SIMAZINE

This substance was considered by a previous working group, in 1990 (IARC, 1991). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

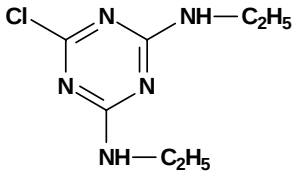
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 122-34-9
Deleted CAS Reg. Nos: 11141-20-1; 12764-71-5; 39291-64-0; 119603-94-0
Chem. Abstr. Name: 6-Chloro-*N*,*N*′-diethyl-1,3,5-triazine-2,4-diamine
IUPAC Systematic Name: 2-Chloro-4,6-bis(ethylamino)-*s*-triazine
Synonyms: 2,4-Bis(ethylamino)-6-chloro-*s*-triazine; 4,6-bis(ethylamino)-2-chloro-triazine

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_7H_{12}ClN_5$ Relative molecular mass: 201.66

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Crystals (Budavari, 1996)
(*b*) *Melting-point*: 226°C (Lide, 1997)
(*c*) *Density*: 1.302 g/cm^3 at 20°C (Lide, 1997)
(*d*) *Solubility*: Practically insoluble in water; slightly soluble in dioxane (Budavari, 1996)
(*e*) *Volatility*: Vapour pressure: 8.1×10^{-7} Pa at 20°C (National Toxicology Program, 1991)
(*f*) *Octanol/water partition coefficient (P)*: log P, 2.18 (Hansch *et al.*, 1995)
(*g*) *Conversion factor*: mg/m^3 = 8.25 × ppm

1.2 Production and use

Information available in 1995 indicated that simazine was produced in Brazil, Israel, Italy, Japan, Romania, the Russian Federation, South Africa, Switzerland and the United States (Chemical Information Services, 1995).

Simazine is used as a herbicide (Budavari, 1996). It is recommended for the control of broad-leaved and grass weeds in deep rooted crops, as a pre-emergence herbicide and as a soil sterilant. Simazine is used extensively on citrus and maize and, to a lesser extent, on other crops such as apples, grapes, peaches, nectarines, walnuts and almonds. In the United States, it has also been used to control algae in farm ponds, fish hatcheries and other surface waters (National Toxicology Program, 1991; National Library of Medicine, 1998a). [The Working Group estimated that the production of simazine was approximately 9700 tonnes in 1996 and 5900 tonnes in 1998.]

1.3 Occurrence

1.3.1 *Natural occurrence*

Simazine is not know to occur naturally.

1.3.2 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 1998), approximately 360 chemical industry workers in the United States were potentially exposed to simazine. No data were available on the number of agricultural workers exposed. Occupational exposure may occur through dermal contact or inhalation during the manufacture, formulation or application of this herbicide.

1.3.3 *Environmental occurrence*

According to the Environmental Protection Agency Toxic Chemical Release Inventory for 1996, 2100 kg simazine were released into the air and 42 kg were discharged into water from manufacturing and processing facilities in the United States (National Library of Medicine, 1998b).

The worldwide use of simazine as a pre-emergent herbicide on a broad variety of crops and for weed control in industrial areas and effluents from manufacturing sites have resulted in its release into the environment in various waste streams.

Simazine and its degradation products have varying degrees of persistence in different soil types and seasons under aerobic and anaerobic conditions. The general mobility and stability of simazine are such that it has been detected at low concentrations in ambient rural and urban air, rainwater, surface and groundwater and, less frequently, in drinking-water. Simazine and its degradation products are detected less frequently than atrazine in ground- and surface waters and at lower concentrations (Environmental Protection Agency, 1988, 1990; Kolpin *et al*., 1997; Tierney *et al*., 1998; National Library of Medicine, 1998a). No residues of simazine (> 0.04 mg/kg) have been reported in surveys of various foods and feeds in the United States (Elkins *et al*., 1998).

1.4 Regulations and guidelines

WHO (1993) has established an international drinking-water guideline for simazine of 2 mg/L.

2. Studies of Cancer in Humans

No data on simazine alone were available to the Working Group (see the monograph on atrazine).

3. Studies of Cancer in Experimental Animals

Previous evaluation

Simazine was tested for carcinogenicity in mice and rats by oral and subcutaneous administration and in mice by skin application. The studies were considered inadequate for an evaluation of carcinogenicity (IARC, 1991).

New studies

Oral administration

Mouse: Simazine was tested for carcinogenicity in a partly described study in CD-1 mice by administration in the diet at concentrations up to 400 mg/kg (ppm). Simazine did not increase the incidence of benign or malignant tumours (Hauswirth & Wetzel, 1998). [The Working Group considered this study to be inadequate for evaluation, since no data were available on the numbers of animals, numbers of dosed groups, study duration or observed tumour rates.]

