Toxicology of Chlorobenzilate

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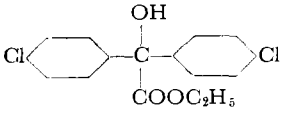
The toxicology of chlorobenzilate, a chlorinated hydrocarbon with acaricide properties, has been investigated in laboratory animals to evaluate hazards of use. The maximum tolerated dietary level for rats is approximately 500 p. p. m. Dogs tolerated daily doses of 64.1 mg. per kg. for 35 weeks without signs of toxicity or gross or microscopic pathology. Metabolism studies indicated that chlorobenzilate is rapidly excreted in the urine and that there is no significant storage in tissues. This study indicates that chlorobenzilate offers little or no hazard from repeated usage.

CHLOROBENZILATE, formerly called Geigy 338, was first introduced approximately 3 years ago and has found wide acceptance in the United States, Canada, and Europe as an acaricide. The following studies were undertaken to evaluate the hazard of use.

Chlorobenzilate is 2-hydroxy-2,2-bis-(4-chlorophenyl)ethyl acetate, which is a synonym for 4,4'-dichlorobenzilic acid ethyl ester. It has the following chemical structure:



The pure compound is a yellowish brown viscous liquid with a boiling point of 141° to 142° C. at 0.06 mm. of mercury (*4*). The technical product contains approximately 90% of the above compound and is a brownish liquid which has a specific gravity at 20°/4° of 1.2816 (*4*). Chlorobenzilate is only slightly soluble in water but very soluble in organic solvents such as benzene, acetone, methanol, and deodorized kerosine. No decomposition of the technical product has been observed in the wettable powders or emulsion concentrates when stored at room temperatures. The xylene emulsion and wettable powder were made using technical chlorobenzilate.

Acute Oral Administration to Mice and Rats

Method The acute oral toxicities of technical chlorobenzilate, 25% xylene emulsion, and 25% wettable powder were studied in both mice and rats. The technical chlorobenzilate and the xylene emulsion were administered either undiluted or as a solution in Wesson oil. The 25% wettable powder was administered as a suspension in distilled water. The concentrations administered are indicated in Table I; they were selected in such a manner that the maximum volume of material administered to rats and mice did not exceed 5.0 and 1.0 ml., respectively.

Following oral administration, the animals were housed in groups of five to seven animals, with food and water available at all times. Gross autopsies were performed upon the animals that died, unless a state of advanced autolysis made this unfeasible. The surviving animals were observed for gross signs of systemic toxicity for a period of 1 week, after which they were sacrificed and gross autopsies performed. Where the data were adequate, the LD_{50} was computed by probit analysis (*3*). The limits within which the true value of the LD_{50} might be expected to fall were computed at the fiducial probability of 95%.

Results **Technical Chlorobenzilate.** The acute oral LD_{50} in mice was found to be 729 mg. per kg., while for rats it was found to be 702 mg. per kg. The dosage levels, mortalities,

Table I. Summary of Acute Oral Administration of Technical Chlorobenzilate, 25% Xylene Emulsion, or 25% Wettable Powder to Male Albino Mice and Rats

(Dosages are as chlorobenzilate. Values presented are number of animals dead per number of animals tested.)

Dose, Mg./Kg.	Technical		25% Xylene Emulsion		25% Wettable Powder	
	Mice	Rats	Mice	Rats	Mice	Rats
100	0/13	...	...	...	...	...
200	2/13	...	...	...	...	...
300	2/13	...	...	...	...	...
398	...	...	...	0/10	...	...
501	...	...	0/13	2/10	...	...
631	5/13	...	...	2/10	...	...
794	...	...	0/13	6/10	...	...
1000	...	14/21	0/26	9/10	...	...
1260	10/13	12/21	...	9/10	0/5	8/10
1580	...	15/17	6/13	10/10	0/5	9/10
1800	12/13	...	...	...	...	...
2000	...	16/17	12/13	10/10	4/5	10/10
2510	...	8/10	...	10/10	3/5	10/10
3160	10/13	9/10	...	10/10	4/5	9/9
LD_{50}, mg./kg.	729	702		735		
Fiducial limits	604–880	581–848		682–792		

