controls (Figure 2). This was also true of males fed on aldrin at these levels. The incidence of mortality among female rats fed on a diet containing aldrin at 25.0 p.p.m. was significantly greater than that among the controls, at the end of either 79 or 100 weeks. The corresponding effect was sustained by female rats fed on aldrin at 2.5 and 12.5 p.p.m. only at the 100th week. The interpretation of the data on females is difficult, because the mortality in the control groups fed on pellets and on a ground diet varied widely, the latter being considerably less (10%) than that encountered normally in controls fed over a 2-year period. Therefore, if the results obtained on the aldrin-fed females are compared with those obtained on the controls fed on the pellets in this experiment, no significant difference occurred. Thus it is believed that aldrin fed to female rats at levels of 2.5, 12.5, or 25.0 p.p.m. over periods of 2 years did not induce any increase in mortality.

The average lengths of survival (Figure 3) of either male or female rats fed on diets containing dieldrin or DDT at the level of 25.0 p.p.m., or of male rats fed on diets containing this concentration of aldrin, were not significantly less than those of corresponding controls. Male rats fed on a diet containing DDT at 25.0 p.p.m. survived significantly longer than did the corresponding controls. The average periods of survival, expressed in weeks, for female rats fed on aldrin at levels of 2.5, 12.5, and 25.0 p.p.m., were 81.5, 91.1, and 85.1, respectively. The values associated with levels of 2.5 and 25.0 p.p.m. were significantly less than the exceptionally high figure which characterized the corresponding controls (100.7).

The growth of all of the experimental groups fed on diets containing aldrin, dieldrin, or DDT was as great as that of the corresponding controls. For example, after 40 weeks the female rats fed on control pellets had achieved an average gain in weight of 201 grams, whereas the average gains of groups of female rats fed on diets containing aldrin, dieldrin, or DDT ranged from 197 to 220 grams. After 120 weeks, the male rats fed on control pellets had gained 312 grams, and the groups of male rats fed on diets containing dieldrin or DDT had

Figure 2. Percentage of mortality among control rats and rats fed on diets containing aldrin, dieldrin, or DDT for 2 years

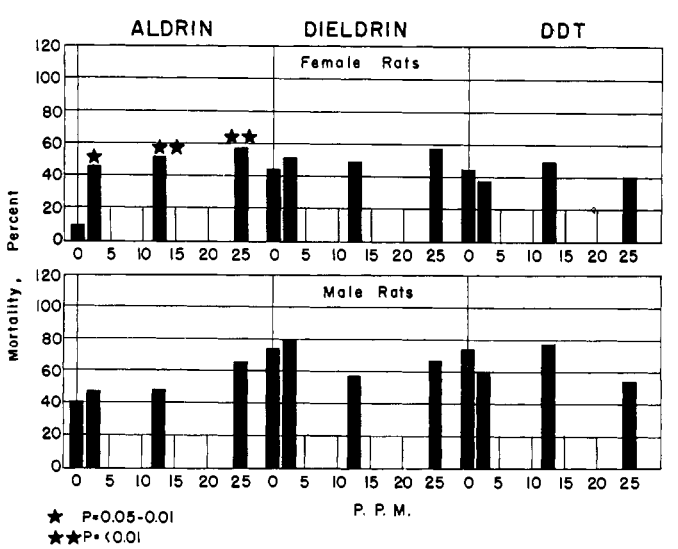
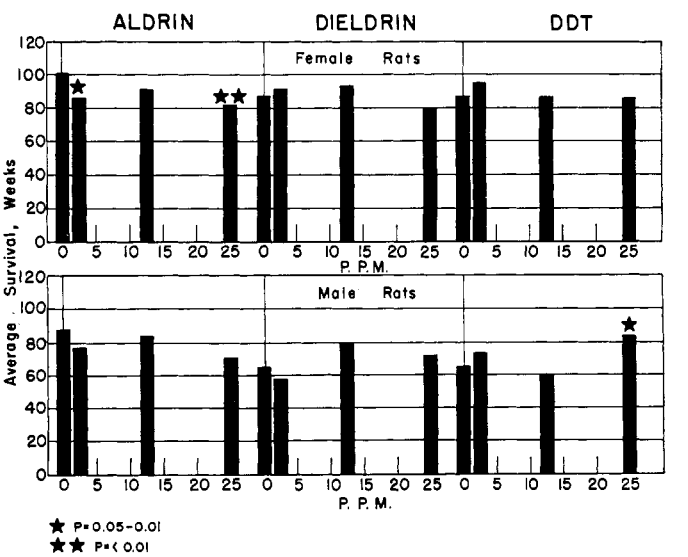


