

# Studies on the Toxicity of DDT for Domestic and Laboratory Animals

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**I**N THE studies reported below, commercially pure DDT, identified as Geigy's GNB-A-DDT, was used. The experiments are recorded under the headings of acute and chronic toxicity tests. While the former were carried out on a variety of domestic and laboratory animals, the latter were restricted to a smaller number of animal species.

## Trials on Animals for Acute Toxicity

**Large domestic animals.**—These experiments comprised feeding of DDT and spraying with the drug. For oral administration DDT was dissolved in corn-oil, while for spraying a coal oil—"Mentor oil 29" mixture served as a vehicle. In addition, the effect of DDT on the conjunctiva of cattle was tested, when applied in form of corn-oil solutions. In chickens the oral toxicity of DDT oil solutions was examined only.

**Laboratory animals.**—Guinea pigs and rats were given DDT subcutaneously and orally in form of corn-oil solutions and aqueous suspensions. In the remaining species the toxicity of oil solutions only was tested. In addition, feeding trials with DDT powder and spraying experiments were carried out on rats.

**Cattle.**—Single oral doses of 150 and 450 mg./kg. DDT were given to two 8 months old heifers.

TABLE I. — ACUTE TOXICITY TESTS WITH DDT ON CATTLE.

Oil solutions

Number of animals	DDT oil solution, per cent	Mode of application	Dose	Symptoms	Return to normal
1	7	Oral	150 mg/kg.	No effect	—
1	15	"	450 mg/kg.	Slight tremors; paresis of leg muscles	8th day
1	5	Body surface	100 cc.	No effect	—
4	5 and 10 resp.	Conjunctival instillation	0.2 cc. to 0.4 cc.	No effect	—

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One animal weighing approximately 180 kg. was exposed to a single thorough spraying of the entire body surface.

Four heifers were used to test the effect of DDT on the conjunctiva. The reaction of this tissue to the drug was studied for the reason that, in large-scale practical application of DDT in form of sprays, contact with the conjunctiva is apt to occur. The results of the toxicity tests on cattle are summarized in Table 1.

*Swine.*—Three 8 weeks old pigs were fed 150, 400 and 1000 mg./kg. DDT respectively.

Four hogs of an average weight of 55 kg. and one pig weighing 11.4 kg., received one spray, covering the entire body surface. The findings in these experiments are compiled in Table II.

TABLE II. — ACUTE TOXICITY TESTS WITH DDT ON SWINE.

Oil solutions

Number of animals	DDT oil solution, per cent	Mode of application	Dose	Symptoms	Return to normal
1	7	Oral	150 mg/kg	No effect	—
1	15	"	400 mg/kg	Localized, intermittent muscle tremors; 13th to 16th day	—
1	15	"	1000 mg./kg	Slight tremors	5th day
4	2	Body surface	20 cc.	No effect	—
1	5	"	20 cc.	No effect	—

TABLE III. — ACUTE TOXICITY TESTS WITH DDT ON SHEEP AND GOATS

Oil solutions

Number and species of animals	DDT oil solution, per cent	Mode of application	Dose	Symptoms	Return to normal
1 sheep	7	Oral	150 mg./kg	No effect	—
1 sheep	15	"	450 mg./kg	Slight tremors; paresis of leg muscles	5th day
1 sheep	15	"	750 mg./kg	Slight tremors; incoordination of gait	6th day
1 goat	15	"	750 mg./kg	Slight and coarse tremors; incoordination of gait	7th day
1 sheep	5	Body surface	85 cc.	No effect	—

**Sheep and goats.**—Three sheep, approximately 18 months of age, were given oral doses of 150, 450 and 750 mg./kg. DDT and one adult male goat received a 750 mg./kg. dose. A spraying experiment was carried out on one sheep, weighing 36 kg. The results are summarized in Table III.

**Chickens and rabbits.**—These two animal species were tested only for the oral toxicity of DDT, using 7 per cent corn-oil solutions for the lower and 15 per cent for the higher doses, respectively.

Six chickens, approximately 5 to 7 weeks old and of closely comparable weight, were divided into three equal groups and were given 150, 300 and 600 mg./kg. DDT, respectively.

The eight full-grown rabbits available for the tests differed somewhat in age and weight and the oral doses of DDT administered, varied between 150 to 1000 mg./kg. Table IV summarizes the particulars of these tests.

TABLE IV. — ACUTE TOXICITY TESTS WITH DDT ON CHICKENS AND RABBITS

Oil solutions

Animal species	Number	Mode of application	Dose mg./kg.	Symptoms	Mortality, per cent
Chicken	2	Oral	150	No effect	0
"	2	"	300	Slight tremors; paresis (50%)	50
"	2	"	600	Coarse tremors; paresis (100%)	100
Rabbit	1	Oral	150	No effect	0
"	2	"	300	Tremors	50
"	1	"	500	Tremors	0
"	1	"	600	—	100
"	1	"	750	Slight tremors	0
"	2	"	800 & 1000	—	100

TABLE V. — ACUTE TOXICITY TESTS WITH DDT ON GUINEA PIGS.

