California Chem
from Lois' book
2/20/91
1-13-89

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Toxicology Branch (EPA) Review of Simazine and Differences as Seen by the California Department of Food and Agriculture

TOX Chem No.: 740

FROM: Henry Spencer 1/13/89
Review Section II
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (TS-769C)

TO: William Burnam, Acting Director
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THRU: Marion P. Copley, D.V.M., Acting Section Head
Review Section II
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (TS-769C)

EPA's responses to each deficiency noted in the California Department of Food and Agriculture (CDFA) summary are presented below.

Study

1-Year Dog Study, dated March 28, 1988, Study Report No. 87122.

CDFA Deficiency No. 1

No adverse effect indicated or no significant dose-related effect at any level.

EPA Response

EPA review states that weight gains in females were decreased at the highest dose tested with corresponding lowered feed efficiency. One animal in four at the middle dose was also affected.

NOEL = 20 ppm and LEL = 100 ppm established for decreased body weight gain in females and reduced RBC, Hgb and Hct.

EPA does not concur with CDFA that the study is a data gap. An MTD in this type study is not required. The present study (1986) supercedes the older (1964) study.

Core-Grade

The classification of the dog study remains unchanged at Minimum.

Study

Teratology in the Rat, dated April 7, 1986, Study Report No. 83058.

CDFA Deficiency No. 2

Data gap - inadequate study - no adverse effect indicated.

EPA Response

1. The study inadequacy due to lack of purity was overcome by noting the purity of the active ingredient (ai) from the same batch seen in a 90-day dog study.

2. EPA notes that maternal toxicity NOELs and LELs were the same as stated by CDFA.

3. EPA notes that the same adverse toxicity to the fetus (ossification delays at 300 mg/kg and NOEL of 30 mg/kg) were reported by CDFA as by EPA.

4. EPA notes that the lack of test dose analysis was reported in both reviews.

EPA Evaluation

Supplementary but upgradable with additional test material data required which include:

1. How was material prepared (i.e., pulverized, etc., in suspension)?

2. Particle size and distribution.

3. Dosing material analysis.

4. Purity of the ai.

Core Grade remains supplementary per review of D. Anderson dated 10/3/88. Review to be included in FRSTR and also forwarded to RD in FRSTR.

Study

Reproduction in Rat, dated September 14,1965, by Woodard Research Corporation.

CDFA Deficiency No. 3

Lists the study as a data gap with no adverse reproductive effects identified.

EPA Comments

EPA is aware of the several CDFA stated shortcomings in the study and has downgraded the study in a more recent review by H. Spencer 2/89 to Supplementary upon the completion of the FRSTR review (March 1989).

The study was originally commenced under a different concept of toxicity testing than has been evolving over the last 10-12 years.

Under the standards of 1982 guidelines, the Toxicology Branch had allowed a mislabeling of the study review to occur. Upon reevaluation of the rat reproduction study the Tox Branch finds the study as:

1. A data gap.

2. Inadequate because of a lack of information with regard to reproductive parameters.

EPA disagrees with CDFA on the ~~lack~~ need of a reproductive effect being necessary, since the guidelines only suggest that toxicity be evident at the HDT. The reviewer notes a significant weight gain reduction in the males at both 50 and 100 ppm. A reduction in females is also seen but more sporadically. Therefore the adverse effect referred to in the GL's has been met!

EPA agrees with the lack of dose selection justification and no diet analysis as well as the lack of food consumption or individual pup wts.

EPA also notes that fewer than the 20/sex/group for mating were present. Only two doses were used.

There were cases of infertility that were not examined or reported.

Pups were not weighed between birth and weaning for lactational effects and the length of gestation was not reported.

The reproductive NOEL can not be determined due to the lack of so many parameters now required.

Only the fact that animals were able to continue in their reproductive capacity is one able to assume a NOEL >100 ppm in the study.

Mutagenicity

CDFA

No data gaps in any of the three areas of mutagenicity testing.

EPA Comments

EPA does not have record of reviews on these studies in the 1-liner. There is a data gap for all three areas of mutagenicity.