Table II. Summary of Body Weights, Food and Compound Consumption, and Survival Data for Male and Female Albino Rats Receiving Basic Laboratory Diet, or Basic Diet Containing 0.005 or 0.05% Chlorobenzilate for 2 Years

(Per cent of survival based on length of survival as well as number of animals)

Chlorobenzilate in Diet, %	Sex	No. of Rats		Average Body Weight, Grams		Food Consumed, Grams	Chlorobenzilate Consumed, Mg.	Survival, %
		Start	Finish	Initial	Final	Av./rat/day	Av./rat/day	
0	M	20	16	71	441	16.1	...	95.2
	F	20	12[a]	66	299	14.4	...	95.0
0.005	M	20	13	69	400	16.1	0.81	91.5
0.05	M	20	14	68	371	14.9	7.47	89.3
	F	20	14[b]	63	312	14.7	7.34	96.6

[a] One rat accidentally killed.
[b] One rat sacrified for microscopic analysis.

LD_{50}'s, and fiducial limits are summarized in Table I.

Following administration in either mice or rats, preening and depression were observed at all levels. There was also some lacrimation, salivation, diarrhea, and deep, rapid respiration. At the higher dosage levels many animals had sprawling of the hind limbs, absent righting, placement, and pain reflexes, followed by coma and death. Autopsies of the animals that died showed hemorrhagic lungs and irritated intestines. Autopsies of the survivors after a 1-week observation period revealed no significant gross pathology.

25% Xylene Emulsion. The acute oral toxicity for rats was computed as 735 mg. per kg. in terms of chlorobenzilate. Data for the mice were inadequate for statistical analysis. Table I summarizes the dosage levels, mortalities, LD_{50}'s, and fiducial limits.

All deaths occurred within the first 48 hours. Excitement, preening, and lacrimation were observed, followed by ataxia, rapid and labored respiration, loss of righting and placement reflexes, and then coma and death in many of the animals. Gross autopsies of those animals that died revealed irritated intestines. When the survivors were sacrificed after an observation period of 1 week, no significant gross pathology was observed.

25% Wettable Powder. Table I summarizes the dosage levels and mortality. Data for both mice and rats were inadequate for statistical analysis.

All deaths occurred within 48 hours. Signs of toxicity at the higher levels consisted of depression, lacrimation, preening, ataxia, rapid, labored respiration, coma, and death. Autopsies of those animals that died indicated irritation of the gastrointestinal tract. When the survivors were sacrificed after the 1-week observation period, gross autopsies revealed no significant gross pathology.

Dermal Application to Rabbits

Acute Application Method Single applications of chlorobenzilate were applied to the closely clipped abdomens of six albino rabbits. The animals were wrapped with rubber damming, held in place with gauze and adhesive tape, and technical chlorobenzilate at a dosage of 0.5 ml. per kg. was injected under the damming to one group of three rabbits, and 1.0 ml. per kg. was injected under the damming to the second group of three rabbits. The animals were housed individually and food and water were offered ad libitum.

Results. There were no mortalities, and after an observation period of 18 hours the binders were removed from the abdomen and the treated area was examined. Additional examinations were made for a total of 7 days. One animal in each group had slight edema immediately following removal of the abdominal binder; however, this condition cleared within 24 hours and all animals in both groups appeared normal throughout the remainder of the observation period. The animals were sacrificed at the end of 7 days and gross autopsies performed; all of the organs were found to be within normal limits.

Repeated Application Method. Daily applications of technical chlorobenzilate at a dosage of 0.5 ml. per kg. were applied under rubber damming for a period of 2 weeks to six albino rabbits, using the technique described above. The animals were housed individually and food and water were available at all times. Each exposure period was 18 hours, after which time the rubber damming was removed and the abdomen washed with warm water. Observations were made daily, following which a new application of the material was made. The five surviving animals were examined for an additional 10 days following the last application and were then sacrificed.