Oil solutions and Aqueous suspensions.

Number of animals	Vehicle; concentration of DDT per cent	Mode of application	Dose mg./kg.	Symptoms	Mortality per cent
8	Corn oil;	Subc.	300, 600	No effect	0
8	7% DDT.	Oral	800, 1000	Hyperirritability and slight tremors in 50%.	0
20	Water; 5% DDT.	Subc.	10-1000	No effect	0
20	or Tragacanth emulsion; 20% DDT.	Oral	"	No effect	0

**Guinea pigs and rats.**—The toxicity of DDT in oil and aqueous suspensions, the latter containing 0.011 per cent Orvus as wetting agent, was determined for the subcutaneous and oral route in both species. For the administration of higher doses, 20 per cent aqueous suspensions were prepared with the aid of a tragacanth emulsion.

The experiments with rats also included toxicity trials with the drug fed as dry powder in gelatine capsules, and exposure of the entire body surface to one single DDT-oil spray.

The average age and weight of the animals was approximately 3 months and 500 gms., respectively, for the guinea pigs, and 4 months and 190 gms., respectively, for the rats. The findings are compiled in Tables V and VI.

TABLE VI. — ACUTE TOXICITY TESTS WITH DDT ON RATS.  
Oil solutions, aqueous suspensions and dry powder

Number of animals	Vehicle; concentration of DDT per cent	Mode of application	Dose mg./kg. (cc.)	Symptoms	Mortality per cent
6	Corn oil; 2 & 5% DDT	Subc.	50, 100, 150	No effect	0
4		"	200, 300	Survivors hyperirritable	50
4	"	Oral	50, 100	Hyperirritability (100 mg.)	0
2		"	150	"	100
4		"	200, 300	Coarse tremors	100
6	Water; 5% DDT; or Tragacanth emulsion; 20% DDT	Subc.	5, 25, 125	No effect	0
2		"	250, 500	Slight & coarse tremors (50%)	0
2		"	1000	Slight tremors (50%)	0
2		"	1500	No effect	0
2		"	2000	Coarse tremors (50%)	0
2		"	2500	"	50
6	"	Oral	5, 25, 125	No effect	0
4		"	250	Slight and coarse tremors (50%)	0
2		"	500	Coarse tremors (100%)	50
2		"	1000	"	50
2		"	1500	"	100
2		"	2000	"	0
2		"	2500	"	100
9	Dry powder	Oral	150, 300	No effect	0
6	form	"	500 700, 1000	Coarse tremors (16.6%)	33
16	Coal, oil-Mentor oil; 5% DDT	Body surface	2.5 (cc)	Hyperirritability and fine tremors (75%)	31.2

**Mice.**—Young white mice of 20 gms. average weight were used for the determination of subcutaneous and oral toxicity of DDT oil solutions. In the subcutaneous tests, groups of 3 mice each received doses of 50, 100, 200 and 300 mg./kg. DDT, while similar oral doses were administered to groups of 6 mice each. The results are summarized in Table VII.

TABLE VII. — ACUTE TOXICITY TESTS WITH DDT ON MICE  
Oil solutions

Number of animals	Mode of application	Dose mg./kg.	Symptoms	Mortality per cent
6	Subc.	50, 100	—	0
6	"	200, 300	—	33
6	Oral	50	—	0
5	"	100	—	20
6	"	200	—	33
6	"	300	—	66

## Trials on Animals for Chronic Toxicity

The effect of DDT fed in small amounts over a prolonged period was studied on rabbits, guinea pigs, rats and chickens. These experiments are grouped under three headings:

1. Feeding of DDT-dusted cabbage leaves to rabbits and rats.
2. Feeding of parings from DDT-sprayed apples to rabbits, guinea pigs and rats.
3. Feeding of flies, knocked down by DDT oil spray, to chickens.

*Cabbage feeding experiments.*—Three lots of cabbages were used, all dusted with 3 per cent DDT at roughly 60 lb. per acre. Lots 1 and 2 received one treatment, 2½ and two months respectively before harvesting. Lot 3 was dusted twice, 22 and 11 days before harvesting. Each cabbage

TABLE VIII. — FEEDING EXPERIMENTS WITH DDT-DUSTED CABBAGE

Animal species	Number of animals	Average Weight Gms.	Cabbage Lot No.	Rate of DDT-Dusting	Duration of feeding days	Total intake per animal Cabbage Head (Outer Leaves)	Symptoms and mortality
Rabbit	6	1600	1	3% DDT 60 lb. per acre. dusted once	15	6	Nil
Rat	12	180				1	
Rabbit	6	1900	2	"	28	12½	Nil
Rat	12	180				2	
Rabbit	6	3700	3	3% DDT. 60 lb. per acre. dusted twice	49	25	Nil
Rat	12	170				4½	

lot as fed to 6 rabbits and 12 rats, using only the outer leaves bearing the greatest amount of residual DDT.

