Simazine; CASRN 122-34-9

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Simazine

File First On-Line 09/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/01/1993
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Simazine
CASRN — 122-34-9
Last Revised — 09/01/1993

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Reduction in weight gains; hematological changes in females **2-Year Rat Feeding Study** **Ciba-Geigy Corp.,1988a**	NOAEL: 10 ppm (0.52 mg/kg-day) LOAEL: 100 ppm (5.3 mg/kg-day)	100	1	5E-3 mg/kg-day

*Conversion Factors and Assumptions — Actual dose tested

I.A.2. Principal and Supporting Studies (Oral RfD)

Ciba-Geigy Corp. 1988a. MRID No. 40614405; HED Doc No. 007240, 007449 Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Groups of Sprague-Dawley rats were fed technical simazine for 2 years at dietary levels of 0, 10, 100 or 1000 ppm (Male: 0, 0.41, 4.2, 45.8 mg/kg-day; Female: 0, 0.52, 5.3, 63.1 mg/kg-day). Animals tested for chronic toxicity effects consisted of 40 rats/sex in the control and high-dose groups and 30/sex in the low- and mid-dose groups, while 50/sex/dose were tested for carcinogenicity. After approximately 52 weeks of treatment in the chronic toxicity test, 10 rats/sex/group were sacrificed and an additional 10 rats/sex from the control and high-dose groups were maintained on an untreated diet for approximately 52 weeks at which time all the remaining animals were sacrificed. After 104 weeks of treatment, all remaining animals from the chronic toxicity and carcinogenicity test were sacrificed.

Mean body weights for high-dose male and female rats were statistically significantly lower than the control group beginning on day 7 of study and continuing to study termination. Mid-dose female rats had statistically significant lower mean body weights compared with controls both at different time intervals throughout the study and at study termination. Mean body weight gains

were also statistically significantly lower in high-dose male and female rats as compared with controls throughout the study. For mid-dose male and female rats, statistically significantly lower body weight gains were seen occasionally at different time intervals but not at study termination. A statistically significant reduction in food consumption was observed in high- dose male rats beginning at day 7 through 700 of the study. Statistically significant depression of food intake was also reported for high-dose female rats on days 7 through 560 on study, but not during the final 6 months of the study. The reduced food consumption in high-dose animals was correlated with decreased body weight and body weight gains in the same groups throughout the study. Changes in food consumption of low- and mid-dose animals were seen only rarely during the study.

A number of hematology parameters appeared were affected by simazine treatment. These apparent treatment-related effects were pronounced mainly in the high-dose females on most sampling days. Statistically significant differences between the control and high-dose group values were seen in females as follows: the red blood cell (RBC) count was depressed at all sample times; hemoglobin (HGB) was depressed on days 361, 537, and 725 on study; hematocrit (HCT) was depressed on days 361, 537, and 725 of sampling; mean corpuscular hemoglobin (MCHB) was elevated on days 361, 537, and 725 of sampling; mean corpuscular hemoglobin concentration (MCHC) was elevated on days 174 of sampling; white blood cell (WBC) count was elevated on days 174, 361, 537, and 725 of sampling; the percent of neutrophils was elevated on day 316 of sampling; and lymphocytes were depressed on day 361 of sampling. Changes in these parameters, although only occasionally statistically significant, were also observed in the mid-dose females. Comparable changes between the control and high-dose groups were also seen in females of the recovery group. In males, the MCHC was statistically significantly higher in the high-dose group compared with the control group on day 361 of sampling (with an apparent dose-related trend); while the leukocyte count was statistically significantly lower than controls in the mid- and high-dose groups on day 537 of sampling. Other changes seen were not considered treatment-related. For males in the recovery group, hematology parameter values were comparable for the most part between the high-dose group and the control groups. Statistically significantly lower values were seen on day 537 for mean corpuscular volume (MCV) and on days 537 and 725 for MCHB.

Based on decreased body weight gains and hematologic parameters in females, the LEL for systemic toxicity of Simazine is 100 ppm (5.3 mg/kg-day). The NOEL for systemic toxicity is 10 ppm (0.52 mg/kg-day).

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 100 reflects 10 for interspecies extrapolation and 10 for intraspecies variability.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Reduction in body weight gains with accompanying hematologic deficits were the toxic endpoints for simazine. These effects are seen across all studies that lasted at least 1 year, including the 2-year rat feeding study, the 2- year mouse feeding study, and the 1-year dog feeding study. The effects are also seen in both the rat and rabbit gavage developmental toxicity studies. The data from these gavage studies support the findings of other studies which related the reduction in body weight to simazine and not to a palatability effect, as has been suggested in the feeding studies.