Results. One animal died on the second day of the experiment, but the cause of death was undetermined, as gross autopsy showed only slight irritation of the intestine which, in all likelihood, was unrelated to the experiment. The five remaining animals appeared healthy and gained weight during the course of the experiment. Examination of the skin disclosed the development of a slight to mild irritation, characterized by erythema, slight atonia, and desquamation at the site of application, with some variation in time of onset and duration among the individual animals. The skin returned to normal shortly after cessation of the applications. Gross examination at autopsy disclosed that all organs were within normal limits.

Chronic Feeding

Rats **Method.** Weanling male and female rats of the Carworth Farms strain were selected at random and housed individually in wire-mesh cages elevated above the droppings. Water and the appropriate diets were offered ad libitum. Weekly records were kept of the individual body weights and food consumption of each rat during the course of the 2-year study. In addition, weekly observations were made as to the general appearance, condition, and behavior of each animal.

The following groups of rats were initiated, the chlorobenzilate being added to each diet on a weight basis:

Level	Number of Rats	
	Male	Female
Control	20	20
0.005% technical chlorobenzilate (50 p.p.m.)	20	
0.05% technical chlorobenzilate (500 p.p.m.)	20	20

After 2 years of dietary feeding, all surviving animals were sacrificed by exsanguination and autopsied. The livers, kidneys, spleen, and testes were weighed. Tissues from the brain, pituitary, thyroid, lung, stomach, large and small intestine, liver, testes, spleen, pancreas, kidneys, adrenals, bone, and muscle were preserved from a representative number of animals in each group for microscopic examination. Representative tissues were also preserved from any skin lesions or tumors that were present.

Results. Table II presents the summary of body weights, food and compound consumption, and survival data for the rats. The per cent survival is based not only on the actual number of survivors, but also on the length of time that the animals survived. There was

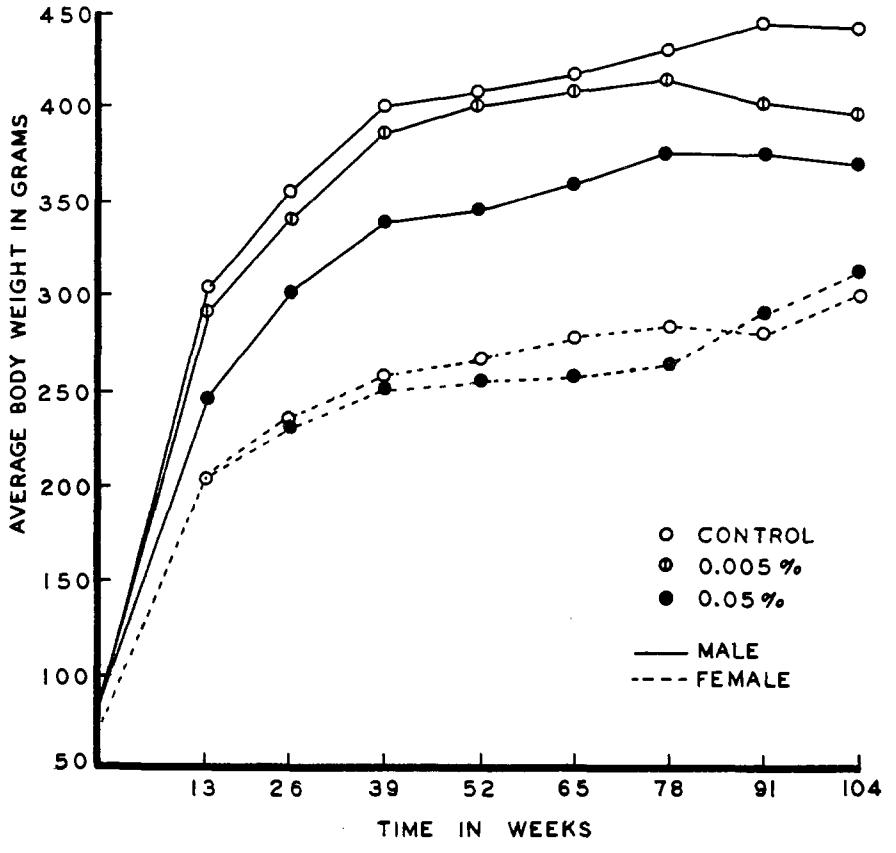


Figure 1. Growth curves for male and female albino rats receiving chlorobenzilate in the diet for 2 years

no significant difference in the survival rate of the experimental groups and their controls.