Figure 3. Average length of survival of male or female rats fed on control diets or on diets containing aldrin, dieldrin, or DDT



gained 307 to 323 grams. The first of these periods represents that in which the rate of growth is at its maximum; a subsequent decrease in rate characterizes the longer period. The curves in Figure 4 represent the average weight at weekly intervals of groups of male rats fed on diets containing dieldrin at 2.5, 12.5, and 25.0 p.p.m., as well as male rats fed on control pellets.

Table VI. Toxicity of Recrystallized Aldrin, Dieldrin, Endrin, or DDT Maintained on Skin of Rabbits for 2 Hours per Day 5 Days per Week for 10 Weeks

Insecticide	Range of Minimum Lethal Dosage: Dry powder that passed 100-mesh	In vegetable oil	In Ultrasene
	Total Dose per Day, Mg.		
DDT	600–900	300–600	>100
Aldrin	100–300	25– 50	<12
Dieldrin	100–300	50–100	<12
Endrin	<75	...	...
	Daily Dose, Mg./Kg.		
DDT	213–489	109–257	>46
Aldrin	35–123	10– 26	<4.8
Dieldrin	40–163	19– 50	<5.3
Endrin	<30	...	...

After male rats had been fed on the diets containing dieldrin for 18 months, the average ratios of the weights of their livers to their body weight were significantly greater than that of the corresponding controls. The ratios relevant to the levels of dieldrin in the diets were as follows: 25.0 p.p.m., 3.29 grams of liver per 100 grams of body weight ($P < 0.01$); 12.5 p.p.m., 3.13 grams of liver per 100 grams of body weight ($P = 0.05$ to 0.01); and 2.5 p.p.m., 2.92 grams per 100 grams ($P = 0.05$ to 0.01). (P is the probability that the experimental and control values are from the same universe.) The corresponding value in the control group of males was 2.55 grams per 100 grams of body weight.

After either 18 months or 2 years, the average ratios of the weight of the livers to the body weight of male rats fed on either aldrin or dieldrin at 2.5 p.p.m. or DDT at 25.0 p.p.m., or of female rats fed on either dieldrin or DDT at 2.5 p.p.m. or aldrin at 12.5 p.p.m., were significantly greater than that of the corresponding controls. This was not true of males fed on DDT at either 2.5 or 12.5 p.p.m.