Rat: Groups of 80–90 female Sprague Dawley rats [age unspecified] were fed diets containing 0, 10, 100 or 1000 mg/kg of diet (ppm) simazine (purity, 96.9% [impurities unspecified]) for 24 months. There was a significant ($p < 0.01$) decrease in the rate of survival at the intermediate and high doses. Significantly ($p < 0.01$) increased incidences of mammary gland fibroadenoma (control, 27/90, low dose, 28/80, intermediate dose, 19/80; high dose, 41/80) and mammary gland adenocarcinoma (16/90, 13/80, 20/80, 40/80) were observed at the high dose (Stevens *et al*., 1994). In addition, the body-weight gain of animals at this dose was less than 30% that of controls (Hauswirth & Wetzel, 1998). The combined incidences of adenomas and carcinomas were 39/90 in controls, 33/88 at the low dose, 31/80 at the intermediate dose and 61/80 ($p < 0.01$) at the high dose. The incidence at the high dose was outside the range seen in historical controls (33–49%). There was also evidence of an earlier onset of mammary gland tumours at the high dose. The incidence of pituitary gland carcinoma was also significantly ($p < 0.05$) increased at the high dose (control, 1/90; low dose, 3/80; intermediate dose, 0/79; high dose, 6/80), but the rate of carcinoma at the high dose (8%) fell within the historical control range for the study laboratory (mean, 3%; range, 0–10%). Moreover, the incidence of pituitary gland

adenoma and carcinoma (combined) was similar in all groups (74/90, 60/80, 63/79, 67/80) (Stevens *et al*., 1994). In the same study [no detailed data reported], male Sprague Dawley rats receiving simazine did not show increased incidences of tumours (Hauswirth & Wetzel, 1998).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

The primary route of metabolism for simazine in rats, rabbits and other species *in vivo* and *in vitro* is mono-N-dealkylation (Böhme & Bär, 1967; Adams *et al.*, 1990). Minor metabolites, other than some oxidation products of the alkyl side-chains, have not been identified. The chlorine group, which is linked directly to the aromatic ring, is a reactive site for the formation of glutathione conjugates, as in the case of atrazine (Timchalk *et al.*, 1990).

The metabolism of triazine herbicides (simazine and atrazine) has been evaluated *in vitro* with hepatic supernatant (10 000 × *g*) or microsomal systems from rats (Sprague-Dawley and Fischer 344), mice, goats, sheep, pigs, rabbits and chickens. All the species evaluated produced mono-deethylated metabolites of simazine and deisopropylated metabolites of atrazine. There was considerable variation among the species in the rate of metabolism and in the site-specificity of the reaction (Adams *et al.*, 1990).

4.2 Toxic effects

4.2.1 *Humans*

Simazine has been implicated as a cause of occupational contact dermatitis (Elizarov, 1972).

4.2.2 *Experimental systems*

Simazine toxicosis in sheep was reported to be associated with chronic ingestion of contaminated forage. Affected sheep had generalized muscular tremors that progressed to mild tetany, followed by collapse of the rear legs. Death occurred within two to three days after the onset of clinical signs. Histopathological evaluation revealed acute focal myocardial degeneration, focal non-suppurative encephalitis and hepatic congestion. Elevated simazine concentrations were found in affected tissues from the sheep that died (Allender & Glastonbury, 1992).

Sprague-Dawley rats were fed technical-grade simazine for two years at dietary concentrations of 0, 10, 100 or 1000 mg/kg of diet (ppm) with 40 rats of each sex in the

control and high-dose groups and 30 rats of each sex at the low and intermediate doses. After approximately 52 weeks of treatment, 10 rats of each sex per group were killed, and an additional 10 rats of each sex from the control and high-dose groups were maintained on untreated diet for approximately 52 weeks, at which time all of the remaining animals were killed. After 104 weeks of treatment, all remaining animals were killed. The mean body weights and the mean body-weight gain of male and female rats at the high dose were significantly lower than those in the control group from day 7 of the study until the end. Females at the intermediate dose had significantly lower mean body weights than controls throughout the study and at termination (from National Toxicology Program Chemical Repository Database and USEPA Integrated Risk Information System, cited by Keith, 1997).