Figure 1 presents the growth curves for these groups of rats in the 2-year chronic feeding study. Only the males receiving 500 p.p.m. showed a significantly lower weight gain as compared with the controls. There was, however, no significant difference in food consumption in any of the experimental groups compared with the controls, as can be seen from Table II.

There was an obvious increase in incidence of the following signs in both the male and female groups receiving 500 p.p.m.: blood-tinged crust about the nose, blood-tinged crust about the eyes, and unthriftiness. Of the many other recorded signs there appeared to be approximately an even distribution throughout all groups, including the controls. These signs included wheezing, rapid respiration, nasal discharge, protruding eyes, rough or discolored fur, body sores, alopecia, and hunched back.

Organ weights of liver, kidneys, testes, and spleen were recorded for all animals at termination. In the males receiving 500 p.p.m. there was a large incidence of small, soft testes, but from past experience this appeared to be due to senility and has been encountered even in control groups. Of the remaining organs, the weights were not significantly different from their respective controls.

Gross pathological findings of largest incidence were infected lungs, small testes, enlarged pituitaries, cystic ovaries, mammary tumors, enlarged thyroids, and enlarged adrenals. Incidence of these gross pathological findings follows:

Findings	Control		50 P.P.M.,	500 P.P.M.	
	Male	Female	Male	Male	Female
Infected lungs	4	2	7	5	6
Small and/or soft testes	4	..	9	14	..
Cystic ovaries	..	5	..	..	8
Enlarged pituitary	0	4	1	1	3
Mammary tumors	..	3	..	..	1
Enlarged thyroid	2	3	2	2	0
Enlarged adrenals	0	9	1	1	4

These findings were observed at least as frequently in the controls as in the experimental groups, except for the incidence of small, soft testes. Nonspecific changes of spleen, liver, and kidneys were also noted in some animals, but were seen as frequently in the controls as in the experimental groups. In addition, the following abnormalities were found: one abdominal abscess in the control males; one enlarged bladder with hard nodules in the control females; one mediastinal tumor in the 50 p.p.m. male group; and one petechial hemorrhagic stomach and two instances of irritated intestines with bloody fluid in the 500 p.p.m. male group.

Microscopic Findings. The following is a brief summary of V. J. Dardin's detailed microscopic description of the various sections.

There was no histological difference in the sections of testes of experimental animals *vs.* the controls, or with rats from other 2-year feeding studies; hence, it appears that the atrophy noted was due to senility.

The pituitary enlargements which had been noted were found to be chromophobic cell hyperplasia or pseudoadenomatous basophilic hyperplasia. There were also vascular ectasia and congestion of the pituitaries.

Other incidental findings included slight arteriosclerosis of the kidney, occasional fatty metamorphosis of the liver, vascular ectasia, and congestion of the adrenal, as well as occasional slight hypertrophy of the adrenal cortex. However, as differential stains were not used, a concrete diagnosis of adrenal pathology cannot be rendered.

Sections of tumor masses were as follows: The mediastinal tumor was a lymphosarcoma, the mammary tumors were benign adenofibromas, and the bladder tumor was found to be a papilloma or squamous cell carcinoma on one side with a leiomyoma or fibrosarcoma on the other. Also, there was a lymphosarcoma involving the lung, an adenoma of the cells of Langerhans in the pancreas, a chronic salpingitis, and several acute ulcerations of the skin.

Dogs

Method. Male and female mongrel dogs were used in this study. Preexperimentally, the dogs were immunized against rabies and adapted to laboratory conditions and diet in order to establish a stable body weight. The technical chlorobenzilate was administered orally by capsule 5 days a week for a total of 35 weeks. There were two 5-day periods during which the compound was not administered, in order to follow the rapidity of excretion. One male and one female dog were used at each dosage level.

