UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: Decisions Resulting from Conference of November 7, 1974 with Representatives of Diamond Shamrock Chemical Company on Pathologic Effects of Daconil (2,4,5,6-Tetrachloroisophthalonitrile) in Rats

DATE: December 13, 1974

FROM:

TO: Mr. Jesse E. Mayes, Acting Chief
Coordination Branch
Registration Division (WH-567)

Rec'd Chem. Br. DEC 31 1974 PP# 1230

File 2F1230

Pesticide Petition No. 2F1230

Diamond Shamrock Chemical Co.
300 Union Commerce Building
Cleveland, Ohio 44115

Attached is a memo of the conference.

(1) The petitioner should be notified that my decision as a result of the conference is that another rat feeding study of 3 or 4 months' duration on Daconil will be necessary to establish the exact type of renal change at the lowest levels which have been tested, 4 to 60 ppm, and to attempt to determine the true no-effect level, as insufficient evidence has been presented to prove that the changes found at these low levels, i.e., vacuolation and severe degeneration of the epithelium of the proximal tubules in the juxta-medullary portion of the cortex, were not related to the administration of Daconil. However, although I originally thought another 2-year study would be needed, I now believe that one of only 3 or 4 months should be sufficient, as vacuolation first appeared at the lowest dose, 4 ppm, at 3 months. I suggest the Charles River C-D strain, as this was used in previous studies, and a broad dosage range as far down as 2 and 1 ppm. Laboratory tests will not be necessary. As there is no indication that other organs are affected at these low levels, only the kidneys need be examined, but microscopic study of these organs from every rat is essential. To ensure that drying artefacts and autolysis do not occur, there should be absolutely no delay in getting kidneys into formalin (or other fixative) after removal from the body.

(2) In reviewing new data submitted on the 4-hydroxy metabolite of Daconil, I was disturbed by the high spontaneous incidence of moderate to severe renal disease at all levels, including the controls, in the 4-month feeding study in the Sprague-Dawley rat, as this makes detection of any possible effect of treatment very difficult. Also, animals that develop such severe disease so early in life (by 6 months of age) are not apt to survive until the termination of a 2-year rat

experiment. In view of this, I should like to suggest that, if the 2-year rat feeding study on this metabolite has not already been started, a strain with less spontaneous kidney disease be used. The diet should also be checked for nutritional adequacy as well as for the possible presence of toxic agents. Consideration might be given to using Purina Rat Chow, which has given excellent results in my experience.

Eleanor L. Long, M.D.
Pathologist
Toxicology Branch
Registration Division (WH-567)

Eleanor L. Long

cc:
CB ✓
EEEB
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PP No. 2F1230

Attachment

Init:CHWilliams 12/13/74
ELLong/ccw 12/13/74