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

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Caswell # 740

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DEC 18 1986

MEMORANDUM

SUBJECT: Review of Metabolism Study Performed on Simazine Submitted by Ciba-Geigy Corporation. EPA ID Number 100-541

TO: Richard F. Mountfort, PM 23
Registration Division (TS-767)

FROM: Brian Dementi, Ph.D.
Review Section #1
Toxicology Branch/HED (TS-769)

Brian Dementi 12/16/86

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

12/17/86

12/18/87

Applicant: Ciba-Geigy Corporation
Greensboro, NC

Re: Simazine Registration Standard

In response to deficiencies identified earlier in a simazine metabolism study (see review of G.W. Robinson, 9/9/85), Ciba-Geigy submitted a follow-up metabolism study, the review of which is submitted herewith.

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Reviewed By: Brian Dementi, Ph.D.
Section 1, Toxicology Branch (TS-769C)
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DATA EVALUATION REPORT

Study Type: Metabolism (Disposition in the Rat)

Accession Number: 262646

Test Material: Simazine

Synonym: 2-chloro-4,6-diethylamino-s-triazine

Caswell Number: 740

Project Number: 1852

Study Number: ABR-86032

Sponsor: Ciba-Geigy Corporation, Greensboro, NC.

Testing Facility: Stanford Research Institute (SRI), Menlo Park, CA and Ciba-Geigy Laboratories, Greensboro, NC.

Title of Report: Disposition of Simazine in the Rat.

Author(s): G.R. Orr and B.J. Simoneaux

Date Issued: April 30, 1986

Conclusions:

At the low dose of administration (0.5 mg/kg) of ^{14}C-radiolabeled simazine, the principal route of excretion was via the urine, however, at the higher dose (200 mg/kg) the principal route of excretion was via the feces. Significant radioactive residues remained in the tissues of the rat for extended periods of time. Results indicate that 94 to 99 percent of the elimination of radioactive material occurred within 48 to 72 hours with a half-life of 9 to 15 hours. Elimination of the remaining radicactivity exhibited 21- to 32-hour half-life values. Heart, lung, spleen, kidney, and liver appear to be principal sites of retention of radioactivity. However, erythrocytes concentrated radioactivity to higher levels than did other tissues, perhaps due to high affinity of the triazine ring for cysteine residues of hemoglobin, a phenomenon apparently unique to rodent species.*

In addition to the single studies at the two doses indicated, a third study conducted at the same lower dose, but preconditioned with cold simazine for 14 days in general affirmed that saturation of binding sites occurs in most tissues examined. An exception was the erythrocyte, where following preconditioning with cold simazine, radiolabeled simazine was more effectively retained in comparison to other tissues. This suggests a greater potential for erythrocytes to accumulate this compound.

Classification: Core - Minimum

Special Review Criteria

A. Materials

1. Test Compound: Radiolabeled simazine (^{14}C-triazine ring), Description: 0.83 Ci/mg (high dose expt.) and 15.6 Ci/mg (low dose expt.), Purity = ≥ 98% radioactive purity

2. Test Animals: Species: Rat, Strain: Charles River CD, Weight: 160-225 g, Source: Charles-River Breeding Laboratory, Wilmington, MD

B. Study Design:

1. Animal Assignment - Animals were assigned 5 (M,F) each to the following test groups:

Test Group		Dose
a.	Control	Dosing vehicle
b.	Low	0.5 mg/kg (15.6 Ci/mg), single dose
c.	High	200 mg/kg (0.83 Ci/mg), single dose
d.	Preconditioned	14 days with 0.5 mg/kg unlabeled simazine followed by 0.5 mg/kg (15.6 Ci/mg), single dose

Compound administered orally via stomach tube, vehicle was polyethylene glycol (Carbowax 200)

2. Diet Preparation - Test compound was not administered via diet.

3. Animals received food, "Standard Laboratory Diet," and water ad libitum.

4. Statistics - Statistical methods of analysis employed not discussed. At certain points in the discussion of the data, the authors refer to significant differences between various groups, but results as tabulated do not identify which differences are statistically meaningful.

5. Quality assurance was addressed by the manager of Regulatory Affairs and Quality Assurance. It was certified that "any deviations from the approved protocol and standard operating procedures were made with proper authorization and documentation."

C. Methods and Results:

Urine and feces were collected at specified time points during the 7-day dosing period for radioassay. Also, at the time of sacrifice, cages were washed with acetone/water mixture for radioassay. At the termination of the dosing period, blood was obtained from each animal and was fractionated into plasma and red blood cells for radioassay. All animals were then sacrificed and portions of selected tissues removed in the indicated order for purposes of radioassay: heart, lung, spleen, kidneys, liver, fat, gonads, uterus, muscle, brain, bone, and carcass.

Radioactivity Analysis: Tissue and feces were homogenized by grinding at liquid nitrogen temperature. Weighed portions of these homogenates were combusted and counted. Urine and cage wash samples were counted directly. Counting was performed using a Beckman Model 3801 Liquid Scintillation Counter and efficiency was determined by external standardization.

Results: Total recovery of radiolabel ranged from 78.3 to 91.5 percent. Excretion via the urine was the preferential route of elimination for the low and preconditioned low dose studies (50.5 to 66.0%), females exhibiting the higher levels in this range. However, in the high dose experiment, excretion was primarily via the fecal route (54.9 to 63.2%) with females displaying the higher values. These higher values for females are probably not statistically significant findings.

Just why the principal route of elimination shifts from the urine at the low dose to the fecal route at the high dose cannot be satisfactorily explained given the limited information available. The shift could be speculated as due to saturation of metabolic capability via the urinary route, or perhaps as due to limited solubility or poor absorption of the compound by the G.I. tract.

Radioactive residues remained in the tissues of animals from all three test groups. These values ranged 2 percent in the high dose group, 8 percent in the preconditioned dose groups, and 12 percent in the low dose group (re: Table 1). Lower retention levels in the high and preconditioned-low dose groups are considered to be due to relative saturation of simazine binding sites. The study authors indicate (p. 6) that highly perfused, metabolically active tissues such as liver, kidney, lung, and heart in addition to erythrocytes show significant residues in all three test groups. The spleen should also be included in this observation (re: Table 2-3, Fig. 1-2). It should be noted, however, that Tables 2 and 3 referred to by the authors as supporting this claim, do not indicate which points are significantly different.

An interesting finding was that erythrocytes have greater potential to accumulate or concentrate simazine than the other tissues examined. The study authors cite a publication* which is claimed to indicate this as due to "Covalent binding of the triazine ring to an exposed cysteine residue in the chain of rodent hemoglobin. This sulfhydryl moiety is apparently unavailable for binding in the hemoglobin of other mammalian species." A copy of this cited publication has been requested for Toxicology Branch inspection.

Reference

* Hamboeck, H.; Fischer, R.W.; Di Iorta, E.E.; Winterhalter, K.W. (1981) Molecular Pharmacology, 20, 579-584.