Group 1. Control
Group 2. 12.8 mg./kg./day, corresponding to 10 cu. mm. of technical chlorobenzilate per kg. of body weight per day
Group 3. 64.1 mg./kg./day, corresponding to 50 cu. mm. of technical chlorobenzilate per kg. of body weight per day

One dog which was initiated on the high level developed distemper and died during the fourth week of the study; it was replaced by another dog of the same sex. Each animal was observed daily for signs of systemic toxicity and body weights were recorded weekly. The animals were housed in pairs; food was offered once a day, and water was available at all times.

Results. During the 35 weeks all

dogs either maintained their body weight or made slight weight gains. All dogs exhibited normal behavior, had good appetite, and showed no gross signs of toxicity throughout the entire study.

Complete blood counts, blood urea nitrogen determinations, bromosulfthalein liver function tests, and urine analyses were conducted on each dog initially, at various intervals throughout the study, and at termination. The results of all of these studies were within normal limits.

At termination of the 35-week study all the animals were sacrificed and examined grossly, and sections of thyroid, lung, heart, liver, spleen, kidneys, adrenals, stomach, small and large intestine, pancreas, urinary bladder, bone marrow, muscle, and testes of ovaries were prepared for microscopic examination. Gross and microscopic examination revealed no significant pathology which could be attributed to the oral ingestion of chlorobenzilate.

Excretion of Chlorobenzilate by Dogs

Method. The method for determination of chlorobenzilate was essentially the same as given in an unpublished procedure of Harris (*5*). The principle involved the separation of fat from an alcoholic extract by saponification and subsequent determination of the chlorobenzilate by a modified Schechter-Haller procedure. As the presence of interfering substances proved to be negligible in urine, an ether extract was made after acidification and this was carried directly through the Schechter-Haller procedure (*7*). It was found that the troublesome emulsions formed during the ether extraction of water-protein solutions of the tissues could be satisfactorily handled by the addition of saturated ammonium sulfate. Standard solutions of chlorobenzilate were run simultaneously with each set of analyses. By adding known quantities of chlorobenzilate to control tissues, urine, and feces, satisfactory recoveries were obtained.

In the excretion studies 24-hour stool and urine collections were taken from each dog. These daily collections of urine were analyzed individually, except for the initial collections. Feces were pooled and analyzed at the end of the collection period. After two preliminary studies the following technique was established. Urine and feces were collected for a total of 10 days. During the second 5-day period the compound was not administered in order that the rapidity with which the compound was excreted could be followed.

Results. The results are presented in Table III. Chlorobenzilate was excreted in the urine in large quantities, an indication that the compound is absorbed rapidly and excreted through the kidneys. Only small amounts of chlorobenzilate were found in the feces. After the compound was withheld, the amount of chlorobenzilate in the urine rapidly diminished until no chlorobenzilate could be analyzed following the third day of withdrawal from the compound. These studies were performed twice during the chronic feeding experiments with the dogs, with essentially identical results.

Urine from the two low-level dogs was collected and extracted with ether, both before and after acidification. Only 17% of the compound was found to be extracted without acidification. Approximately 83% would therefore appear to be in a water-soluble form. A 7-day collection of urine from the high-level dogs was extracted with ether after acidification and the ether extract evaporated on the steam bath. This resulted in a dark-brown, semisolid material. No ester group could be demonstrated in this material.

Because one of the requirements for chlorobenzilate's acaricide activity is the ethyl ester group (*7*), a portion of the extract was tested for such activity with negative results. However, as the compound excreted gave the Schechter-Haller reaction, the molecule must contain the 4,4′-dichlorodiphenyl methyl group.

Ultraviolet absorption curves of the excreted material failed to give identifying absorption maxima. Absorption curves of the colored complex formed in the Schechter-Haller reaction gave identical curves with the excreted product and chlorobenzilate. The melting points of the nitrated materials proved to be the same (206° uncorrected).

