

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
SIMAZINE

Chemical Code # 531, Document Processing Number (DPN) # 213

SB 950 # 129

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Revised dates: 10/8/87, 11/6/87, 6/15/88, 7/20/89, 8/6/90, 1/8/93, 10/8/93, 1/5/06, and 1/25/08

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	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.

File name: t20071115.wpd

Revised by M. Silva on 6/15/88; J. Gee on 7/20/89; Kishiyama & Silva, 8/6/90; Kishiyama & Silva, 1/8/93; M. Silva, 10/8/93; Kishiyama and Aldous, 1/5/06, and Aldous, 1/25/08.

All record numbers for the above study types through 151769 (Document No. 213-160) were examined or cited in this Summary for future examination. This includes all relevant studies indexed by DPR as of 11/15/07.

In the 1-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

NOTE: The Summary of Toxicology Data for ATRAZINE, a congener of simazine, contains some studies which include simazine.

NOTE: Revision of EPA 1-liners pertaining to the EPA Memorandum (1/13/89) was performed 12/12/89 (M. Silva).

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED, RAT

****213-067 067849** "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 CrI: 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. See next paragraph for a subsequent analysis of this study.

****213-067 067849** McCormick, G. C., "Simazine Technical: Combined chronic toxicity/oncogenicity study in rats," Ciba-Geigy Corp., Greensboro, NC, April 12, 1988. Laboratory Study # 852004. Re-examination of data in 2007 was performed largely to provide tables and additional analysis to aid risk assessment. Sprague-Dawley [CrI: VAF/Plus™ CD@ (SD)Br] were dosed in diet with 10, 100, or 1000 ppm Simazine Technical (purity 96.9%) in a 104-week oncogenicity phase (50 rats/sex/group), and in a chronic phase with 3 components: (1) 10/sex/group were dosed for 52 weeks, then sacrificed, (2) 20/sex/group were dosed for 104 weeks, then sacrificed, and (3) 10/sex of controls and high dose levels were dosed for 52 weeks, then taken off treatment for 52 additional weeks prior to sacrifice. Mean achieved dose levels in the oncogenicity phase treated rats were 0.41, 4.17, and 45.8 mg/kg/day for increasing doses in males and 0.52, 5.34, and 63.1 mg/kg/day for corresponding females. NOEL for males = 100 ppm [findings at 1000 ppm included decreased body weight (24% decrement at 1 year) and markedly decreased food consumption]. High dose males had decreased mortality (likely associated with reduced food consumption). NOEL for females = 10 ppm (based on significantly reduced body weights in 100 ppm females during much of the study, with a 6% decrement at 1 year). Major findings in 1000 ppm females included decreased body weight (decrement of 29% at 1 year); markedly decreased food consumption; highly significantly elevated incidences of mammary carcinomas, mammary fibroadenomas, and mammary cystic glandular hyperplasia, with secondary increases in hematopoiesis (particularly evident in spleen); and statistically significant depression of RBC counts, Hb levels, and HCT, with some

compensatory increase in platelet counts. Uncommon kidney tubular cell tumors were observed, strictly in 1000 ppm rats (1 adenoma and 2 carcinomas in males, and 2 adenomas in females). These should be considered as possible treatment effects. The cited mammary tumors are “possible adverse effects,” observed to occur in this study only at a dose in excess of an MTD. Acceptable. Re-examination by Aldous, 1/24/08.

213-059 056393-056394 Interim report (1 year) for 067849. Gee, 11/6/87.

213-0140 139433 Supplementary information for study 213-067 067849, above, already accepted by DPR. Apparently data were submitted on request of U.S. EPA. This report provides GLC, MS, IR, and NMR data on Batch FL 850614. Purity of technical was noted in the original DPR worksheet. No DPR review is needed for these supplementary data. Aldous, Nov. 2, 2007.

213-0123 138085 104-week Oral Chronic Toxicity and Carcinogenicity Study in Rats (Ovarian Re-evaluation) (Includes Protocol) (73p.), Ciba-Geigy Corp. Safety Evaluation Facility Summit, NJ, 09/01/1993. M. Silva summarized the supplementary data as follows: “Re-evaluation indicates an increase in the incidence of ovarian atrophy and Sertoli cell hyperplasia incidence/severity. Ovarian neoplasia or Sertoliform tubular adenomas did not increase.” Tables of incidences and mean severity of the above observations are recorded in Worksheet Number T950000 of the simazine directory (D00213). (Draft worksheet by M. Silva was produced on or after 7/7/95).

