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Simazine in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as International Standards for Drinking-Water. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

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GENERAL DESCRIPTION

Identity

CAS no.: 122-34-9
Molecular formula: $C_7H_{12}ClN_3$
Simazine is the common name for 6-chloro-*N*,*N*'-diethyl-1,3,5-triazine-2,4-diylamine.

Physicochemical properties (*1–3*)

Property	*Value*
Melting point	225–227 °C (decomposes)
Density	1.302 g/cm^3 at 20 °C
Water solubility	5 mg/litre at 20 °C
Vapour pressure	8.1×10^{-4} Pa at 20 °C
Log octanol–water partition coefficient	2.1

Major uses

Simazine is a pre-emergence herbicide used to control broad-leaved and grass weeds in artichokes, asparagus, berries, broad beans, citrus fruits, coffee, cocoa, hops, maize, oil palms, olives, orchards, ornamentals, sugar-cane, tea, tree nurseries, turf, and vineyards, as well as in non-crop areas (*1*).

Environmental fate

Under normal climatic conditions, volatilization and photodegradation are not expected to be important processes in the dissipation of simazine from soil (*2*) [Source: Hazardous Substances Data Bank. Bethesda, MD, National Library of Medicine]. Its half-life in soil has been reported as 46–174 days (*3*). Simazine can be degraded through hydrolysis and *N*-dealkylation (*4,5*). It is mineralized slowly [Source: Hazardous Substances Data Bank. Bethesda, MD, National Library of Medicine]. Even though it has a low solubility in water, it has been classified as a leacher (*6*).

ANALYTICAL METHODS

Simazine can be determined by a capillary column gas chromatographic method applicable to the determination of certain nitrogen/phosphorus-containing pesticides in water. In this method, the sample is extracted with methylene chloride, the extract is concentrated, and the compounds are separated by capillary-column gas chromatography, after which they are measured by means of a nitrogen–phosphorus detector. The estimated detection limit is 75 ng/litre (*7*).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Water

Typical levels of 1–2 µg/litre have been reported in groundwater in the USA (*8*). Contamination of groundwater by simazine has also been reported in Italy and Germany (*9,10*).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Simazine is absorbed by the gut of rats and mice and distributed to various tissues; the highest concentrations are found in the spleen, liver, and kidney (*11*). In 24-h urine samples from female rats given simazine orally, conjugated mercapturates of hydroxysimazine, 2-hydroxy-4-amino-6-ethylamino-s-triazine, and 2-hydroxy-4,6-diamino-s-triazine were found, accounting for 6.8%, 6.1%, and 14% of the administered dose, respectively (*12*). In 24-h urine samples from male rats that had received simazine by gavage, the di-*N*-dealkylated metabolites were present at higher levels than the mono-*N*-dealkylated ones (*13*). Following oral administration in rats, most simazine was excreted within 7 days, mainly in the urine (*11*).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

Oral LD_{50}s for simazine have been reported to be greater than 5000 mg/kg of body weight in the rat, mouse, and rabbit (*1,2*).

Long-term exposure

Dogs (2 per sex per dose) were treated orally for 105 weeks with 0, 15, 150, or 1500 mg of simazine per kg of feed. No deaths or evident toxic effects were caused by the treatment, apart from a transitory increase in aspartate aminotransferase in two out of four animals at the highest dose. The NOAEL was 150 mg/kg, corresponding to 5 mg/kg of body weight per day (*14*).

Dogs (4 per sex per dose) were treated for 2 years with doses of 0, 20, 100, or 1250 mg/kg in the diet. At the highest dose, the treatment caused cachexia in one animal of each sex, as well as reduced weight gain in one female, accompanied by a transitory reduction in food consumption. There was also a reduction in erythrocyte parameters in both males and females and an increase in thrombocytes in males. At 100 mg/kg, there were both reduced weight gain and reduced erythrocyte parameters in females. From this study, a NOAEL of 20 mg/kg, corresponding to 0.8 mg/kg of body weight per day, can be derived (*15*).