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

SIMAZINE

SB 950-129, Tolerance # 213

August 11, 1986
Rev. October 8, 1987
Rev. November 6, 1987
Rev. June 15, 1988

I. DATA GAP STATUS

Combined (chronic + onco) rat:	No data gap, possible adverse effect.
Chronic dog:	✓Data gap, inadequate study, no adverse effect indicated.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	— ✓Data gap, inadequate study, no adverse effect indicated. now — indg 88. — indg 90.
Teratology, rat:	✓Data gap, inadequate study, no adverse effect indicated.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome mutation:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T880615
Toxicology Summary updated by M. Silva on 6/15/88.

J. Parker 7-1-88
MC 6/15/88

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II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED CHRONIC TOXICITY/ONCOGENICITY - RAT

** 067 67849 "Simazine Technical: 104-Week Oral Chronic Toxicity and Carcinogenicity Study in Rats," (Ciba-Geigy Corporation, Summit NJ, 4/12/88). Simazine technical (Batch FL 850614; purity = 96.9%) was administered in diet to Crl: VAF/Plus CD (SD)Br rats at 0 (90/sex), 10 and 100 (80/sex) and 1000 ppm (90/sex) for 104 weeks. NOEL = 10 ppm (Increased mortality in females; decrease in body weight gain at 1000 ppm--males and 100 & 1000 ppm females; decrease in food consumption at 1000 ppm in both sexes; a decrease in RBC, HGT and HCT was observed in females at 1000 ppm; in males an increase in relative brain, liver, testes/epididymus weights and a decreased heart and relative heart weight at 1000 ppm; in females an increased relative brain, kidney and liver weights at 1000 ppm). **Possible adverse effect** (The incidence of mammary carcinomas, fibroadenomas and cystic glandular hyperplasia was increased significantly at 100 and 1000 ppm in females; at 1000 ppm females showed an increased incidence of a rare kidney tubular adenoma). **Acceptable.** M. Silva, 6/8/88.

059, 56393-56394 "FIFRA Section 6 (a) (2) Report Simazine Rat Chronic/Onco Study Status Report No. 2," Ciba-Geigy, Greensboro, North Carolina, 3/30/87. 87-Week Interim Report. Simazine (no purity stated) at 0, 10, 100 or 1000 ppm in the diet to 80 rats/sex/group; 52-week interim sacrifice of 10/sex/group - **Possible adverse effects:** Increase in mammary gland hyperplasia in 100 (2/10, not statistically significant) and 1000 (6/10) ppm males, Increase in mammary gland adenocarcinoma in 1000 ppm females (5/10), Increase in pituitary gland adenoma in 100 (2/10, not statistically significant) and 1000 (6/10) ppm females; Supplemental data (Interim report). NOEL to date = 100 ppm. NLH, 11/2/87 and J. Gee, 11/6/87.

Conclusion: The interim report (volume/record #'s: 059 56393-56394) stated that a significant increase in mammary gland hyperplasia was observed in 1000 ppm-treated males (6 of 10 rats). In the full report (volume/record #: 067 67849) this finding was not substantiated. At ≤ 1000 ppm, no incidence of mammary lesions (cystic glandular hyperplasia, fibroadenoma, carcinoma or adenoma) were significantly increased over control when statistically tested by Fischer's 1-Tailed Exact Test and Peto's Time-Adjusted Trend Test. **Therefore,** CDFA does not view mammary hyperplasias observed in this study as being related to simazine treatment in male Crl: VAF/Plus CD (SD)Br rats.

058 No record number. SB-950 Rebuttal to #21594, Ciba-Geigy, 2/24/87: States that a new chronic toxicity/oncogenicity study is in progress and will be submitted by April 17, 1988. Record 56393 is a brief interim report. The study has been received at CDFA and reviewed (see above, volume/record #: 067/67849).