A number of haematological parameters appeared to be affected by treatment with simazine, mainly in females at the high dose. Significant differences between the controls and those at the high dose were as follows: the erythrocyte count was depressed at all sampling times; haemoglobin concentration and haematocrit were depressed when assayed on days 361, 537 and 725, while the mean corpuscular haemoglobin content was elevated on these days; the leukocyte count was elevated on days 174, 361, 537 and 725; the percentage of neutrophils was elevated on day 316; and the lymphocyte count was depressed on day 361. The mean corpuscular haemoglobin concentration of males at the high dose was significantly higher than that of controls on day 361, and the leukocyte count of males at the intermediate and high doses was significantly lower than that of controls on day 537. In summary, reductions in body-weight gain with accompanying haematological deficits appear to be the toxic end-points for simazine. These effects were seen in all studies that lasted at least one year, including a two-year feeding study in rats, a two-year feeding study in mice and a one-year feeding study in dogs (Keith, 1997).

In a one-year feeding study, dogs (four per sex per dose) were given simazine at dietary concentrations of 0, 20, 100 or 1250 mg/kg (ppm). Toxicity was manifested in males at the high dose by decrements in body-weight gain, variable but reversible decreases in erythrocyte counts, haemoglobin concentration and haematocrit and significant increases in platelet counts. Toxicity was manifested in females at the high dose by significantly larger decreases in body-weight gain and in females at the intermediate and high doses by decrements in erythrocyte counts, haemoglobin concentration and haematocrit. In males and females at the high dose, the absolute organ weights and the organ:brain weight and organ:body weight ratios were increased for the adrenal glands, kidney (males only) and liver and decreased for the spleen (males only) and thyroid/parathyroid (decreased in males, increased in females); however, the changes in organ weights were not accompanied by any histological findings (Keith, 1997).

Simazine did not induce luciferase activity *in vitro* in an oestrogen assay with a recombinant receptor–reporter gene construct integrated into HeLa cells (Balaguer *et al.*, 1996). Simazine also failed to induce oestrogen receptor-mediated responses *in vivo* in immature Sprague-Dawley rat uterus and *in vitro* in an oestrogen-responsive MCF-7 human breast

cancer cell line and the oestrogen-dependent recombinant yeast strain PL3. Chloro-*s*-triazine also had no agonist activity and did not antagonize oestradiol-induced luciferase activity in MCF-7 cells transiently transfected with a Gal4-regulated luciferase reporter gene (17m5-G-Luc). These results taken together suggest that the oestrogenic and anti-oestrogenic effects of simazine are not mediated by the oestrogen receptor (Connor *et al*., 1996).

It was reported in an abstract that the short-term effects of feeding female Sprague-Dawley rats with simazine at 100 or 1000 mg/kg bw of diet (ppm) included modification of the oestrus cycle with increased duration, a change in the uterotrophic response, alterations in the affinity of oestrogen and its receptors and changes in hormone concentrations in serum (Wetzel *et al*., 1990).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

It was reported in an abstract that subcutaneous injection of simazine to neonatal rats on days 4–7 after birth prolonged the period of vaginal opening (Zeljenkova & Vargova, 1996).

Simazine altered the development of the gonads in birds (Didier & Lutz-Ostertag, 1972). In one study reported as an abstract, no developmental toxicity was seen in rats exposed by inhalation to concentrations up to 317 mg/m^3 on days 7–14 of gestation (Dilley *et al*., 1977), while teratogenic effects were seen in rats in another study after exposure to a much lower concentration (0.2 mg/m^3) throughout pregnancy (Mirkova & Ivanov, 1981). [The Working Group noted that the effects in the latter study might have been due to an unspecified impurity.] Embryolethality and fetal growth retardation were seen in a study in which rats received oral doses > 312 mg/kg per day during organogenesis on days 6–15 of gestation (Chen *et al*., 1981; see also IARC, 1991).

Simazine was a component of mixtures designed to mimic the contaminants of groundwater by agricultural practices that were evaluated for developmental and reproductive toxicity. The mixture contained several other pesticides, fertilizers and other organic substances commonly found in groundwater in the State of California (United States). The concentrations of simazine in drinking-water were 0, 0.3, 3 and 30 ng/mL, equivalent to 1, 10 and 100 times the median concentration of simazine in the groundwater. Swiss CD-1 mice were tested in a continuous breeding protocol, and a standard developmental toxicity study was conducted in which Sprague-Dawley rats were exposed on days 6–20 of gestation. In mice, no effects were noted on reproductive performance of F_0 or F_1 individuals or on spermatogenesis, epididymal sperm concentration, percentage of motile sperm, percentage of abnormal sperm or testicular tissues. In rats, no evidence of developmental toxicity was observed (Heindel *et al*., 1994).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

In single studies, simazine did not induce differential toxicity in *Bacillus subtilis* or *Salmonella* strains. It was inactive in the SOS DNA-repair assay in *Escherichia coli* and did not induce gene mutation in bacteriophage, bacteria or *Saccharomyces cerevisiae*, whereas mixed responses were obtained for mutation in plants. Simazine did not give rise to micronucleus formation in *Tradescantia*, but it induced chromosomal aberrations in various other plant species.