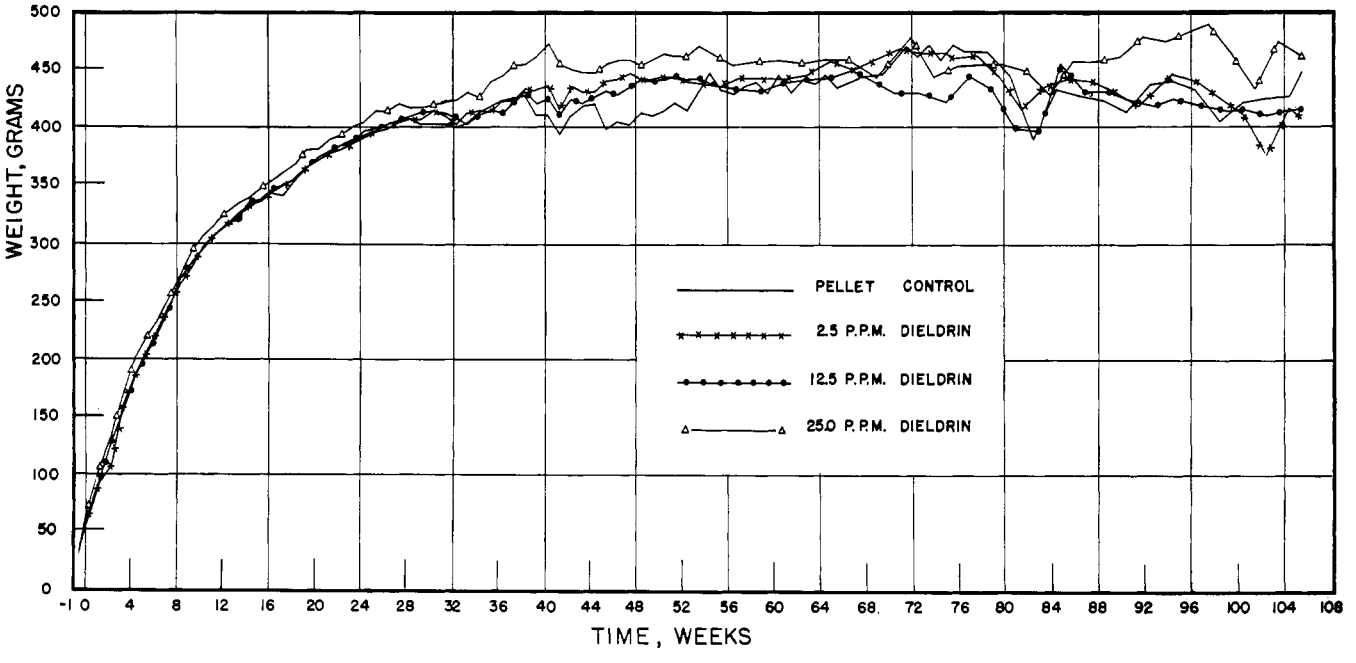
During the 2 years of feeding there were no deaths among these animals that could be attributed directly to toxic effects of the insecticides. Rats that were killed after 18 months or after 2 years exhibited minor, and from the histologic viewpoint, nonspecific, degenerative changes in the hepatic cells that have been described as being characteristic (*6*) of the effects of the absorption of the chlorinated hydrocarbon type of compound. At the end of 2 years the alteration of the liver cells occurred with more frequency in animals fed on diets containing DDT than on those containing aldrin or dieldrin.

Table VII. Fate of Dogs Given Recrystallized Aldrin in Diet or in Capsules

Daily Dosage in Relation to Body weight, mg./kg.	Daily Dosage in Relation to Food, p.p.m.	Sex and Number of Dogs	Period of Time on Diet	Fate
7.2 –9.1	50	F (1)	10 days	Died
3.0 –4.5	25	M (2) F (3)	9–15 days	Died
1.3 –3.0	25–50	M (3) F (2)	2 days— 3.2 months	Died
0.9 –1.8	10	M (3) F (2)	12 days— 6.7 months	Died
0.12 –0.25	3	M (2) F (2)	15.6 months	Survived
0.043–0.091	1	M (2) F (2)	15.6 months	Survived

Dogs Dogs were more susceptible than rats to the toxic effects of aldrin or dieldrin. Diets that contained aldrin in the concentration of 10 to 50 p.p.m., when fed on 5 or 6 days of each week, induced fatalities after periods of feeding ranging from several days to several months (Table VII). Younger dogs appeared to be somewhat more susceptible than older dogs—for example, two males and one female, each given the first dosage of 3.0 mg. of aldrin per kg. when they were 11 days of age, died after being given 2, 23, and 24 doses (5 doses per week), respectively, but a male dog which was 19 months of age when the aldrin was first incorporated into his diet survived but was killed in a moribund state 3.2 months later; this dog had been given dosages equivalent to 2.1 to 3.1 mg. of aldrin per kg. on 6 days per week, over this period of time. Two

Figure 4. Average weekly weights of male rats fed on diets containing dieldrin to extent of 25.0, 12.5, 2.5, and 0.0 p.p.m.