1) 2-Year Feeding/Oncogenicity - rat: Principal study -- see previous discussion; core grade minimum (Ciba-Geigy Corp., 1988a)

2) 2-Generation Reproduction - rat: Dietary levels tested: 0, 10, 100, and 500 ppm (Male: 0, 0.56, 5.61, and 28.89 mg/kg-day; Female: 0, 0.7, 7.04, and 34.96 mg/kg-day); Groups of Sprague-Dawley rats (30/sex/dose) were fed diets containing simazine technical over 2 generations. Compound-related parental toxicity was observed at 100 and 500 ppm. At 500 ppm, significant decreases were consistently present in food consumption, body weight, and body weight gain. The relative increases in testicular and ovarian weights were considered secondary effects because of the weight loss observed in the animal dose. At 100 ppm, a consistent, but not always significant, decrease was observed in body weight. Due to the fact that this decrease in body weight was present in both sexes and generations and occurred in a dose- related manner, the effects at 100 ppm are considered to be compound-related. The sporadically decreased food consumption noted at 100 ppm was not considered to be compound-related. Based on decreased body weight, the LEL for parental toxicity is 100 ppm (Male: 5.61 mg/kg-day; Female: 7.04 mg/kg- day). The NOEL for parental toxicity is 10 ppm (Male: 0.56 mg/kg-day; Female: 0.7 mg/kg-day). No compound-related effects were observed in this study. The mean numbers of stillborn pups per litter were slightly but insignificantly increased for the F1 pups at 10 and 100 ppm, and for F2a and F2b pups at 500 ppm. In each of these groups, an increased number of dead pups (9-16) in one single litter was responsible for this increase. These increases were not considered compound-related but rather normal variations, since they occurred in only one litter in each respective dose group; they did not occur in a dose-related manner; and no consistent pattern was noted across two generations. This conclusion is further supported by the fact that no

changes were noted in the numbers of viable neonates per litter in the live birth indices. The percentage of males was slightly decreased at 500 ppm for F1 pups (46%) and F2b pups (44%). These decreases were not significant because they did not occur among F2a pups. When survival indices to day 21 were reported separately for males and females, no differences were noted between sexes, the dose groups, or the generations. Based on these results, the NOEL for reproductive toxicity is equal to or greater than 500 ppm (Male: 28.89 mg/kg-day; Female: 34.96 mg/kg-day). Core grade minimum (Ciba-Geigy Corp., 1991)

3) 1-Year Feeding - dog: Dietary levels tested: 0, 20, 100, and 1250 ppm (Male: 0, 0.68, 3.4, and 43 mg/kg-day; Female: 0, 0.76, 3.6, and 45 mg/kg- day); Groups of beagle dogs (4/sex/dose) were fed diets containing simazine for 1 year. An additional 4 dogs/sex/dose were used for a clinical study (pre-dose and weeks 14, 25, and 52). Toxicity was demonstrated in high-dose males by decrements in body weight gain; variable but reversible decrements in red blood cell counts, hemoglobin concentration and hematocrit; and statistically significant increases in platelet counts. Similar toxicity was demonstrated in high-dose females by statistically significant larger decrements in body weight gain, and in mid- and high-dose females by decrements in the red blood cell counts, hemoglobin concentration, and hematocrit. Slight increases occurred in platelet counts in high-dose females. Decreased body weight gain occurred in one mid-dose female; this decrement was considered compound-related, although no other effects were noted in this animal. The efficiency of food utilization was apparently decreased in in high-dose females. In high-dose males the absolute organ weight, organ-to-brain weight, and organ-to-body-weight ratios were increased for the adrenals (130%), kidneys (111%), and liver (108%); and decreased for the spleen (69%) and thyroid/parathyroid (60%). In high-dose females the weight of the adrenals (129%), liver (104%), and thyroid/parathyroid (114%) weights may have been increased. These and other organ weight effects were not accompanied by any findings at histological examination, and thus, they may be incidental to the study. Based on decreased body weight gain; decreased RBC, Hgb, and HCT; and nominally increased platelet count in females, the LEL for systemic toxicity is 100 ppm (3.6 mg/kg-day). The NOEL for systemic toxicity is 20 ppm (0.76 mg/kg-day). Core grade minimum (Ciba- Geigy Corp., 1988b)

4) Developmental Toxicity - rat: Dose levels tested: 0, 30, 300, and 600 mg/kg-day; Groups of pregnant CDL COBS CD SD BR rats (25/dose) were administered simazine in 2% carboxymethylcellulose by gavage on gestation days 6 through 15. Maternal toxicity was demonstrated by statistically significant decreases in body weight and body weight gain, and decreases in food consumption and relative efficiency of utilization at the mid- and high- dose levels during treatment. Based on the above effects, the NOEL and LEL for maternal toxicity are 30 and 300 mg/kg-day, respectively. Developmental toxicity was also demonstrated at the two highest dose levels. The incidence of additional centra/vertebrae was statistically significantly increased in litters at the mid- and high-dose levels. Several other skeletal parameters indicating dose-related toxicity at these doses were statistically significant on a fetal basis, but not on a

litter basis, such as head not completely ossified, teeth not ossified, centra/vertebrae not ossified, rudimentary rib and sternebrae not ossified. These parameters were nominally elevated in litters. Most of the parameters affected frequently occur in association with maternal toxicity, and although some may disappear in fetuses after birth, these effects are considered indicative of developmental toxicity. Based on the above effects, the NOEL and LEL for developmental toxicity are 30 and 300 mg/kg-day, respectively. Core grade supplementary (additional data must be submitted) (Ciba-Geigy Corp., 1986)