Mutations were induced at the *tk* locus in mouse lymphoma L5178Y cells, but DNA damage, as indicated by unscheduled DNA synthesis, was not induced in cultured human fibroblasts. Neither gene conversion nor mitotic recombination was induced in *S. cerevisiae*, nor aneuploidy in *Neurospora crassa*.

In single studies, simazine induced somatic mutation, sex-linked recessive lethal mutations, dominant lethal effects, but not aneuploidy, in *Drosophila melanogaster*.

Simazine did not induce sister chromatid exchange in cultured human lymphocytes or Chinese hamster cells, nor did it induce chromosomal aberrations in cultured Chinese hamster cells.

It did not induce micronucleus formation in bone-marrow cells of mice exposed *in vivo*.

4.5 Mechanistic considerations

Long-term feeding of 100 mg/kg of diet simazine per day for two years increased the incidence of mammary tumours in female Sprague-Dawley rats, but few data are available to establish a mechanism for that effect. Simazine administered at a high dose (300 mg/kg per day) for 14 days significantly prolonged the oestrous cycle in Sprague-Dawley rats (Wetzel *et al*., 1990), suggesting that simazine may have a mechanism of action on the mammary gland similar to that of the structurally related atrazine (Stevens *et al*., 1999).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to simazine occurs during its production, formulation and use as a herbicide. Simazine and its degradation products have been detected at low levels in ambient rural and urban air, rainwater, surface and groundwater and, less frequently, in drinking-water samples.