The shortest feeding trial was 15 and the longest 49 days. Rabbits and rats consumed 6 and 1 cabbage heads, respectively, in the shortest trial and 25 and 4½, respectively, in the longest. The most heavily dusted leaves (Lot 3) were fed during the 49 day test. No toxic symptoms were observed and the animals gained weight normally. The experimental data and results are summarized in Table VIII.

*Feeding of DDT-sprayed apple parings.*—Two lots of apples were used in these experiments. Both had received four cover sprays of DDT, differing principally in that a refined petroleum oil (Marcol HX) was incorporated into the series of sprays applied to Lot 2. Chemical analysis demonstrated the presence of 1.06 mg. DDT per apple in Lot 1 and 2.91 mgs. in Lot 2. The average weight of one apple paring was 14 gms.

Feeding to two groups of rabbits, guinea pigs and rats was commenced approximately 2½ months after the last spraying at a rate of 14 gms. of parings per rabbit, corresponding to the paring of one average apple; 3 gms. per guinea pig, and 1 gm. per rat daily for a total of 161 days. The animals gained weight normally and no toxic symptoms were noted. The experiments are compiled in Table IX.

TABLE IX. — FEEDING EXPERIMENTS WITH DDT-SPRAYED APPLE PARINGS

Animal species	Number of animals	Average Weight Gms.	Apple Lot No.	DDT residue per apple Mgm.	Duration of feeding Days	Total intake per animal Parings	Symptoms and mortality
Rabbit	6	2100	1	1.06	161	161	Nil
Guinea Pig	12	520				34.5	
Rat	12	160				11.5	
Rabbit	6	3120	2	2.91	161	161	Nil
Guinea Pig	12	535				34.5	
Rat	12	225				11.5	

*Feeding chickens with flies, knocked down by a DDT oil spray.*—Five 6-weeks old chickens were fed with flies knocked down by a 4 per cent DDT coal oil spray. The daily dosage of the individual bird ranged from 5 to 25 flies and was given for 13 days. The doses were then doubled for an additional three days. On the 4th and 5th days two birds, one receiving the smallest and the other the greatest number of flies respectively, died with coccidiosis. The remaining three birds showed no toxic symptoms and appeared well at the end of the feeding schedule.

**Pathology**

**Macroscopic.**—Gross pathological changes in acute cases of DDT poisoning were not constant and, if present, were slight. Occasional liver damage was indicated by pallor of small, scattered areas of the parenchyma but involved in some instances a larger portion of the organ. Slight hyperaemia of the lungs and infiltration or oedema, occurring separately or concurrently, were regarded as being terminal manifestations. Hyperaemia of the stomach mucosa with occasional pinhead sized haemorrhages combined frequently with dark brown intestinal contents.

No lesions definitely attributable to the action of DDT were found in animals killed during various stages of the chronic toxicity tests.

**Microscopic.**—Two hundred and ten animals were examined, representative of those used in the various experiments. The most constant lesion was a degeneration of the liver, of variable character, but usually a vacuolar degeneration of the cytoplasm of the liver cell. In severely affected organs the centre of the cells appeared empty or contained a finely reticular, faintly staining material. The cell periphery was dense and stained deeply. Fat was not demonstrated. There was little alteration of the nuclei. The lesion occurred more often in the central lobular area than in the mid or

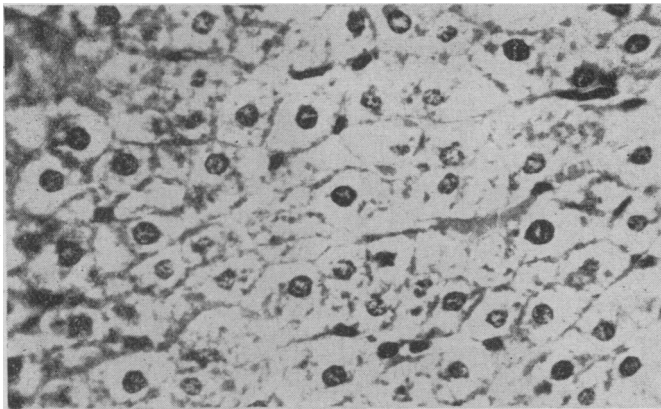


Figure No. 1.— A Typical Liver Lesion. The cytoplasm of all cells is extensively damaged. H. and E. 440 X.

peripheral zones. The damage appeared capable of repair and an apparent tolerance to the drug action was suggested, inasmuch as in many instances animals exposed to the drug for long periods did not exhibit this lesion. Unfortunately, as the study progressed into the winter a dietetic liver damage occurred in the guinea pigs and made recognition difficult of the significant lesion.

