

Memorandum

TO : Dr. H. Blumenthal, Chief
Petitions Review Branch (SC-970)
Division of Pharmacology and Toxicology

FROM : Dr. Eleanor L. Long
Pathology Branch (SC-940)
Division of Pharmacology and Toxicology

DATE: September 16, 1969

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P-144_a-69

SUBJECT: Daconil (tetrachloroisophthalonitrile). Also called DAC-2787

PESTICIDE PETITION NO. 9FO-743

Diamond Shamrock Company
Painesville, Ohio
(AF 25-202)

I have reviewed slides and data on Daconil on 2 previous occasions. In the first part of this memo (P-144-69) dated August 8, 1969, I reported on slides from dog project 200-206 which Dr. R.E. Voelker, one of the pathologists from Hazleton Laboratories, Inc. (which has been performing the animal studies on Daconil) and I studied together.

In this communication, I shall review Hazleton rat project 200-175, which was submitted some time ago, but has not been reviewed previously as, due to a mistake, it was not received by PRB until August 6 of this year.

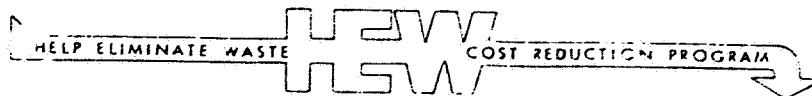
TABLE 1

Group	Rats Started	Dietary Level		No. Rats Sacrificed			No. Exam. Micros.	
			PPM	20Wk.	23Wk.	76Wk.	20-23Wks.	76Wks.
1 (Control A)	30	0	0	10	0	20	10	20
2	30	0.05	500	10	0	20	10	20
3	30	0.1	1000	10	0	20	10	20
4	30	0.5	5000	0	30	--	10	--
		In 10% corn oil from week 5.						
5 (Control B) Begun 2nd wk.	30	0	0	0	30	--	10	--
		(10% corn oil)						

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A. Methods

Groups of rats equally divided by sex were treated with Daconil (a mixture of DAC-2787 with minute amounts of related compounds similar to what has been fed in the other animal studies and what I have termed "DAC Mixture"



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in previous memos) as indicated in Table 1. Because of refusal of food, Group 4 was taken off Daconil the second week (at which time Group 5 was started) and fed the basal, corn oil-enriched diet only for 3 weeks; from weeks 5-18 the feeding of 0.5% Daconil in corn oil was resumed, the animals being pair-fed with Control B. During life, a record was kept of growth and food consumption. When rats were killed (at time intervals indicated in the table) they were autopsied and their organs weighed. Microscopic examination was performed on equal numbers of males and females, the organs so studied being liver and kidney at 20 and 23 weeks; and liver, kidney, bladder, and thyroid at 76 weeks.

The terms "significant" or "significantly" used below refer to statistical significance, with $p=0.05$.

B. Effects

1. Depression of growth at 0.5% in comparison with Control A but not B.
2. Significantly higher food consumption and somewhat increased rate of growth in 0.1% females in comparison with Control A.
3. Decreased survival after 76 weeks in the 0.1% males (3/10) in comparison with Control A males (6/10).
4. Absolute and relative increase after 76 weeks in kidney weight in the 0.1% males (6.23 grams and 1.04% body weight) in comparison with those of Control A (4.29 grams and 0.633%); the kidneys of the 0.1% females were somewhat (but not significantly) larger than those of their respective controls.
5. Significant increase in weights of the female caca, both full and empty, at 0.1% after 76 weeks.
6. Dose-related histopathologic changes in the kidneys comparable to those found in the other rat studies and primarily involving the proximal tubule, after 5 months the terminal segment or pars recta only but after 18 months the entire length. After 5 months the males at all 3 dosages showed tubular hypertrophy ranging from slight at 0.05% to moderate at 0.5%, but in the females the lesion was limited to slight vacuolation of the epithelium and was seen only at the 2 upper levels (0.1% and 0.5%). After 18 months, however, the tubules in both sexes at both treatment levels revealed abnormalities ranging from moderate at 0.05% to severe at 0.1% in the males, and slight to moderate at corresponding levels in the females; in both sexes the changes consisted not only of hypertrophy and vacuolation but also of epithelial cell irregularity and protein imbibition and, in the males, tubular dilatation also. Another

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18-month change recorded was pigmentation. Though only of slight degree and present in 3/8 female rats at 0.1%, it may have been of some significance in this sex as it was absent in all the other female groups at both time intervals. Though absent in the 18-month male controls, its presence in slight to moderate degree in both male test groups at this period is of dubious significance, as at 5 months all 5 male groups, control as well as treated, showed approximately this amount. Furthermore, as in the other studies, there seems to be no correlation of microscopic pigment with gross greenish cortical discoloration, which was stated to have been present in 4/10 0.1% rats though 4 of the 9 had no recorded microscopic pigment and only a few animals with microscopic pigment in the other groups had this gross discoloration. The only point that is clear is that data on renal pigmentation due to Daconil continue to be conflicting.

7. Mild but dose-related histopathologic changes after 18 months in the liver at both 0.1 and 0.05%, consisting of a slight to moderate increase in bile duct proliferation in comparison with the very small amount in the controls and portal fibrosis (the latter in 3 test rats but no controls); there were also solitary hyperplastic nodules in 3/12 rats at 0.1% but in only 4/12 at 0% and 1/15 at 0.05%. Hazleton states that there was no effect on the liver at these levels but the data prove otherwise.

DISCUSSION AND CONCLUSIONS:

In this rat study, the feeding of Daconil for 18 months produced changes in both liver and kidneys at doses as low as 500 ppm. The kidney changes elicited in this experiment are of the same type produced by the many others done on Daconil at both higher and lower levels. The major lesion seems to be within the proximal tubule (at least in rats). The only unsettled question in regard to the kidney (except that of whether very low doses will induce changes after prolonged feeding, the answer to which should be forthcoming when rat study 200-205 now in progress is completed) concerns pigment. As noted above, the data are conflicting, but from the slides I have examined I am inclined to believe that this compound has been responsible for renal pigmentation. However, its nature remains a question, although the finding of slightly elevated urinary bilirubin in dogs at 120 ppm suggests the possibility of subclinical hemolysis.

The finding of pathological changes in the liver at 1000 and 500 ppm are unexpected, as in previous chronic studies there seemed to be no changes at a dose as high as 1500 ppm. The apparent discrepancy may be the result

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of examining too few animals at the higher doses. The pathology at these lower levels would also be somewhat alarming were it not for the fact that other rat studies have shown no effect on the liver after 3 to 4 months from doses below 500 ppm, i.e., from 4 ppm up to 250 ppm, and for the negligible residue tolerance being requested no more is necessary.

In summary, rat project 200-175 has supplied additional information on the nature of the changes induced by Daconil. None of this provides any reason to deny the negligible residue tolerance which has been requested for this fungicide.

cc: SC-970 (Dr. Whitmore)
SC-330
SC-310
SC-903 (Dr. Friedman)
SC-940 (Dr. Richardson)(Dr. Long 2)
VM-100
PP No. 9FO-743

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