CASWELL FILE

(1846) 7-15-86

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JUL 15 1986

MEMORANDUM

SUBJECT: Mancozeb (NRDC) - Submission of Metabolism Data in Response to Data Call-In Notice of January 17, 1983
EPA Accession Nos. 262864 and 262865

Caswell 913A

FROM: Irving Mauer, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769C)

07-10-86

TO: Arvella Farmer, PM 68
Special Review Branch
Registration Division (TS-767C)

THRU: Jane E. Harris, Ph.D., Head
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

7/11/86

7/15/86

Registrant: Rohm & Haas

Action Requested:

Screen the following submitted study for adequacy to satisfy data requirements for a metabolism study in response to the Data Call-In (DCI) Notice of January 17, 1983.

"Rat metabolism study," reported in three parts:

1. Mancozeb Pharmacokinetic Study in Rats, L.J. DiDonato and S.L. Longacre, Report No. 85R-123, May 22, 1986 (EPA Accession No. 262834), representing details of the in-life phase, as well as pharmacokinetic relationships derived from levels of total radioactivity.

2. Summary of ETU and EBDC Analyses in Plasma, Liver, and Thyroid after Mancozeb Administration, S.L. Longacre, May 21, 1986 (EPA Accession No. 262834), which extends the pharmacokinetics to include residue data on this EBDC (as CS_2) and ETU based upon specific chemical analyses in these tissues.

3. Metabolism of C-14 Mancozeb in Rat, S.S. Nelson, Technical Report No. 31H-86-02, May 21, 1986 (EPA Accession No. 262835), which describes the identity and distribution of metabolites in excreta of treated rats, and proposes likely metabolic pathways.

Toxicology Branch (TB) Conclusions:

This memorandum only addresses Registration Division's (RD's) request for a rapid turnaround to assess adequacy of the data. [TB requests RD submit a new buck-sheet for full review and evaluation of this study.]

A preliminary screening indicates this three-part report appears to satisfy the data requirements for a metabolism study in rats, conducted according to acceptable FIFRA Guidelines for General Metabolism (85-1), and designed to show the in vivo conversion of mancozeb employing the radioactively-labeled technical grade (as specified in the January 17, 1983, DCI Notice).

The following summarizes the study procedures and reported results.

Animals:

Young adult (6-wk) Sprague-Dawley male and female rats from Charles River Lakefield, Newfield, NJ.

Test Material:

14^C-Mancozeb (TD 85-136) lot 476.0201, 11.54 mCi/g (= 25,619 dpm/ug)

Dosage Groups (3-5/sex/group):

Group A - Single oral dose of 1.5 mg/kg 14^C-mancozeb

Group B - Single oral dose of 100 mg/kg 14^C-mancozeb

Group C - Two weeks dietary administration of 15 ppm (ai) nonlabeled mancozeb (TD 85-015, lot 43339, 84% ai), followed by single oral pulse dose of 1.5 mg/kg 14^C-mancozeb

Group D - Single oral dose of 1.5 mg/kg ^{14}C-mancozeb

Group E - Single oral dose of 100 mg/kg ^{14}C-mancozeb

Organs/Tissues Sampled:

Groups A, B, and C--Urine/feces, whole blood, plasma, liver and thyroid collected at various times after dosing, and analyzed for ^{14}C-label. Spleen, kidney, heart, lung, brain, bone marrow, fat, gonads and muscle collected at autopsy (96-hr postdose), and analyzed for ^{14}C-label.

Groups D and E--Excretion in bile assessed 6 and 24 hours after dosing.

Reported Results:

- Overall recovery = 92.01 to 124.4% of administered dose for all groups.

- Excretion in feces and urine: by 24 hr, 73.95 to 94.14% of dose; by 96 hr, 87.57 to 119.7% (95-98% of recovered label). In bile, 6.3 to 8.8% (low-dose) and 2.0 to 3.8% (high-dose) within 24 hr.

- Absorption: Low-dose--t 1/2 = 0.7 to 1.0 hr. peaking at 0.32 to 0.33 ppm in plasma within 3 hr. High-dose--t 1/2 = 1.7 hr, peaking in plasma at 18.1 - 18.7 ppm in 6 hr.

- Distribution: Highest in thyroid, peaking in 6 hr (low-dose) and 24 hr (high-dose), decreasing between 24 and 48 hr, then increasing slightly or remaining constant from 48 to 96 hr. Plasma, liver, thyroid, and biliary excretion results suggest nonlinear kinetics between high-dose and low-dose ^{14}C-mancozeb treated rats.

- Overall absorption: 54.8 to 57.7% of an oral dose.

cc: Judy Hauswirth(with CBI, Acc. Nos. 262864/262865)
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