00213-0141 139452 Tacey, R. L., “Simazine technical: measurement of various hormones in rat serum.” Supplementary analytical assays were performed at Hazleton Laboratories America, Inc., Vienna, VA, on March 7, 1990, HBC Project No. 300-038. Serum samples for the present report were taken at 2-year termination of the oncogenicity study: Ciba-Geigy Corp., Greensboro, NC, April 12, 1988, Laboratory Study # 852004, EPA MRID 40614405, DPR Document No. 213-067, Record No. 067849. Males were evaluated for adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), thyroxine (T_4), triiodothyronine (T_3), dihydrotestosterone (DHT), and testosterone. Females were evaluated for estradiol (E_2), prolactin (Prl), follicle stimulating hormone (FHS), progesterone, LH, growth hormone (GH), TSH, T_4 , T_3 , and ACTH. Rats were sampled only once (i.e., not at intervals during the day in order to capture diurnal variation). For technical reasons, sample volumes were typically insufficient to allow a given rat to be evaluated for every desired parameter, hence aliquots were designated for particular hormone assays according to a prioritization scheme. Only 2 to 6 rats/sex/group were evaluated for a given hormone. Body weight gains in high dose males and females were reduced compared to controls by 30% and 40%, respectively. Female 100 ppm body weight gains were slightly reduced (6%). **Due to the above considerations, results of these assays must be interpreted with caution.** Hormone levels appeared unaffected in males. Several changes were notable in females, as follows. It appears that prolactin was increased at 100 and 1000 ppm (dose-related), hence apparent NOEL = 10 ppm for females, and 1000 ppm for males. Estradiol was markedly reduced at 1000 ppm. Other statistically significant trends which may be biologically relevant suggested elevated GH and reduced FSH at 1000 ppm. Progesterone and T_3 had significant trends toward reduction with treatment, but these were of questionable biological significance. Supplementary data. Aldous, 1/25/08.

CHRONIC TOXICITY, RAT

213-034 021594 "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, two tumors in control animals not examined. Nominal NOEL \geq 100 ppm. UNACCEPTABLE with insufficient information, no effect reported. (J. Gee, 5/1/85)

EPA 1-liner: No grade. Systemic NOEL > 100 ppm (HDT)

213-039 924023 Summary (1964) of 021594

Summary: The two long-term studies in the rat do not agree but the study (volume/record # 067/067849), tested at a much higher dose level than the earlier study, showed an effect at the high dose. Therefore, the adverse effect from study 067849 is considered noteworthy. Silva, 6/88.

CHRONIC TOXICITY, DOG

**213-064 067846 "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). NOAEL > 1250 ppm (No significant dose related effects observed at any level). NOEL = 20 ppm (marginal effects on body weight gain at 100 ppm, slight effects in erythroid parameters). No adverse effect indicated. Initially reviewed as not acceptable (No MTD). CDFA requested the pilot study mentioned in the report. Considered possibly upgradeable with submission of the pilot study. M. Silva, 6/3/88. CDFA # 071979 in 213-076 was submitted for dose justification. CDFA Record # 071978 in 213-076, attachment 1, discusses the rationale for dose selection. The study is upgraded to ACCEPTABLE status with no adverse effect identified. (Gee, 7/19/89).

EPA 1-liner: NOEL = 20 ppm and LEL = 100 ppm (decreased body weight gain in females and reduced RBC, Hgb and Hct (1/13/89).

213-076 071978 Copy of an internal memo of Ciba-Geigy discussing the rationale for dose selection for the 52-week study - CDFA # 067846. No worksheet. (Gee, 7/19/89).

213-034 021593 "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 \geq 1500 ppm. UNACCEPTABLE with insufficient information, no adverse effect identified; 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.