In some instances the colloid of the thyroid gland was diminished in amount and the staining reaction altered. Voluntary muscle necrosis was not observed. Occasionally myocarditis associated with pneumonia was found. Pulmonary changes varying from congestion to definite pneumonia and marked desquamation and necrosis of lining epithelium of the digestive tube in animals that died were regarded as not being significant.

Discussion

Under the experimental conditions described, large domestic animals as a group showed greater resistance to massive, single doses of DDT than the laboratory animals. No deaths occurred even from the highest doses administered and incoordination of gait or paresis of the muscles of the hind legs were the only striking symptoms, especially pronounced and persistent in cattle. Coarse tremors developed only in the goat.

According to the severity and persistence of symptoms, cattle appeared to be most susceptible to the toxic action of the drug, followed closely by goats and sheep, while swine showed an exceptionally high tolerance.

The results of the spraying experiments demonstrated the complete harmlessness of a single spray with a 5 per cent DDT-oil solution, covering the entire body surface.

The negative findings after conjunctival instillations indicated that 5 and 10 per cent solutions of DDT may be used without danger of conjunctival irritation, provided that an inert material is used as a vehicle.

In contrast to the large domestic animals, chickens showed a greater susceptibility and their behavior in this respect resembled that of the laboratory species tested.

The acute toxicity tests in laboratory animals brought out two main factors: (1) After oral administration higher toxic levels were obtained, than after subcutaneous injection. (2) Oil solutions of the drug, irrespective of the route, proved to be more toxic than the corresponding aqueous suspensions, the increase being about ten fold in the rat.

It was noted, furthermore, that in serial tests the toxicity of the drug varied considerably, especially when using aqueous suspensions. These irregularities were manifested by great differences in the intensity of symptoms following the administration of graded subcutaneous doses and by an uneven mortality rate after feeding. Such behaviour was interpreted as being due partly to irregular absorption and partly to variations in individual susceptibility.

The absorption seemed to be still more retarded and irregular when DDT was fed in dry powder-form and resulted in a considerably decreased toxicity, as observed in the experiments conducted on rats.

With oil solutions of the drug, variations in toxic action occurred less frequently; they were pronounced only in the rabbit group.

Based on the results obtained with solutions of DDT in corn-oil, which in itself proved to be harmless to the health of the animals, the following oral toxicity levels were established for the laboratory species tested: Rabbits: LD 50 = 300 mg./kg., MLD = 600 mg./kg., guinea pigs: MLD = <100 mg./kg.; rats: MLD = 150 mg./kg.; mice: LD 05 = >200 mg./kg., MLD = >300 mg./kg.

Chickens behaved similarly to the rabbits in their response to DDT oil solutions.

While there were no symptoms after continued feeding of small amounts of the drug, microscopical lesions in several organs revealed, nevertheless, the potential danger of prolonged ingestion of the drug.



Summary

Toxicological studies with commercially pure DDT were carried out on a variety of domestic and laboratory animals. The results were:

1. The acute toxicity of DDT in large domestic animals was lower than in laboratory animals.
2. In the laboratory species tested, higher toxic levels were obtained after oral administration than after subcutaneous injection of the drug; oil solutions proved to be more toxic than aqueous suspensions.
3. Variations in species susceptibility were generally well marked. Individual variations remained within limits which permitted the grouping of the species according to drug susceptibility. Of the animals tested the rats showed the highest susceptibility, guinea pigs and swine the greatest resistance. Mice, rabbits and chickens, cattle, goats and sheep occupied intermediary positions, their resistance increasing in the approximate order given.
4. No symptoms were produced by feeding DDT-dusted cabbage leaves and sprayed apple parings to rabbits, guinea pigs and rats; nor by feeding flies knocked down by a DDT spray to chickens.
5. Gross pathological changes after large single doses occurred mainly in the liver. In the chronic toxicity tests there were no changes.
6. The histopathological findings were similar in the acute and chronic toxicity tests, the difference being only in degree of severity. The principal lesion was a degeneration of the liver.

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## Dr. E. P. Benoit

LES ANCIENS diplômés de l'Ecole de Médecine comparée et de Science vétérinaire de Montréal apprendront avec regret la mort du Dr E. P. Benoit, M.D. leur ancien professeur de matière médicale. Il était âgé de 76 ans.

Ses grandes connaissances scientifiques, son charme personnel et son dévouement à la cause vétérinaire contribuèrent beaucoup au rapprochement de nos deux professions.

Nous prions la famille en deuil d'accepter nos plus sincères condoléances.

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