



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

MAR 21 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Estimation of metabolites of Dimilin, (Diflubenzuron)

Tox Chem No. 346A

TO: HED Metabolism Committee
Health Effects Division (H 7509C)

FROM: Henry Spencer, Ph.D. *Handwritten: 3/9/94*
Review Section 3
Toxicology Branch 1
Health Effects Division (H 7509C)

THRU: Karen Hamernik, Ph.D. *Handwritten: K. Hamernik*
Section Head
Review Section 3
Toxicology Branch 1
Health Effects Division (H 7509C)

and Karl Baetcke, Ph.D. *Handwritten: Karl Baetcke 3/21/94*
Chief,
Toxicology Branch 1
Health Effects Division (H 7509C)

COMMENTS AND CONCLUSIONS:

At the request of the HED Metabolism Committee, Toxicology Branch 1 was requested to provide an estimate of the amount of Dimilin, (Diflubenzuron) which would be converted to 4-chloroaniline following ingestion of the parent compound.

The metabolism study completed by Inveresk Research International Limited, Scotland, ITI Project No. 139768, Report No. 6255, and listed by MRID No. 419190-01 has been reviewed recently and was found to be only partially complete with several deficiencies existing in the study.



Recycled/Recyclable
Printed with Soy/Canola Ink on paper
contains at least 50% recycled fiber

The deficiencies include: 1. a thorough attempt to identify Region 3 metabolites in the urine; 2. a discussion regarding altered radioactivity following enzymatic hydrolysis; and 3. a proposed pathway of metabolism for diflubenzuron.

Following a 14 day dosing of "cold" chemical at 5 mg/kg/day and a 5 mg/kg radiolabeled dose on day 15, a 24 hour composite urine sample was collected and analyzed for the various metabolites present. Distribution of the metabolites found in the 24 hour urine for both male and female rats indicated that about 8.1 percent of the total sample residue could have been either 4'-chlorophenylurea or 4'-chloroaniline, or a combination of the two moieties. The total sample residue was approximately 22 percent of the administered radiolabeled dose.

Therefore, the possible amount produced and found in urine from a 5 mg/kg/day 15 day multiple dosing in this study would be between 1 and 2 percent (1.7%) of the final dose.

Additionally, the metabolism study of the 4'-chloroaniline, MRID 41088201 provides limited information on the presence and characterization of metabolites formed following either oral or iv dosing. This limits any attempt to evaluate and/or quantitate PCA formation and its subsequent metabolism to PCAA and beyond from Diflubenzuron exposure.

However, the value of 1.7% does not include the amount of 4'-chlorophenylurea or aniline moieties which would still be attached to various molecular species in such areas as the red blood cell, and highly reactive sites such as the cells of liver and kidney. This value (1.7%) most probably significantly underestimates the amount of 4'-chlorophenylurea and or 4'-chloroaniline which is formed in the body following ingestion of the parent, diflubenzuron.