ONCOGENICITY, RAT

213-108 117094 An adverse effects disclosure statement was submitted by Ciba-Geigy (July 24, 1992). In the letter it was stated that in June of 1989, Ciba-Geigy initiated two new oncogenicity studies on simazine using female Sprague-Dawley rats derived from the F2b generation of the rat reproduction study (DPR document/record #: 213-103/096434). These animals were exposed to simazine in utero and for 24 months post partum at dietary levels of 0, 10, 100 and 500 ppm. In addition, an age-matched group of control Sprague-Dawley females was employed in the study. The following two separate studies were performed: **Study I:** Treated and control rats were allowed to mate with untreated males, then delivered and nursed the pups through lactation day 21. **Study II:** Animals in this group were treated the same as those in Study I, except they were not mated. The in life portion of this study was completed in June of 1991. The following results were observed after histological examination:

Simazine Technical: Ovarian Neoplasia/Hyperplasia Incidence in Female Sprague-Dawley Rats

In Utero Exposure/Oncogenicity Study

Feeding Level (ppm)	0a	0b	10	100	500
Lesion/Tumor					
<u>NULLIPAROUS FEMALES:</u>					
Hyperplasia (Sertoli Cells)	12/50	9/25	20/50	21/50	31/50
Sertoliform Adenoma	0/50	0/25	0/50	1/50	5/50
<u>PRIMIPAROUS FEMALES:</u>					
Hyperplasia (Sertoli Cells)	17/50	7/25	14/48	14/47	28/49
Sertoliform Adenoma	0/50	0/25	0/48	0/47	1/49

a - The test and control groups were derived from the F2b litter of the 2 generation reproduction study (DPR document/record #: 213-103/096434).

b - This control group was comprised of age-matched Sprague-Dawley females obtained from Charles River Laboratories.

The letter also stated that the incidence of ovarian tumors was not elevated in the combined study previously submitted and reviewed at DPR (DPR document/record #: 213-067/067849), in which animals were dosed up to 1000 ppm. Therefore, the ovarian findings in the two studies described above constitute a new potential adverse effect. M. Silva, 12/31/92 (No worksheet.)

213-0160 151769 This is a communication from Ciba-Geigy to U.S. EPA dated 7/13/92, disclosing a "possible adverse effect" (the Sertoli cell hyperplasias and adenomas shown immediately above). No DPR review of this letter is needed, since the study has been reviewed by DPR. Aldous, 10/23/07.

ONCOGENICITY, MOUSE

**213-066 067848 “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. NOAEL \geq 4000 ppm. 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, Gee, 7/19/89).

213-034 021592 “Carcinogenicity Study with Simazine Technical in Albino Mice.” **Invalid IBT study.**

REPRODUCTION, RAT

** 213-103, -110 096434, 122625 “Simazine Technical: Two-Generation Reproductive Toxicology Study in Rats”, (D.L. Epstein, J. R. Hazelette, & E.T. Yau, Ciba-Geigy Corporation, Research Department, Pharmaceuticals Division, Laboratory Study No.: 882095, 2/12/91). Simazine Technical (purity 96.9%) was fed in diet to Sprague-Dawley rats (30/sex/group) at 0, 10, 100, or 500 ppm for two generations. Systemic Parental NOEL = 10 ppm based on decreased body weight gain and decreased food consumption in both sexes of both generations at \geq 100 ppm. Reproduction NOEL \geq 500 ppm (There were no reproductive effects at any dose.) Originally reviewed as unacceptable (Kishiyama & Silva, 12/30/92), upon submission and review of the requested information the study is now upgraded to acceptable. (M. Silva, 10/5/93).

213-034 021590 “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. F0 not necropsied. No food consumption, no individual pup weights, only 1 male and 1 female pup per litter for histopathology from F3b. Dose selection not justified, no analyses of diets for actual content. Reproductive NOEL \geq 100 ppm. (J. Gee, 5/1/85)

EPA 1-liner: This study was downgraded from Minimum to Supplementary due to a review by H. Spencer 2/89 and the FRSTR review (March, 1989). NOEL > 100 ppm (HDT).

213-045 021590 Reviewed in volume 034.