5) Developmental Toxicity - rabbit: Dose levels tested: 0, 5, 75, and 200 mg/kg-day; Groups of pregnant New Zealand White rabbits (19/dose) were administered simazine with 3% corn starch by gavage on gestation days 7 through 19. A significant decrease in fetal weights and an increase in skeletal variations were observed at 200 mg/kg-day. Based on the above effects, the NOEL and LEL for developmental toxicity are 75 and 200 mg/kg-day, respectively. Significant decreases in body weight gain and food consumption, tremors, and abortions were observed in dams receiving 75 and 200 mg/kg-day. Based on these effects, the NOEL and LEL for maternal toxicity are 5 and 75 mg/kg-day, respectively. Core grade guideline (Ciba-Geigy Corp., 1984)

Other Data Reviewed:

1) 95-Week Feeding/Oncogenicity - mice: Dietary levels tested: 0, 40, 1000, and 4000 ppm (Male: 0, 5.3, 131.5, and 542 mg/kg-day; Female: 0, 6.2, 160.0, and 652.1 mg/kg-day); Groups of CD-1 mice (60/sex/dose) were fed diets containing simazine for 95 weeks. Mean body weight decreased in both males and females in the mid- and high-dose groups and food consumption decreased in mid- and high-dose males and in mid-dose females. Decreases in erythroid parameters may have been related to weight loss. Other hematologic parameters were not affected. Clinical chemistry values and urinary parameters were normal in all dosed groups. Organ-to-body-weight ratios were increased in high-dose females for several organs; however, there were no histologic correlates and the changes were accompanied by decreased body weights at termination. The incidence of amyloidosis was high in all groups. The LEL for systemic toxicity is 1000 ppm (Male: 131.5 mg/kg-day; Female: 160.0 mg/kg- day) based on decreased weight gain. The NOEL for systemic toxicity is 40 ppm (Male: 5.3 mg/kg-day; Female: 6.2 mg/kg-day). Core grade guideline (Ciba- Geigy Corp., 1988c)

2) 3-Generation Reproduction - rat: Dietary levels tested: 0, 50, and 100 ppm (0, 2.5, and 5 mg/kg-day); Groups of albino rats (strain not specified) were fed diets containing simazine over two generations. Reduced weight gain in parental male and female animals was observed at both dose levels. The weight gain of male was also significantly reduced by approximately 11% in the F0 generation during their premating period when compared with controls. Based on the effects observed at the LDT, the LEL for parental toxicity is 50 ppm (2.5 mg/kg-day). A NOEL for parental toxicity was not established. Reproductive toxicity could not be determined based on

lack of histologic evaluations in apparently sterile males in the F1b generation. Up to 33% of the potential paternal males in the 100 ppm group did not impregnate a female in 2 successive breeding sessions. The small sample size of the F3b pups examined, the length of gestation, and pup and litter weights at 14 and 21 days were not determined. The male and female parents were not examined histologically in any generation. Core grade supplementary (Ciba-Geigy Corp., 1965)

3) 13-Week Feeding - rat: Dietary levels tested: 0, 200, 2000, and 4000 ppm (Male: 0, 13.5, 128.2, and 249 mg/kg-day; Female: 0, 16, 171.3, and 291.1 mg/kg-day); Groups of Sprague-Dawley rats (10/sex/dose) were fed simazine in a powdered feed admixture ad libitum for 13 weeks. Reduced mean feed intake in treated rats is most likely due to the palatability of simazine in the diet. Lower individual body weights and reduced body weight gains paralleled mean food intake in treated rats. The majority of alterations in clinical chemistry values [reduced erythrocyte (males and females) and leucocyte counts (males only); elevated cholesterol and inorganic phosphate levels (males and females)] may be related to feed consumption in rats. Renal calculi and attending hyperplasia were the only dose-related lesions detected microscopically. Based on the effects observed at lowest dose tested, the LEL for systemic toxicity is 200 ppm (Male: 13.5 mg/kg-day; Female: 16 mg/kg-day). A NOEL for systemic toxicity was not established. Core grade supplementary (Ciba-Geigy Corp., 1985a)

