UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 1,3-Dichloropropene - Review of a Metabolism Study in Rats

TOX Chem No.: 324A
HED Project No.: 9-0694
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THRU: Marcia van Gemert, Acting Chief
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Registrant: Dow Chemical USA, Midland, MI

Action Requested

Review of a rat metabolism and pharmacokinetics study, following single or repeated oral administration of cis/trans-1,3-dichloropropene.

Conclusions

1,3-Dichloropropene, when administered to rats at 5 mg/kg, either as a single oral dose or repeated oral doses (14 consecutive days), is rapidly absorbed from the gastrointestinal tract, distributed to all tissues examined, and rapidly eliminated in the urine and CO_2, and to a lesser extent in the feces.

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Four major and five minor urinary metabolites were isolated but only two major metabolites were positively identified (1,3-D-mercapturic acid and the sulfoxide derivative) while a third metabolite was tentatively identified as the sulfone.

Discussion

Briefly, the conduct of the study and the results were as follows:

Fischer 344 rats (5/sex) were administered orally (gavage) unlabeled 1,3-dichloropropene (1,3-D) daily for 14 days at the dose level of 5 mg/kg. On day 15, all animals received a single dose of 5 mg/kg of ^{14}C-1,3-D. Urine, feces, and CO_2 were collected for 48 hours after dosing with ^{14}C-1,3-D; the animals were sacrificed (48 hours postdosing) and major tissues were examined for radioactivity content. Additionally, two rats/sex were administered a single dose of 5 mg/kg of ^{14}C-1,3-D and animals were processed as above. Metabolites were isolated from urine (from both groups of rats) and the major ones were characterized using cochromatography with authentic standards.

Results presented by the authors indicate that:

1. 1,3-D is rapidly absorbed from the gastrointestinal tract of male and female rats.

2. 1,3-D is distributed to all tissues examined with higher concentrations found in the nonglandular stomach and urinary bladder in both sexes, 48 hours after dosing.

3. 1,3-D was rapidly eliminated by male and female rats so that within 24 hours postexposure over 90 percent of the test article (and/or metabolites) was eliminated, and by 48 hours postexposure only small amounts remained in the tissues.

4. 1,3-D is excreted rapidly in the urine (63 to 65% of the administered dose) and as CO_2 in the expired air (26 to 27% of the administered dose). A small percentage of the dose (5%) was excreted in the feces. No apparent differences in absorption, distribution, and excretion were observed between sexes.

5. Metabolites were isolated from urine of male and female rats at different time intervals either after repeated exposure or after single exposure to 1,3-D. A total of nine metabolites were present in the

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urine; four major and five minor metabolites were isolated. Two of the major metabolites were positively identified as: 1,3-D-mercapturic acid (representing 26 to 29% of urinary radioactivity), and the sulfoxide derivative (representing 6 to 7% of urinary radioactivity). A third major metabolite was tentatively identified as the sulfone (representing 7 to 8% of the urinary radioactivity). No other metabolites were identified, and no parent compound (1,3-D) was present in the urine. There were no qualitative differences in metabolites between sexes or between singly dosed and repeatedly dosed rats, although minor quantitative differences were observed.

Conclusions

Based on the available data, cis/trans-1,3-dichloropropene, when administered to male and female rats by oral gavage either as a single or repeated doses of 5 mg/kg, is rapidly absorbed, distributed to all tissues examined, and completely metabolized to at least nine metabolites (found in urine). Clearance of 1,3-D-derived radioactivity from the tissues was fast so that within 48 hours postdosing only insignificant quantities remained in the body. No sex-related differences were seen in the absorption, distribution, metabolism, and excretion of 1,3-D. No apparent qualitative differences were seen in metabolites between singly dosed and repeatedly dosed rats. This study is Acceptable.

Additional metabolism data have been earlier submitted by the sponsor and reviewed by the Agency (see memorandum from Q. Bui to L. Rossi dated February 24, 1987 and titled: "Review of 2 Pharmacokinetic Studies with Telone II"). These data (single low oral dose and single high oral dose) were found to be Acceptable. Taken collectively, the available data on the metabolism and pharmacokinetics of 1,3-D in the rat, appear to satisfy the Guideline requirements.

Note: Presently, only two out of nine urinary metabolites were positively identified by the sponsor. We recommend that an attempt be made by the sponsor to identify at least the remaining major metabolites in the urine.

Attachment