TERATOLOGY, RAT

**213-105 053580 “Simazine Technical: A Teratology Study in Rats,” (Ciba-Geigy Corporation, Summit, NJ, 4/7/86, Study #83058). Simazine technical (batch no FI-821846; purity = 98.2%) was administered by gavage to mated (presence of sperm = day 0 of gestation) CRL COBS CD (SD) (BR) rats at 0 (vehicle = 2.0% carboxymethylcellulose), 30, 300 and 600

mg/kg during days 6 to 15 of gestation, 25/group. Maternal NOEL = 30 mg/kg/day (decreased weight gain and food consumption at 300 and 600 mg/kg/day. Developmental NOEL = 30 mg/kg/day (increase in head not completely ossified, teeth not ossified, centrum/vertebra not ossified and rudimentary 14th rib). Initially reviewed as having No adverse effect indicated and NOT ACCEPTABLE (no analysis of dosing material) but upgradeable. (Y. Luthra, 10/87 and M. Silva, 6/23/88). Document 213-073, record # 070893 contains the analyses of dosing solutions including homogeneity and stability in the vehicle over 15 days. The study is upgraded to ACCEPTABLE status. (Gee, 7/17/89).

EPA 1-liner: Core Grade is supplementary per review of D. Anderson 10/3/88.

213-073 070893 Analysis of dosing solutions for homogeneity and stability and content. Upgrades CDFA # 053580. No worksheet. Gee, 7/18/89.

213-065 067847 Exact duplicate of 053580.

213-0140 139411 Wetzell, L. T., Simazine Technical: A supplement to teratology study in rats," [relates to study 213-105 053580, above, previously accepted by DPR]. Information submitted per U.S. EPA request includes particle size characteristics of the milled technical material, retrospective evaluation of 2% CMC suspensions such as were used in the study, and source of the animals (Charles River Laboratories, Inc., Kingston, NY). Useful supplementary data. Aldous, Nov. 2, 2007.

TERATOLOGY, RABBIT

**213-044 020194 "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.

GENE MUTATION

Microbial Systems

**213-068 067850 "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 µg/plate on Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537 and TA1538 with and without rat liver S-9. No mutagenicity was observed with any tester strain at any dose. Positive controls functioned as expected. ACCEPTABLE. (M. Silva, 6/9/88).

213-042 020200 "Comparative Mutagenicity Studies with Pesticides," Summary of various mutagenicity screenings -UNACCEPTABLE with no effects noted.

213-050 038561-038562 “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 µg/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

213-050 038566 “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 g/ml +/- rat liver S9, 5 hours; one trial, one culture/concentration, no increase in mutation frequency; precipitation at 40-80 g/ml. UNACCEPTABLE, not upgradeable - no confirming trial. (J. Gee, 2/20/86)

CHROMOSOME EFFECTS

**213-088 086391 “Structural Chromosomal Aberration Test Micronucleus Test, Mouse”, (Dr. Carla Ceresa, Ciba-Geigy Limited, Basle, Switzerland, Laboratory Study no. 881189, 9/15/88). Technical simazine (G 27 692, purity = 99.6%) was administered in one oral dose (gavage) to 8 mice (Tif: MAGF, SPF)/sex/group. Part I: Harvest was at 16, 24 and 48 hours for control (0.5% Carboxymethyl cellulose) and simazine (5,000 mg/kg--limit test). Part 2: Harvest was at 24 hours for control (0.5% CMC) and simazine (1250, 2500, and 5,000 mg/kg--limit test) treatments. 1000 polychromatic and normochromatic erythrocytes each were scored/animal (5/sex/group) for micronucleus assessment. The PCE/NCE ratio/animal was determined by counting a total of 1000 erythrocytes. Polychromatic erythrocytes with micronuclei did not increase relative to negative controls, after treatment with simazine. ACCEPTABLE. (Kishiyama & Silva, 7/24/90).

**00213-0141 139446 Hertner, Th., “Simazine Technical: Structural chromosomal aberration test, micronucleus test, mouse,” Ciba-Geigy Corp., Greensboro, NC, 8/27/92. Laboratory Study # 921086. Investigators used young male and female Tif: MAGf (SPF) mice, 5/sex/group, in a micronucleus study with Simazine Technical (previously called G 27692 Tech.), Batch FL-850614, 96.9% purity. Arachis oil was the vehicle at 10 ml/kg. Investigators, blind to treatment, evaluated 1000 PCE's per mouse from stained femoral bone marrow cell preparations. Investigators first determined that mice could tolerate the limit test level of 5000 mg/kg simazine. The definitive study had pre-treatment intervals of 16, 24, and 48 hours. Controls and 5000 mg/kg groups were conducted at all three intervals, whereas 1250 and 2500 mg/kg groups were conducted at 24 hr interval only. A functional positive control group (cyclophosphamide, 64 mg/kg) was employed at 24-hr pre-treatment only. All tests were negative. Acceptable, with no adverse effects. Aldous, Nov. 6, 2007.