CHRONIC TOXICITY, RAT

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034 21594 "Two-Year Dietary Feeding Study - Albino Rats," Hazleton, Falls Church, VA, 1/15/60; Thirty/sex/dose were fed 0, 1, 10 or 100 ppm for 2 years. Purity of Simazine 50W = 49.9 %. mean values rather than individual data, no histopathology on animals dying during study, notation of advanced autolysis in many animals dying during study, notation of advanced autolysis in many animals, two tumors in control animals not examined. Nominal NOEL > 100 ppm. Unacceptable with insufficient information, no effect reported. (J. Gee, 5/1/85) EPA 1-liner: No grade. Systemic NOEL > 100 ppm (HDT)

039 924023 Summary (1964) of 21594

Summary: The two studies in the rat do not agree but the study (volume/record #: 067/67849), tested at a much higher dose level than the earlier study, showed the effect at the high dose. Therefore, the adverse effect from study 67849 is considered noteworthy.

CHRONIC TOXICITY, DOG

064 67846 "Simazine - 52-Week Oral Feeding Study in Dogs," (Ciba-Geigy, 3/28/88). Simazine technical (FL #840988, purity = 96.5%) was administered in the diet for 52 weeks to Beagle dogs at 0, 20, 100, and 1250 ppm (4/sex/group). NOEL > 1250 ppm (No significant dose related effects observed at any level). **No adverse effect indicated. Not acceptable** (No MTD. CDFA requests the pilot studies mentioned in the report). **Possibly upgradeable** with submission of the pilot studies. M. Silva, 6/3/88.

034 21593 "Simazine 80W Safety Evaluation by Oral Administration to Dogs for 104 Weeks," Woodard Research Corp., Herndon, VA, 3/9/64; Three dogs/sex/group were fed 0, 15, 150 or 1500 ppm for 2 years. Nominal NOEL> 1500 ppm. Unacceptable with insufficient information, no adverse effect indentified; No dose or diet analysis, no purity of test article, no clinical observations., no age given, doses not justified and may not have been high enough. (J. Gee, 5/1/85)
EPA 1-liner: Supplementary. No overt signs of toxicity at 1500 ppm. Chronic toxicity and oncogenic potential could not be determined (too few animals) body weight changes at 150 and 1500 ppm.

058 No record number. Rebuttal to #21593, Ciba-Geigy, 2/24/87: States that a new chronic dog study is in progress and will be submitted by April 17, 1988. The study has been received at CDFA and reviewed (see above, volume/record #: 064/67846).

ONCOGENICITY, MOUSE

** 066 67848 "Simazine Technical, 95-Week Oral Toxicity/Oncogenicity Study in Mice," (Ciba-Geigy Corporation, 4/4/88). Simazine technical, (Batch no.: FL 840988; purity = 96.5%) was administered in diet to Crl:CD 1 (ICR) BR mice at 0 (90/sex/group), 40 and 1000 (80/sex/group), and 4000 (90/sex/group) ppm for 95 weeks. NOEL = 40 ppm (decrease in body weight gain, food and water consumption--observed in both sexes at 1000 and 4000 ppm; transitory increase in brain weight, relative brain, liver and kidney weights--females at 1000 and 4000 ppm and relative adrenal and heart weights--females at 4000 ppm; increase

in relative lung and thyroid/parathyroid weights--females at 4000 ppm). There was no oncogenic effect observed with simazine. **No adverse effect indicated. Acceptable.** M. Silva, 6/6/88.

034 21592 "Carcinogenicity Study with Simazine Technical in Albino Mice." Invalid IBT study.

058 No record number. Rebuttal to #21592, Ciba-Geigy, 2/24/87: States that a new oncogenicity study in progress and will be submitted by April 17, 1987. The study has been received at CDFA and reviewed (see above, volume/record #: 066 67848).

REPRODUCTION RAT

045 21590 Reviewed in volume 034.

034 21590 "Three-Generation Reproduction Study in the Rat," Woodard Research Corp., 9/14/65; Twenty per sex were fed 0 or 100 ppm, and 10 males plus 20 females were added in F1 matings at 50 ppm. Simazine at 80% but diets were adjusted to contain the nominal amount of active ingredient (see 058) Unacceptable, no adverse reproductive effect identified. F_0 not necropsied. No food consumption, no individual pup weights, only 1 male and one female pup per litter for histopathology from F3b. Dose selection not justified no analyses of diets for actual content. Reproductive NOEL ≥ 100 ppm. (J. Gee, 5/1/85)
EPA 1-liner: Minimum. Reproductive NOEL > 100 ppm (only dose tested)

