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BF216

March 1, 1971

Request for tolerances of Daconil (2,4,5,6-tetrachloro isophthalonitrile) and its metabolite 4-hydroxy-trichloroisophthalonitrile, on various crops.

Mr. Frank McFarland
Director, Division of Regulations & Petitions Control (BF-320)

PESTICIDE PETITION No. 1F1024 file

Diamond Shamrock Corporation
Cleveland, Ohio 44115
(AP 25-202)

Attached is a summary of the most recent toxicological studies submitted in support of the safety of Daconil as a fungicide on various crops, done by E. C. Hagan, Division of Toxicology. Data discussed in this evaluation are a teratology study in rabbit and 2-year feeding studies in rat and dog.

Data from the rabbit study show Daconil is not a teratogen in this species.

In both the chronic dog and rat studies basic issues of safety have revolved around kidney pathology described as: fine vacuolation and swelling of cells lining the proximal tubules in the renal cortex. This same lesion has been characteristic of a number of prior feeding studies. The present submission is the last of a series of studies and were designed to reach levels where this lesion would be absent. During the interim sacrifice periods early in these studies slides were examined by Dr. E. Long, Division of Pathology. For all practical purposes, Dr. Long's reading of the slides agreed with those of the pathologist in the laboratory that carried out these studies (Hazleton Laboratories). Thus, although Dr. Long did not examine the slides at termination of the study there is no reason to believe her conclusions would differ materially from those of the Hazleton Laboratory's pathologist. In addition Diamond Shamrock, the sponsor, solicited the opinion of an independent pathologist, Dr. Hans Stemmler of Kettering Laboratories. Dr. Stemmler's opinions are more liberal in that he saw no abnormalities at levels where the Hazleton group reported minimal effects. We are led then to conclude, (a) that Hazleton's pathologist has read the slides conservatively, and (b) that it is likely that their (Hazleton's) conclusions would be in essential agreement with those of Dr. Long.

It should also be kept in mind that even at very high levels of intake (1500 ppm) Daconil did not appear to effect either the general well being or longevity of animals under study. That none of the usual parameters such as electrolyte balance, blood urea nitrogen, urinary pH, transaminase, etc., that should be indicative of kidney or kidney-adrenal axis disturbance,

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deviated significantly from normal values. Finally, it should be noted that at the levels fed in these studies there was a repair mechanism able to erase damage noted at 12 months of feeding, after 24 months on diet.

For all the pathologists there is general agreement that for the dog 60 ppm represents a no effect level with effects at 120 ppm questionable. In the case of the rat although both Dr. Long and Hazleton noted minimal effects at all feeding levels, partway through the study, at termination neither Hazleton or Dr. Stemmler saw effects at 60 ppm. For reasons discussed above it is reasonable to accept this conclusion.

A further argument for this conclusion, i.e., dog no effect c.a. 120 ppm and rat no effect c.a. 60 ppm is the fact that both species respond with an identical lesion which suggests a similarity in susceptibility. Indeed when calculated in a mg/kg bases the no effect levels for both species is c.a. 3 mg/kg.

Mr. Hagan has calculated an estimated daily intake based on the tolerances as requested by the petitioner. These, using a conservative figure for peanuts to include a high consumption of peanut butter, would equate to approximately 1 mg/day.

Employing a 100 fold margin safe intake would be 0.03 mg/kg or approximately 1.8 mg/day. Thus, in terms of Daconil per se the tolerances as requested are safe.

We note, however, that M. F. Cox, DPCT (Jan. 6, 1970) asks a number of questions about the nature of residues in meat and milk as well as some of the crops involved. Until these questions are settled and we have a final estimate for the presence of the hydroxy metabolite we are unable to complete our evaluation.

CONCLUSIONS:

1. Data submitted with this petition show:

   a) Daconil is not a teratogen in rabbits.

   b) No effect levels in a chronic dog study are definitely established at 60 ppm with questionable effects at 120 ppm.

   c) No effect level in a chronic rat study is estimated to be 60 ppm.

2. In terms of Daconil per se the safety of the requested tolerances are supported by this data.

3. Final evaluation as to safety should await answer to questions posed by DFCT, particularly as regards the hydroxy metabolite.

H. Blumenthal, Ph.D.
Chief, Petitions Review Branch
Division of Toxicology (BF-148)

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ADDENDUM:

We have checked back into the record and find that no where has a complete evaluation of the reproduction data been done. It is our opinion that no final decisions on Daconil should be taken before this is done.