**213-068 067867 “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 µg/ml with and without activation to test 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).

213-042 020197. See 020196 under "DNA DAMAGE," below.

213-050 038564 "Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster," (Ciba-Geigy, Basle, Switzerland, 2/20/84) Simazine 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)

213-058 no record # Rebuttal to #38564, Ciba-Geigy, 2/24/87: Indicated that the Ciba-Geigy lab in Basle, Switzerland was to provide the requested additional information by June 30, 1987.

DNA DAMAGE

**213-088 086392, "Tests for Other genotoxic Effects Autoradiographic DNA Repair Test on Rat Hepatocytes", (Dr. Thomas Hertner, Ciba-Geigy Limited, Basle, Switzerland, Laboratory Study No. 891412, 12/7/89). Simazine (G 27 692 technical; purity = 96.9%) at concentrations of 0 (DMSO or culture medium), 1.57, 4.72, 14.17, 42.5, 85 and 170 mg/ml were assayed with primary cultures of rat hepatocytes. Treatment period was for 16-18 hours in both the original and confirmatory tests. Analysis was performed by autoradiography (3 slides/dose, 50 cells were scored/slide). Simazine doses did not induce DNA damage to primary hepatocytes. Positive controls functioned as expected. ACCEPTABLE. (Kishiyama & Silva, 7/23/90).

213-141 138448 This is a clarification of the basis for the highest concentration used in study 213-088 086392, above. Investigators noted that 170 mg/ml caused fine precipitates in the medium, hence higher dose levels were not attempted. Aldous, Nov. 6, 2007 (no worksheet).

213-042 020199 "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.

**213-050 038563 "Autoradiographic DNA Repair Test on Rat Hepatocytes," (Ciba-Geigy, Basle, Switzerland, 12/20/83, report 830640.) Simazine, 99.6%, lot 209158; primary rat hepatocytes exposed to 0, 0.4 2, 10 or 50 g/ml for 5 hours in presence of 3H-TdR; No increase in UDS grains/nucleus. ACCEPTABLE. (J Gee, 2/20/86)

213-0068 67851 (exact duplicate of Record No. 038563, above)

213-050 038565 "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)

213-042 020196 "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)

213-042 020198 See also 020196.

039093 to 039100 - various mutagenicity summaries.

NEUROTOXICITY

Not required at this time.

SUBCHRONIC STUDIES

**00213-052 038849 Tai, C. N., Breckenridge, C., and Green, J. D., "Simazine technical: subacute oral 13-week toxicity study in dogs," Ciba-Geigy, Summit, NJ, April 12, 1985. Laboratory Study # MIN 842226, Toxicology/Pathology Report No. 85022. Four beagles/sex/group were dosed in diet with 0, 200, 2000, or 4000 ppm Simazine tech., 97.5% purity, Batch FL 840988, for 13 weeks. Achieved dose levels were 6.9, 65, and 134 mg/kg/day in treated males, and 8.2, 64, and 137 mg/kg/day in females. NOEL = 200 ppm. Findings in both sexes at 2000 and 4000 ppm included decreased food consumption and decreased body weight gain (marked body weight losses at 4000 ppm). A few additional findings appear to be related to poor nutritional status. Dogs had reduced absolute heart and testes weights at 2000 and 4000 ppm (these organs also reduced in relative weights at 4000 ppm). Both 2000 ppm and 4000 ppm males had reduced circulating albumin and plausibly associated alterations in electrolyte plasma concentrations (calcium reduced and chloride elevated): these changes were observed at week 13 only. Liver relative weights were significantly elevated in 2000 and 4000 ppm males and in 4000 ppm females. Urinalysis findings of ketones and slightly reduced pH appeared to be associated with treatment at these levels. Tremors were observed in all but one dog at 4000 ppm, the first such observation being at week 9. RBC parameters were sharply reduced at 4000 ppm in both sexes (HCT, Hb, RBC counts), with apparent compensatory increases in platelet counts (significant in males). Thymic atrophy appeared to be a response in two 4000 ppm females: likely associated with poor nutritional status. Study is acceptable, with possible adverse effect (tremors). Aldous, 1/25/08.