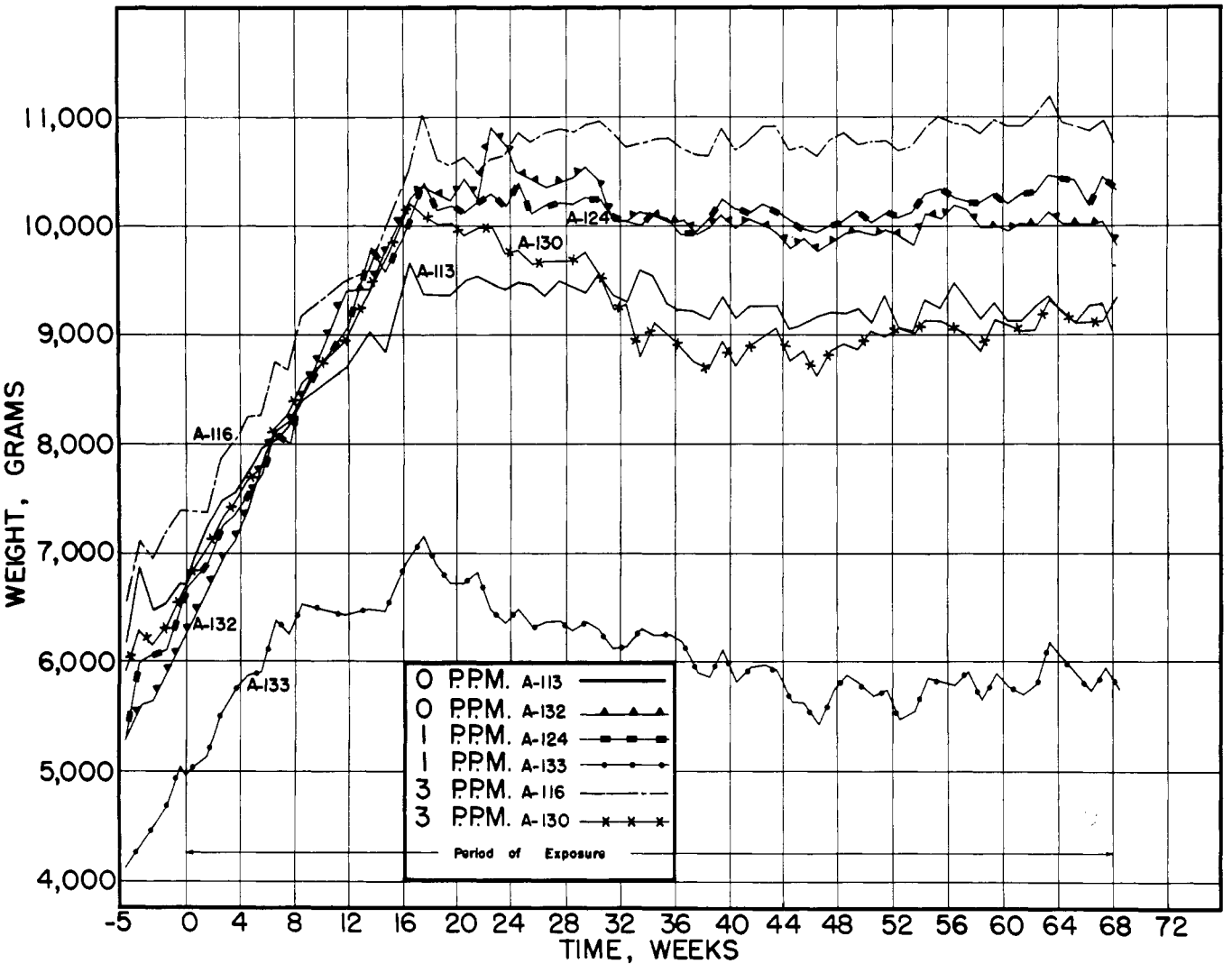


Figure 5. Growth of male control dogs and male dogs fed on diets containing aldrin

other males and one female, each given the initial dosage of 1.5 mg. of aldrin per kg. when they were 11 days of age, died after 12 to 26 doses, but two others, a male and a female, which were 2.1 months of age when aldrin was first introduced into their diet, died after 5.7 and 6.7 months, having been given dosages equivalent to 0.9 to 1.8 mg. of aldrin per kg. on each of 6 days per week over that period of time.