Tissue Storage by Dogs

Method. The method described for the determination of chlorobenzilate was used. The tissues analyzed for chlorobenzilate were obtained from the dogs undergoing the chronic feeding test and at the time of sacrifice at termination of the 35-week study. Tissues examined included the blood, liver, kidney, fat, muscle, and brain of each dog.

Results. The results of these analyses are given in Table IV. Some chlorobenzilate was found in blood, liver, and kidney. As the amount found in the liver and kidney was essentially identical to that found in the blood, it appears that the amounts analyzed in these tissues could be attributed wholly to the relatively large quantities of blood in these organs. Therefore, chlorobenzilate is evidently not stored in any of the tissues of the animal body.

Table III. Excretion of Chlorobenzilate in Dogs

(Urine analyzed daily, feces pooled and analyzed at end of 10-day period)

	12.8 Mg./Kg./Day						64.1 Mg./Kg./Day					
	Dog C-187, Male			Dog C-188, Female			Dog C-194, Male			Dog C-190, Female		
Day of Collection	Compound administered, mg.	Compound Found, Mg. Urine	Feces	Compound administered, mg.	Compound Found, Mg. Urine	Feces	Compound administered, mg.	Compound Found, Mg. Urine	Feces	Compound administered, mg.	Compound Found, Mg. Urine	Feces
1	92.3	22.3		78.2	16.2		551.1	125.3		621.6		
2	92.3	37.5		78.2	19.0		551.1	116.3		621.6	176.7	
3	92.3	63.2		78.2	39.4		551.1	99.3		621.6		
4	92.3	30.7		78.2	34.4		551.1	168.5		621.6	122.3	
5	92.3	32.5		78.2	41.5		551.1	33.6		621.6		
6	0	6.3		0	5.6		0	40.7		0	164.3	
7	0	8.1		0	7.5		0	14.9		0		
8	0	0		0	0		0	1.3		0	7.0	
9	0	0		0	0		0	0		0	0	
10	0	0		0	0		0	0		0	0	
Total	461.5	200.6	19.8	391.0	163.6	29.5	2755.5	599.9	182.0	3108.0	470.3	205.0
% of amount administered		42.67	4.30		41.84	7.54		21.77	6.61		15.13	6.60
Total excreted, mg.		220.4			193.1			781.9			675.3	
Total % of amount administered		46.97			49.38			28.38			21.73	

Table IV. Determination of Chlorobenzilate in Tissues of Dogs and Rats

Dog No.	Chlorobenzilate Administered, Mg./Kg./Day	Chlorobenzilate Found, P.P.M.					
		Blood	Brain	Fat	Liver	Kidney	Muscle
C-187	12.8	8.5	1.3	2.4	3.2	1.3	0
C-188	12.8	9.4	0	0	22.5	12.5	0
C-190	64.1	31.6	0	0	23.6	29.4	5.2
C-194	64.1	17.3	5.6	0	0	12.6	0
Rat No.	*P.P.M. in Diet*						
3409–3410	500 (17 wk.)	...	5.9	4.8	25.1	...	3.9
4420–4422	800 (44 wk.)	...	8.3	9.5	18.4	27.0	6.7
4423–4425	800 (44 wk.)	...	0	6.4	15.2	24.7	0
4426–4431	800 (44 wk.)	...	3.8	7.2	35.1	9.4	5.0
4433–4435	800 (44 wk.)	...	3.1	4.4	14.7	13.5	5.1
4438–4439	800 (44 wk.)	...	4.4	8.5	14.8	17.9	5.1

Tissue Storage by Rats

Method. Liver, fat, muscle, and brain from rats which had been fed a diet containing 500 p.p.m. of technical chlorobenzilate for 17 weeks, and liver, fat, muscle, brain, and kidney from rats fed a diet containing 800 p.p.m. for 44 weeks, were analyzed for storage of this material, according to the method described above. It was necessary to pool tissues from several rats in order to obtain a sufficient sample for analysis.

Results. The results of this study are presented in Table IV. Insignificant quantities of chlorobenzilate were found in muscle, fat, and brain, while quantities found in the liver were comparable to that found in the liver of dogs. Although no blood analyses were performed in rats, it appears that these studies confirm the tissue analyses in dogs and that the quantity of material found in the liver can be attributed to the large quantity of blood present in this organ.