**00213-051 038848 Tai, C. N., Breckenridge, C., and Green, J. D., "Simazine technical: subacute oral 13-week toxicity study in rats," Ciba-Geigy, Summit, NJ, April 10, 1985. Laboratory Study # MIN 842225, Toxicology/Pathology Report No. 85018. Ten Sprague-Dawley [CrI: COB® CD® (SD)BR] rats/sex/group were dosed in diet with Simazine technical, 97.5% purity, Batch FL 840988, for 13 weeks in a subchronic study at 0, 200, 2000, or 4000 ppm. Achieved doses in treated males were 12.6, 126, and 247 mg/kg/day, respectively, and in

females were 15.9, 158, and 305 mg/kg/day, respectively. NOEL = 200 ppm (12.6 and 15.9 mg/kg/day in M and F, respectively). Mean food consumption was reduced 26% and 36% in 2000 and 4000 ppm males and by 16% and 22% in corresponding females. Body weight gains were remarkably reduced in both sexes at 2000 and 4000 ppm. Body weight gains (% increase from baseline) were 110%, 94%, 49%, and 28% in male controls through 4000 ppm, respectively. Gains in females were 60%, 52%, 26%, and 23%, respectively. Hematology effects included significantly reduced RBC counts in both sexes at 2000 and 4000 ppm, reduced HCT in 4000 ppm males and in 2000 and 4000 ppm females, and compensatory increases in platelets in 2000 and 4000 ppm females. Clinical chemistry generally indicated nutritional deficiencies by changes such as slightly but significantly reduced glucose in 2000 and 4000 ppm males, and slightly but significantly increased cholesterol in 2000 and 4000 ppm males and females. There were also slight changes in some electrolytes. Small increases in urinary ketones in 2000 and 4000 ppm males were plausibly related to treatment. Relative and/or absolute organ weights were often statistically significantly affected at 2000 and 4000 ppm, without clear indications of specific organ toxicity. There was a sufficient increase in the incidence of calculi in the lumen of the kidney pelvis at 2000 and 4000 ppm in both sexes to be considered treatment-related. Testicular atrophy incidence was 0, 0, 1, and 2 (N = 10) in controls through 4000 ppm, respectively, suggestive of a treatment effect. Data clearly show that 2000 ppm is excessive for future lifetime studies. Acceptable, with no adverse effects, Aldous, 1/25/08.

213-0086 90533 This is an U.S. EPA DER on the above rat subchronic study, located a few pages after the last tab in the volume. Aldous, 11/15/07.

213-0086 90534 This is an U.S. EPA DER on the above dog subchronic study, located a few pages after the last tab in the volume, immediately following the DER for the rat subchronic study. Aldous, 11/15/07.

213-076 071979 This is the same study as 00213-052 038849 (examined by Gee, 7/18/89).

213-0041 046096 Subchronic Oral Administration to Rats, G-29367 (50% WP Formulation of Simazine). This was a half-page summary of a 4-week study conducted by W. Hungerbuehler in 1956. Doses were by gavage, with water as diluent. There were no deaths at 2500 mg/kg/day, but 90% died at 5000 mg/kg/day. Symptoms were torpor, weight loss, and death. No reviewable data. Aldous, 10/24/07.

213-0009 046075 This is a 1-paragraph summary of 90-day subchronic oral rat toxicity study, apparently using simazine technical or a WP formulation, and clearly pre-dating the 1982 cover letter in the volume. Stated NOEL > 1000 ppm. There is no evident reason to request this report, considering that there are more rigorous studies available. Aldous, Nov. 2, 2007.

213-0004 45183 This is a half-page summary of a 4 week study for formulation No. G 29367 P. 8 (= 50% G 27692), dated 06/01/1956. There is no useful information in this record. Aldous, 11/15/07.

213-0009 923985 This is a half-page summary of a 4-week IBT study in mice, used as a range-finding study for later long-term studies. No need for DPR evaluation. Aldous, 11/15/07.