Each of two male and two female beagles was so fed that each of three weighed meals per day on 5 days per week contained aldrin at the level of 3 p.p.m., as did also the first meal on the sixth day. The other meals were weighed, but contained no insecticide. These dogs, and a similar group, fed on a diet containing aldrin at 1 p.p.m., survived 15.6 months, at which time they were killed.

Dogs given dieldrin in their diet to the extent of 25.0 or 50.0 p.p.m. on 6 days per week died after a few days to 1.3 months; other dogs survived for 9.0 months, when their food contained 10 p.p.m. (Table VIII). Groups of four beagles fed on diets containing dieldrin at 3 and 1 p.p.m. survived 15.7 months, as did also corresponding groups of dogs fed on DDT at 10 and 30 p.p.m., or on lindane at 15 p.p.m. (Table VIII).

The rates of growth of the experimental and control beagle dogs (eligible for registration with the American Kennel Club) were not different, as examined by inspection of the slopes of the curves which represent their growth during the most rapid period. The curves in Figure 5 present the weekly changes in weight over this and subsequent periods of the four male dogs fed on aldrin at levels of either 3 or 1 p.p.m., and of two control male dogs. The average

Table VIII. Fate of Dogs Given Recrystallized Dieldrin, DDT, or Lindane in Diet

Insecticide	Daily Dosage in Relation to Body weight, mg./kg.	Daily Dosage in Relation to Food, p.p.m.	Sex and Number of Dogs	Period of Time on Diet	Fate
Dieldrin	9.8	50	F (1)	5 days	Died
	2.0 –4.2	25–50	M (1)	11 days—	
			F (3)	1.3 months	Died
	0.73 –1.9	10	M (1)		
			F (1)	9.0 months	Survived
	0.14 –0.23	3	M (2)		
			F (2)	15.7 months	Survived
	0.033–0.10	1	M (2)		
			F (2)	15.7 months	Survived
DDT	1.2 –2.5	30	M (2)		
			F (2)	15.7 months	Survived
	0.45 –0.81	10	M (2)		
			F (2)	15.6 months	Survived
Lindane	0.66 –1.6	15	M (2)		
			F (2)	15.6 months	Survived

change in weight (expressed as percentage of the initial weight over the entire period) of the dogs fed on aldrin was 45.0, on dieldrin 49.2, on DDT 57.3, and on lindane 54.2 (controls 48.4).

The beagles fed on diets containing aldrin at 3 p.p.m., or dieldrin at 3 or 1 p.p.m., had livers that were significantly larger than those of the controls; this was not true of beagles fed on diets containing DDT at 30 or 10 p.p.m. or lindane at 15 p.p.m. (Table IX). The corresponding ratios for the kidneys, heart, brain, spleen, or fat of all groups of beagles fed on one of the four insecticides were not significantly different from those of the controls.

Table IX. Average Ratio of Weight of Liver to Body Weight of Dogs Fed on Diets Containing Recrystallized Aldrin, Dieldrin, or DDT for More than 15 Months

(Two male beagles and 2 female beagles at each level)

Insecticide	P.P.M.	Ratio of Liver to Body Weight, G./100 G.
Aldrin	3	3.84[a]
Aldrin	1	3.37[b]
Dieldrin	3	3.51[a]
Dieldrin	1	3.27[a,c]
DDT	30	2.71
DDT	10	2.77
Lindane	5	2.95
Controls	0	2.68

[a] $P < 0.02$.
[b] Deviation large.
[c] Deviation small.
P is the probability that the experimental and control values are from the same universe.