Discussion

The results of the acute oral administration studies with mice and rats indicate that chlorobenzilate is typical of the chlorinated hydrocarbons in that there is a relatively nonspecific type of toxicity. As a result, the data are somewhat erratic—that is, the mortality does not increase smoothly with an increase in dosage level. This is a frequent observation in dose-mortality curves having a shallow slope.

The results of the analytical studies indicate that chlorobenzilate administered orally to dogs is readily absorbed and rapidly excreted in the urine and feces and is not appreciably stored in the tissues. These results are in contrast to those that have been found following oral administration of other chlorinated insecticides. Dichlorodiphenyltrichloroethane (DDT), which may be considered as one of its most closely related analogs in this field, has been found to be excreted slowly over a long period of time (*2, 6*), and to be stored in the tissues of animals, especially in the fat (*2, 6*).

DDT appears to be metabolized in the body by dechlorination to the corresponding acetic acid, which probably accounts in part for the products found in the urine of animals fed DDT. Chlorobenzilate also appears to undergo a change in the body which results in the acid form. This is a much simpler change than that which occurs with DDT and involves only the hydrolysis of the ethyl ester.

From the metabolism studies previously presented, it is apparent that the metabolism of chlorobenzilate has resulted in a molecule that contains the unchanged 4,4′-dichlorodiphenyl methyl group and that it is probably excreted as the dichlorobenzilic acid, although the hydroxyl group has not been identified.

The results of the tissue analyses indicate that there is probably no storage of chlorobenzilate. The relatively higher amounts found in the liver and kidney can probably be explained by the greater amounts of blood found here than in other tissues.

Summary

The acute oral administration of technical chlorobenzilate in mice and rats indicated that the LD_{50}'s for either of these species is slightly greater than 700 mg. per kg. The acute oral administration of 25% xylene emulsion to rats also indicated an LD_{50} slightly greater than 700 mg. per kg. in terms of chlorobenzilate. Data for rats with the wettable powder and for mice with the emulsion and wettable powder were inadequate for analysis.

The acute and repeated dermal applications indicated that only a mild to moderate degree of skin irritation occurs, which rapidly subsides after the material is removed from the skin of rabbits. No systemic toxicity or mortality could be attributed to chlorobenzilate.

A 2-year chronic feeding study with rats indicated that the maximum tolerated dietary level is approximately 500 p.p.m. No significant difference was observed between the mortality occurring in the experimental animals and the controls. No significant gross or microscopic pathology could be attributed to the feeding of chlorobenzilate during this 2-year period.

Dogs tolerated technical chlorobenzilate at levels as high as 64.1 mg. per kg. per day for 35 weeks without signs of toxicity or gross or microscopic pathology. Metabolism studies performed upon the dogs undergoing the chronic feeding study indicated that the 4,4′-dichlorodiphenyl methyl portion of the chlorobenzilate is rapidly excreted in the urine and that there is no significant storage in tissues. Similar studies in rats substantiated these data.

Literature Cited

(1) Alexander, C. C., Geigy Agricultural Chemicals, Bayonne, N. J., personal communication.

(2) Finnegan, J. K., and others, *Proc. Soc. Exptl. Biol. Med.*, **72,** 357 (1949).

(3) Finney, D. J., "Probit Analysis, A Statistical Treatment of the Sigmoid Response Curve," Cambridge University Press, Cambridge, 1952.

(4) Geigy Chemical Corp., Bayonne, N. J., Technical Bulletin, April 15, 1953.

(5) Harris, H. J., Geigy Chemical Corp., "Tentative Method for the Analysis of Compound G-23992 as Spray Residue," 1953, unpublished.

(6) Laug, E. P., *J. Pharmacol. Exptl. Therap.*, **86,** 332 (1946); **98,** 268 (1950).

(7) Schechter, M. S., and Haller, H. L., *J. Am. Chem. Soc.*, **66,** 2129 (1944).

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