METABOLISM STUDIES

A more substantial body of information is available on the congener, atrazine, which information is likely to be analogous to that which could be obtained from simazine. See atrazine Summary of Toxicology Data.

213-0086 090524 Simoneaux, B. and A. Sy, "Metabolism of simazine and its metabolites in female rats," Ciba-Geigy Corporation, Ardsley, NY, 5/31/71. Female rats were administered 1.5 mg/kg ¹⁴C-simazine once by gavage (after a 1-week regimen of 15 ppm -unlabeled simazine in diets). Excretion was 49% in urine and 41% in feces. Residues at 96-hr termination were highest in blood (0.52 ppm), and 0.28 ppm, 0.23 ppm, 0.15 ppm, and 0.08 ppm in kidney, liver, and fat, and muscle, respectively. Comparatively high concentration of residues in blood is consistent with other triazine study results. Some rats received soluble and insoluble fish metabolites of simazine, which is outside the scope of DPR data review group evaluation. Investigators identified major urinary simazine metabolites as de-alkylated hydroxyatrazines, similar to other early studies, reflecting isolation and separation techniques which have since been improved. No DPR worksheet (not modern, standard technique). Aldous, 11/15/07.

213-0053 38850 Copy of Simoneaux, B. and A. Sy, "Metabolism of simazine and its metabolites in female rats," Document No. 213-0086, Record No. 090524, above.

213-0086 090525 Knaak, J. B. and S. H. Caballa, "The *in vitro* metabolism of ¹⁴C-atrazine and derivatives by rat and sheep liver under tissue culture conditions," Ciba-Geigy Corporation, Ardsley, NY, May 4, 1973. This supplementary study used "liver cubes" in medium to evaluate *in vitro* metabolism of atrazine and of its dealkylated metabolites. Investigators determined that atrazine was partially dealkylated under these conditions, and that atrazine and its metabolites reacted to a small extent with glutathione to form conjugation products. Supplementary data, not suitable for DPR worksheet. Aldous, 11/15/07.

213-0086 090526 Orr, G. R. and B. J. Simoneaux, "Disposition of simazine in the rat," Ciba Geigy Corp., Greenboro, NC, 4/30/86. It appears that in-life portions of this study may have been done at SRI International. Parts of this report were fragmented, sometimes duplicated, and often interspersed with tangentially related material such as U.S. EPA DER's and short published articles. This was a traditional metabolism study, with 5 rats/sex dosed once by gavage (Carbowax 200 polyethylene glycol suspension) with ring-labeled ¹⁴C-simazine at 0.5 or 200 mg/kg, or 14-day treatment with unlabeled simazine at 0.5 mg/kg/day followed by a single labeled dose at 0.5 mg/kg. Excreta were collected for 7 days prior to sacrifice and tissue evaluation. There was no apparent difference in excretion patterns due to sex or to pre-treatment with low doses. Low-dose treatment led to 50-66% urinary excretion, and 13-24% fecal excretion. High dose rats excreted 21-22% of dose in urine and 55-63% in feces. Tissue concentrations in RBC's were generally several-fold higher than in other tissues examined. These patterns have been reported by several investigators from other studies. There is no need for a DPR worksheet, since more recent studies with more standardized techniques are available (at least for the closely related congener, atrazine). DPR apparently used Record No. 090524 for the SRI portion of this study, as well as for the 1971 study above. Aldous, 11/15/07.

213-0086 090529 Hamboeck, H. et al., "The binding of s-Triazine metabolites to rodent hemoglobins appears irrelevant to other species," Molecular Pharmacology **20**:579-584, 1981. See one-liner for this same article in the atrazine Summary of Toxicology Data under DPR Document No. 220-0104 and Record No. 230286. Aldous, 11/15/07.

220-0146 89330 "Review of simazine metabolism in the rat," 06/01/85. This reports summary information on older studies in which triazines were apparently dehalogenated and hydroxylated during preparations for assays, hence providing unreliable data. No worksheet is necessary. Aldous, 11/15/07.

213-0080 75270 Copy of 220-0146 89330, above.

NOTE: There are also extensive human exposure studies and related information indexed at DPR.

See also: U.S. EPA examination: Simazine RED Docket: Epa-hq-opp-2005-0151