Table 1. Genetic and related effects of simazine

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Escherichia coli PQ37, SOS chromotest	NT	–	NR	Mersch-Sundermann *et al.* (1988)
Salmonella typhimurium TA1978/TA1538 and SL525/SL4700, differential toxicity	–	NT	2000 µg/disc	Environmental Protection Agency (1984)
Bacillus subtilis rec strains, differential toxicity	–	NT	1000 µg/disc	Kuroda *et al.* (1992)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	NT	–	NR	Simmon *et al.* (1977)
Salmonella typhimurium TA100, TA98, reverse mutation	–	–	5000 µg/plate	Environmental Protection Agency (1984)
Salmonella typhimurium TA100, TA1535, TA1537, TA1538, reverse mutation	–	–	1000 µg/plate	Environmental Protection Agency (1977)
Salmonella typhimurium TA100, reverse mutation	NT	+[c]	NR	Means *et al.* (1988)
Salmonella typhimurium TA100, TA102, TA97, reverse mutation	–	–	1000 µg/plate	Mersch-Sundermann *et al.* (1988)
Salmonella typhimurium TA1530, TA1531, TA1532, TA1534, G46, reverse mutation (spot test)	–	NT	NR	Seiler (1973)
Salmonella typhimurium (eight unidentified strains), reverse mutation	–	NT	NR	Andersen *et al.* (1972)
Escherichia coli, forward mutation	–	NT	NR	Fahrig (1974)
Escherichia coli WP2 *uvr*, reverse mutation	–	–	1000 µg/plate	Environmental Protection Agency (1984)
Serratia marcescens, reverse mutation	–	NT	NR	Fahrig (1974)
Saccharomyces cerevisiae, gene conversion	–	NT	NR	Fahrig (1974)
Saccharomyces cerevisiae, gene conversion	–	NT	1000[d]	Siebert & Lemperle (1974)
Saccharomyces cerevisiae D3, homozygosis by recombination	–	–	50 000	Environmental Protection Agency (1977)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Saccharomyces cerevisiae D7, mitotic recombination	–	–	25 000	Environmental Protection Agency (1984)
Saccharomyces cerevisiae D7, reverse mutation	–	–	25 000	Environmental Protection Agency (1984)
Saccharomyces cerevisiae D7, gene conversion	–	–	25 000	Environmental Protection Agency (1984)
Saccharomyces cerevisiae, reverse mutation	–	NT	5	Emnova *et al.* (1987)
Neurospara crassa, aneuploidy	–	NT	NR	Griffiths (1979)
Hordeum vulgare, mutation	+	NT	1000	Wuu & Grant (1966)
Hordeum vulgare, mutation	–	NT	200	Stroev (1968a)
Rizobium meliloti, mutation	–	NT	5000	Kaszubiak (1968)
Zea mays, chlorophyll mutation	+	NT	200	Morgun *et al.* (1982)
Zea mays, mutation	+	NT	NR	Plewa *et al.* (1984)
Fragaria ananassa, mutation	+	NT	2	Malone & Dix (1990)
Tradescantia paludosa, micronuclei	–	NT	200	Ma *et al.* (1984)
Hordeum vulgare, chromosomal aberrations	+	NT	500	Wuu & Grant (1966)
Hordeum vulgare, chromosomal aberrations	+	NT	500 spray	Wuu & Grant (1967a)
Hordeum vulgare, chromosomal aberrations	(+)	NT	500	Stroev (1968b)
Hordeum vulgare, chromosomal aberrations	(+)	NT	500[d]	Kahlon (1980)
Vicia faba, chromosomal aberrations	+	NT	200[d]	Wuu & Grant (1967b)
Vicia faba, chromosomal aberrations	+	NT	5	Hakeem & Shehab (1974)
Vicia faba, chromosomal aberrations	(+)	NT	1000	de Kergommeaux *et al.* (1983)
Allium cepa, chromosomal aberrations	+	NT	20	Chubutia & Ugulava (1973)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Crepis capillaris, chromosomal aberrations	+	NT	1000	Voskanyan & Avakyan (1984)
Drosophila melanogaster, somatic mutation	+		2000 µg/g feed	Tripathy *et al.* (1995)
Drosophila melanogaster, sex-linked recessive lethal mutation	–		10 ng/fly inj	Benes & Šrám (1969)
Drosophila melanogaster, sex-linked recessive lethal mutation	+		6 ng/fly inj	Murnik & Nash (1977)
Drosophila melanogaster, sex-linked recessive lethal mutation	–		6000 µg/g feed	Murnik & Nash (1977)
Drosophila melanogaster, sex-linked recessive lethal mutation	+		2000 µg/g feed	Tripathy *et al.* (1995)
Drosophila melanogaster, dominant lethal mutation	+		6000 µg/g feed	Murnik & Nash (1977)
Drosophila melanogaster, aneuploidy	–		6000 µg/g feed	Murnik & Nash (1977)
Gene mutation, mouse lymphoma L5178Y cells *in vitro*, *tk* locus *in vitro*	–	(+)	300	Environmental Protection Agency (1984)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	NT	1700	Environmental Protection Agency (1984)
Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	–	NT	2	Kuroda *et al.* (1992)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	NT	0.01	Biradar & Rayburn (1995)
Unscheduled DNA synthesis, human lung WI 38 fibroblasts *in vitro*	–	–	200	Environmental Protection Agency (1984)
Sister chromatid exchange, human lymphocytes *in vitro*	(+)	NT	NR	Ghiazza *et al.* (1984)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Sister chromatid exchange, human lymphocytes *in vitro*	–	–	10	Dunkelberg *et al.* (1994)
Micronucleus formation, mouse bone-marrow and peripheral blood cells *in vivo*	–	NT	500 po × 2	Environmental Protection Agency (1984)

[a] +, positive; (+), weakly positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; unless otherwise stated, in-vitro test, µg/mL; in-vivo test, mg/kg bw per day; NR, not reported; inj, injection; po, oral
[c] Tested with extracts of simazine-treated *Zea mays*
[d] Commercial pesticide tested

5.2 Human carcinogenicity data

No data were available on simazine alone (see the monograph on atrazine).

5.3 Animal carcinogenicity data

Simazine was tested for carcinogenicity in one experiment by oral administration to Sprague-Dawley rats. It increased the incidences of benign and malignant mammary gland tumours in females.

5.4 Other relevant data

Simazine is metabolized by dealkylation. No interaction with an oestrogen receptor was seen *in vitro*. In Sprague-Dawley rats, simazine was not uterotrophic but prolonged the duration of the oestrus cycle. Long-term administration resulted in haematological effects in rats and dogs.

Simazine did not show developmental toxicity in one study by inhalation in rats, but it was embryolethal and decreased fetal body weights in a study in which it was administered orally.

No data were available on the genetic and related effects of simazine in humans. Simazine was not genotoxic to rodents *in vivo* or in cultured mammalian cells, yeast or bacteria. It induced genetic damage in *Drosophila* and in plants.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of simazine.

There is *limited evidence* in experimental animals for the carcinogenicity of simazine.

Overall evaluation

Simazine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

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