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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Paradichlorobenzene - Rebuttal of Reviews of Two-
Generation Reproduction (Inhalation) Study and 21-Day
Dermal Toxicity Study in Rats

Submission No. S380805
HED Project No. 0-1833
Caswell No. 632

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Action Requested: Respond to rebuttals of reviews of a two-generation reproduction study in rats by the inhalation route and a 21-day dermal toxicity study in rats.

Background and Recommendations: Tox Branch II has reviewed the additional data provided and considered arguments concerning the two referenced studies provided by the Chlorobenzene Producers Association. Based upon further deliberations, Tox Branch II makes the following recommendations:

- 1) Two-Generational Reproduction Study by the Inhalation Route (MRID No. 411088-01) - The original review of this study presented criticisms of the exposure system and sampling methodologies used to monitor chamber concentrations. In addition, the treatment levels used were such that substantial precipitation of the test article on the coats of the rats may have resulted in an exposure that was in large part by the oral route instead of the inhalation route. Finally, the study did not have an acceptable NOEL due to the occurrence of hyaline droplet nephropathy in male rats at all treatment levels.

132

The CPA has presented arguments defending the exposure system, the monitoring procedures used and the acceptability of the dosing regimen in the study. Tox Branch II rejects these arguments and continues in the assertion that the design of the system was flawed. However, Tox Branch II is convinced at this time that the exposures during the study were maximal if not quantifiable and, due to the method used to generate the test atmospheres, far exceeded any anticipated any real world inhalation exposure.

With respect to arguments presented concerning the absence of a systemic NOEL, the Agency is currently considering the significance of α_2 -globulin and hyaline droplet nephropathy in male rats and has not as yet produced a final position on this issue.

Recommendation: This study should be reclassified as Core - Minimum data. Although the study is deficient as described in the DER, no additional information would be gained by repeating this study.

- 2) 21-Day Dermal Toxicity Study (MRID No. 413150-01) - This study was classified as Core - Supplementary on the basis that no treatment related effects were reported, but the highest dose tested did not reflect a limit dose. The CPA argues that there is no need to test higher treatment levels because the anticipated human exposure is already exceeded at 300 mg/kg as used in the current study. This argument is rejected by Tox Branch II on the basis that this study is intended to evaluate an exaggerated use and is not tied to normal exposure levels of the product.

Recommendation: Retain current classification. This remains a data gap which must be addressed.