4) 13-Week Feeding - dog: Dietary levels tested: 0, 200, 2000, and 4000 ppm (Male: 0, 6.9, 65.2, and 133.6 mg/kg-day; Female: 0, 8.2, 64.3, 136.7 mg/kg- day); Groups of beagle dogs (4/sex/dose) were fed a dietary admixture of simazine ad libitum for 13 weeks. It appears that reduced mean feed intake in treated dogs is most likely due to the palatability of simazine in the diet. Lower individual body weights and reduced body weight gains paralleled mean feed intake in treated dogs. The majority of the alterations in clinical chemistry values [reduced albumin levels, increased globulin levels, and elevated urinary specific gravity (males only) and increased ketone levels (males and females)] and organ weights observed in the mid- and high-dose groups may be related to feed consumption in treated dogs. Based on the effects observed at the mid-dose, the LEL for systemic toxicity is 2000 ppm (Male: 65.2 mg/kg-day; Female: 64.3 mg/kg-day). The NOEL for systemic toxicity is 200 ppm (Male: 6.9 mg/kg-day; Female: 8.2 mg/kg-day). Core grade minimum (Ciba-Geigy Corp., 1985b)

Data Gap(s): Rat Developmental Toxicity Study

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — High
RfD — High

The principal study is of adequate quality and is given a medium confidence rating. Additional studies, in particular the chronic dog study and the 2-generation reproduction study, are supportive of the NOEL and LEL established in the principal. The quality of the supporting studies is adequate and therefore, the database is given a high confidence rating. High confidence in the RfD follows.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — OPP Registration Standard, 1985

Agency Work Group Review — 06/24/1986, 06/15/1989, 08/14/1991

Verification Date — 08/14/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Simazine conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Simazine
CASRN — 122-34-9

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Simazine
CASRN — 122-34-9

Not available at this time.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Simazine
CASRN — 122-34-9

VI.A. Oral RfD References

Ciba-Geigy Corporation. 1965. MRID No. 00023365, 00080631; HED Doc No. 003689, 007240, 007449. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1984. MRID No. 00161407; HED Doc No. 004535, 005127, 007240. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1985a. MRID No. 00143265; HED Doc No. 004656, 007240. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1985b. MRID No. 00146655; HED Doc No. 004656, 007240. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1986. MRID No. 40614403; HED Doc No. 007240, 007449. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1988a. MRID No. 40614405; HED Doc No. 007240, 007449. Available from EPA. Write to FOI, EPA, Washington, DC. 20460.

Ciba-Geigy Corporation. 1988b. MRID No. 40614402; HED Doc No. 007240, 007449. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1988c. MRID No. 40614404; HED Doc No. 007240, 007449. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1991. MRID No. 41803601; HED Doc No. 008461. Available from EPA. Write to FOI, EPA, Washington, DC. 20460.

VI.B. Inhalation RfD References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Simazine
CASRN — 122-34-9

Date	Section	Description
07/01/1989	I.A.	Withdrawn; new Oral RfD verified (in preparation)
11/01/1989	I.A.	Oral RfD summary replaced; RfD changed
09/01/1991	I.A.	Withdrawn; new Oral RfD verified (in preparation)
09/01/1993	I.A.	Oral RfD summary replaced; RfD changed

Date	Section	Description
12/03/2002	I.A.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Simazine
CASRN — 122-34-9
Last Revised — 09/30/1987

- 122-34-9
- A 2079
- AKTINIT S
- AQUAZINE
- BATAZINA
- 2,4-BIS(AETHYLAMINO)-6-CHLOR-1,3,5-TRIAZIN
- 2,4-BIS(ETHYLAMINO)-6-CHLORO-s-TRIAZINE
- BITEMOL
- BITEMOL S 50
- CAT
- CDT
- CEKUSAN
- CEKUZINA-S
- CET
- 1-CHLORO, 3,5-BISETHYLAMINO-2,4,6-TRIAZINE
- 2-CHLORO-4,6-BIS(ETHYLAMINO)-1,3,5-TRIAZINE
- 2-CHLORO-4,6-BIS(ETHYLAMINO)-s-TRIAZINE
- 6-CHLORO-N,N'-DIETHYL-1,3,5-TRIAZINE-2,4-DIYLDIAMINE
- FRAMED
- G 27692
- GEIGY 27,692
- GESARAN
- GESATOP 50
- H 1803
- HERBAZIN 50
- HERBEX
- HERBOXY

- HUNGAZIN DT
- PREMAZINE
- PRIMATOL S
- PRINCEP
- PRINTOP
- RADOCON
- RADOKOR
- SIMADEX
- SIMANEX
- SIMAZIN
- Simazine
- SYMAZINE
- TAFAZINE 50-W
- TAPHAZINE
- TRIAZINE A 384
- 1,3,5-Triazine-2,4,6-triamine, N-cyclopropyl-
- W 6658
- ZEAPUR