TERATOLOGY, RAT

065 67847 "Simazine Technical: A Teratology Study in Rats," (Ciba-Geigy Corporation, 4/7/86). Simazine technical (batch no F1-821846; purity = 98.2%) was administered by gavage to mated (presence of sperm = day 0 of gestation) CR1. COBS CD (SD) (BR) rats at 0 (vehicle = 2.0% carboxymethylcellulose), 30, 300 and 600 mg/kg during days 6 to 15 of gestation. Maternal NOEL = 30 ppm (decreased weight gain and food consumption at 300 and 600 ppm. Developmental NOEL = 30 ppm (increase in head not completely ossified, teeth not ossified, centrum/vertebra not ossified and rudimentary 14th rib). **No adverse effect indicated. Not acceptable** (no analysis of dosing material). **Upgradeable.** M. Silva, **6/23/88.**

056 053580. "Simazine Technical: A Teratology Study in Rats, (Pharmaceutical Div., Ciba-Geigy Corporation, N.J. Study #83058, April 7, 1986). Simazine Technical, lot # FL821846, no purity data, vehicle: 2% carboxymethylcellulose; treatment by gastric intubation on days 6-15 of gestation (positive vaginal smears = day 0, 30, 300 and 600 mg/kg dose levels. NOEL (Maternal): 30 mg/kg (decrease in weight gain & food consumption). (Developmental): 30 mg/kg (minor ossification changes). Unacceptable: No AI purity data, no test article analysis. Upgradeable. YKL 10/87.

TERATOLOGY, RABBIT

** 044 02194 "A Teratology Study of Simazine Technical in New Zealand White Rabbits," Ciba-Geigy, Summit, New Jersey, 3/29/84. Eighteen per group were given 0, 5, 75 or 200 mg/kg by gavage, days 7-19 of gestation. Test article at 97% purity. Maternal NOEL = 5 mg/kg (decreased weight gain, anorexia, nervous tremors at 75 and 200 mg/kg). Developmental NOEL = 5 mg/kg (late resorptions at 75 and 200 mg/kg; reduced fetal weight at 200 mg/kg). Acceptable with no adverse effect. (J. Gee, 5/2/85. M. Silva, 6/15/88.) EPA 1-liner: Supplementary. Maternal NOEL = 5 mg/kg (tremors, abortions, decreased body weight gain and food consumption; fetotoxic NOEL = additional information required.

MUTAGENICITY, GENE MUTATION

Microbial Systems

** 068 67850 "Simazine Technical: Salmonella/Mammalian - Microsome Mutagenicity Assay (Ames Assay)," (Ciba-Geigy Corporation, Greensboro NC). Simazine technical (batch FL 850614; purity = 96.9%) was used in the Ames test at 0 (vehicle = DMSO), 10, 25, 50, 100 and 250 ug/plate on Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537 and TA1538 with and without S-9. No mutagenicity was observed with any tester strain at any dose. Positive controls functioned as expected. Acceptable. M. Silva, 6/9/88.

042 20200 "Comparative Mutagenicity Studies with Pesticides," Summary of various mutagenicity screenings -Unacceptable with no effects noted.

050 38561-2 "In Vitro and In Vivo Microbiological Assays of Six Ciba-Geigy Chemicals," SRI, 3/77. Salmonella, and host- mediated in mice. TA1535 TA1537, TA98 and TA100 at 0, 50, 100, 500, 5000 up/plate +/- S9, 2 trials, 1 value per concentration: missing data, Unacceptable No increase in revertants. upgradeable when clarify number of plates and purity of test article. In 058 there is a statement that SRI has agreed to provide the additional information if available. J. Gee, 2/20/86 and 11/6/87.