No change occurred in the relative numbers or types of the formed elements in the peripheral blood of the dogs fed on diets containing aldrin, dieldrin, DDT, or lindane over the period of 15.6 or 15.7 months.

Male and female dogs that died after the ingestion of aldrin and dieldrin over various periods of time exhibited diffuse degenerative changes in the brain, liver, and kidneys.

After being fed on diets containing aldrin in the concentration of 3 p.p.m., female dogs were found to have minor changes in the liver, characterized by local hyaline (droplet) degeneration of the hepatic cells and vacuolation of the epithelial cells lining the distal renal tubules. Of the two male dogs, one had hepatic lesions comparable to those found in the females, and the other had slight renal tubular degeneration. When fed on diets containing 1 p.p.m., the males had normal viscera and the females had vacuolation of the distal renal tubules.

Two male dogs and one female, fed on diets containing dieldrin in the concentration of 3 p.p.m., had no toxic changes in their tissues, but one female had vacuolation of the distal renal tubules. The dietary level of 1 p.p.m. induced no gross or microscopic abnormalities in the viscera of either male or female dogs.

Dogs given DDT in their diets at levels of 30 and 10 p.p.m. had normal viscera except for chronic inflammatory processes; the same was true of dogs given lindane.

Control dogs had normal viscera but for the occasional occurrence of incidental low-grade inflammatory lesions.

Effects on Reproductive Capacity

Aldrin, dieldrin, and DDT, at levels of concentration of 2.5, 12.5, and 25.0 p.p.m., were incorporated into the diets of rats (Carworth, original group) for three generations, in the manner described by Fitzhugh (*5*). Two sets of offspring were obtained from each generation of these groups, and groups of comparable controls. The presence of dieldrin in the diet at the level of 2.5 p.p.m. or of aldrin at 12.5 p.p.m. reduced the number of pregnancies, but no such effect was induced by aldrin at the level of 2.5 or of DDT at 25.0 p.p.m. (Table X). When dieldrin was fed over several generations at 2.5 or 12.5 p.p.m., the early evidence of reduction in the number of pregnancies tended to disappear. Ball, Kay, and Sinclair (*1*) observed an effect on the estrus cycle of female rats fed on diets containing aldrin in concentrations comparable to those employed in this experiment.

No reduction in the number of offspring per litter was noted when aldrin, dieldrin, or DDT was present in the diet up to the level of 25.0 p.p.m.

The incorporation of these insecticides into the diets of parent rats, during the period of suckling, had an effect on the incidence of mortality among the offspring, being severe in the case of aldrin or dieldrin at 12.5 or 25.0 p.p.m., but only slight to moderate in the case of either aldrin or dieldrin at 2.5 p.p.m. or in the case of DDT at 2.5, 12.5, or 25.0 p.p.m.

The incorporation of aldrin, dieldrin, or DDT into the diets of parent rats had no effect upon the weight of the young at weaning.

Withdrawal of Food

The complete withdrawal of food from rats previously fed for 7 to 18 months on diets containing aldrin or dieldrin at levels of 5, 10, or 15 p.p.m., did not result in the release of aldrin or dieldrin from the adipose deposits to an extent sufficient to induce symptoms of intoxication of any type.

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Table X. Effect of Aldrin, Dieldrin, or DDT in Diets of Rats upon Reproductive Capacity and Suckling Offspring

(Recrystallized grades used)

	Highest Dosage without Effect, and Lowest Dosage with Effect		
	Aldrin	Dieldrin	DDT
Number of deliveries	2.5, 12.5	<2.5, 2.5	25.0, >25.0
Reduction in number of pups/litter	25.0, >25.0	25.0, >25.0	25.0, >25.0
Incidence of mortality among offspring (1 to 21 days)	2.5[a], 12.5	2.5[a], 12.5	2.5[a], 12.5[a]
Weight of young, 21 days	25.0, >25.0	25.0, >25.0	25.0, >25.0

[a] Slight effect.