Technical simazine (purity not specified) was administered orally for 2 years at doses of 0, 10, 100, or 1000 mg/kg of feed to Sprague-Dawley rats (70 per sex per dose; satellite groups were used in order to study chronic toxicity). The NOAEL for this study was 10 mg/kg (0.52 mg/kg of body weight per day), based on weight changes and haematological parameters (*16*).

Reproductive toxicity, embryotoxicity, and teratogenicity

No reproductive effects were observed in a three-generation study in which technical simazine was administered to rats at doses up to 100 mg/kg of feed (*17*). In studies on rats and rabbits, the compound was not embryotoxic or teratogenic when administered at doses that were not maternally toxic (*18,21*).

Mutagenicity and related end-points

Simazine did not induce micronuclei in mice. It induced a small increase in the frequency of sister chromatid exchange in human cells *in vitro* but not in Chinese hamster cells. It also induced chromosomal aberrations in plants and dominant lethal mutations in *Drosophila*, but not aneuploidy in yeast or gene conversion or mitotic recombination in bacteria (*22*).

Carcinogenicity

Technical simazine (purity not specified) was administered orally for 2 years at doses of 0, 10, 100, or 1000 mg/kg of feed to Sprague-Dawley rats (70 per sex per dose). At the end of the experiment, the numbers surviving were, in order of increasing dose, 27, 24, 31, and 42 in males and 24, 23, 17, and 14 in females. Mortality was frequently related to tumours of the hypophysis, which were observed more often in the females; there were no significant differences between the various treated groups and the controls. In the females treated at 100 and 1000 mg/kg, there was an increase in mammary tumours with, in order of increasing dose: adenomas and fibroadenomas: 24/70, 31/70, 70/70, 45/70; and carcinomas: 14/70, 13/70, 19/70, 35/70. In the group receiving 1000 mg/kg, an increase in cystic glandular hyperplasia was observed. In the males, there was an increase in adenomas and carcinomas of the liver: 1/70, 3/70, 4/70, 6/70; a decrease in pancreatic tumours: 4/70, 14/70, 1/70, 0/70; and a decrease in benign phaeochromocytomas: 12/70, 14/70, 10/70, 3/70. The NOAEL from this study was 10 mg/kg (0.52 mg/kg of body weight per day) (*16*).

The same technical simazine was administered orally for 95 weeks at doses of 0, 40, 1000, or 4000 mg/kg to groups of Swiss CD-1 mice (60 per sex per dose) (*23*). At the end of the experiment, the numbers surviving were, in order of decreasing dose, 19, 15, 13, and 15 in males and 26, 26, 35, and 25 in females. There were no significant differences between the treated groups and the controls for the various types of tumours observed.

EFFECTS ON HUMANS

A total of 124 cases of contact dermatitis were noted in the former USSR among workers manufacturing simazine and propazine. Serious cases lasting 7–10 days involved erythema, oedema and a vesiculopapular reaction that sometimes progressed to the formation of bullae (*24*). One study showed an association between ovarian tumours and exposure to triazine herbicides (*25*), but the number of subjects was small. IARC evaluated the carcinogenicity of simazine in humans and concluded that adequate data were not available (*22*).

GUIDELINE VALUE

Simazine does not appear to be genotoxic in mammalian systems. Recent studies have shown an increase in mammary tumours in the female rat but no effects in the mouse. IARC has classified simazine in Group 3 (*22*).

Based on a study in the rat, a NOAEL of 0.52 mg/kg of body weight per day has been established for carcinogenicity and long-term toxicity (*16*). By applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for possible carcinogenicity), a TDI of 0.52 µg/kg of body weight was derived. An allocation of 10% of the TDI to drinking-water gives a guideline value of 2 µg/litre (rounded figure).

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