Mammalian systems

050 38566 "L5178Y/TK+ Mouse Lymphoma Mutagenicity Test." Ciba-Geigy, Basle, Switzerland, 5/7/84. Simazine, 99.6% lot #209158 at 1, 4, 8, 16, 32, 48, 64 and 80 ug/ml +/- rat liver S9, 5 hours; one trial, one culture/concentration, no increase in mutation frequency; precipitation at 40-80 ug/ml. unacceptable - no confiming trial. (J. Gee, 2/20/86)

MUTAGENICITY, CHROMOSOME ABERRATIONS

** 068 67867 "Chromosome Studies on Human Lymphocytes in vitro," (Ciba-Geigy Limited, 3/24/88). Simazine technical (batch no. 209158; purity= 99.6%) was used on primary cultures of human lymphocytes for 3 hours at 0 (vehicle = DMSO), 6.25, 12.5, 25, 50, and 100 ug/ml with and without activation to test

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for chromosomal aberrations. No increase in chromosomal aberrations was observed with simazine-treated cells when compared to control. Positive controls functioned as expected. Acceptable. M. Silva, 6/10/88.

042 20197 See 20196 in 844.

050 38564 "Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster," Ciba-Geigy, Basle, Switzerland, 2/20/84. 99.6% technical at 0, 1250, 2500 and 5000 mg/kg, orally twice to 6/sex/group; 1000 cells in each of 3/sex/group were analyzed for micronuclei at 24 hours only after second dose. If the effect on cell cycling is not known (report gives no indication) , animals should be sacrificed over 12-72 hours. Also since the LD50 is >5000 mg/kg, dosing to toxic levels as required for the test might be difficult in which case the micronuclei test is not appropriate. No information on PCE/NCE or mitotic index is given. unacceptable - inadequate protocol. No adverse effect. (J. Gee, 2/20/86

058 no record # Rebuttal to #3856, Ciba-Geigy, 2/24/87: Indicates that the Ciba-eigy lab in Basle, Switzerland will provide the requested additional information by June 30, 1987.

MUTAGENICITY, DNA DAMAGE/REPAIR, MISC.

042 20199 "Mutagenicity Screening of Pesticides in the Microbial System" (Mutation Research 10: 19-30 (1986)) Institute of Environmental Toxicology, Japan). Survey of 166 pesticides. No positive effect with simazine reported.

** 050 38563 "Autoradiographic DNA Repair Test on Rat Hepatocytes," Ciba-Geigy, Basle, Switzerland, 12/20/83.) Simazine, 99.6%, lot 209158; primary Rat hepatocytes exposed to 0, 0.4 2, 10 or 50 ug/ml for 5 ours in presence of ^{3}H-TdR; No increase in UDS grains/nucleus. Acceptable (J Gee, 2/20/86)

050 38565 "Autoradiographic DNA Repair Test on Human Fibroblasts," Ciba-Geigy, 12/20/83. Simazine, 99.6% technical, lot #209158; 0, 0.2, 1, 5 and 25 up/ml without activation for 5 hours; No increase in UDS reported fibroblasts CRL1121. Unacceptable Incomplete - no activation. (J. Gee, 2/20/86)

042 20196 "Evaluation of Selected Pesticides as Chemical Mutagens In Vitro and In Vivo Studies," Summary of 20 pesticide survey, UDS/gene conversion - No effects noted. (J. Gee, 5/2/85)

042 20198 See also 20196.

Records #'s 39093 to 39100 - various mutagenicity summaries.

NEUROTOXICITY

Not required at this time.

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Secondary Review of CFDA Responses for Simazine (Jaeger, 2/6/89)

Henry Spencer

Chronic Dog

CDFA reviewed a 104 week dog study (3/9/64) as well as the one which you commented on. They determined the '64 study to be unacceptable. What is EPA's opinion?
Also, please note that CFDA says 1988 Dog study had no MTD. Please comment on the fact that such is not required for dog studies.

Multi-Generation Reproduction Rat

Your wording on page 3 indicates that EPA disagrees that a "lack of a reproductive effect if necessary"; what I believe you mean is that EPA disagrees that a reproductive effect is neccessary and simply because there is no such effect we do not downgrade it, as CDFA does.

CDFA notes that there was no necropsy of F0 parents and overall the impression I'm left with is the lack of sufficient histopath throughout. This is a particular problem for many multi-generation studies reviewed by HED. I'm not sure that HED (formerly TR) has been consistent in their approach to this particular problem, viz. some accept the study, some downgrade it. This has been referred to Bill Burnam in hopes we can resolve the matter collectively. When we discuss it I would like you to be present to participate in the discussions. Thanks.