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Atrazine 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.: 1912-24-9
Molecular formula: $C_8H_{14}ClN_5$
The IUPAC name for atrazine is 6-chloro-*N*-ethyl-*N*'-isopropyl-1,3,5-triazine-2,4-diamine or 2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine (*1*). Most commercial atrazine products are about 95% pure. Common impurities include sodium chloride and other symmetric triazines, such as simazine and propazine.

Physicochemical properties (*1–3*)

Property	*Value*
Melting point	175–177 °C
Density	1.187 g/cm^3 at 20 °C
Water solubility	30 mg/litre at 20 °C
Log octanol–water partition coefficient	2.3
Vapour pressure	40×10^{-6} Pa at 20 °C

Major uses

Atrazine is used as a selective pre- and post-emergence herbicide for the control of weeds in asparagus, maize, sorghum, sugar-cane, and pineapple. It is also used in forestry and for non-selective weed control on non-crop areas (*1*). Several countries have restricted its use.

Environmental fate

Atrazine can be degraded in surface water by photolysis and microorganisms via *N*-dealkylation and hydrolysis of the chloro substituent; the corresponding half-lives are greater than 100 days at 20 °C. Hydrolysis and microbial degradation also take place in soil, depending mainly on temperature, moisture, and pH. Half-lives of 20–50 days at 20–25 °C have been found under laboratory conditions, increasing at lower temperatures (*4*). These are similar to the half-lives found under natural conditions, but longer half-lives have been seen under special conditions (*5*). Degradation rates normally decrease with increasing depth, and atrazine can be fairly stable in groundwater (*6*).

Atrazine's degradation products in soil include 2-chloro-4-amino-6-isopropylamino-1,3,5-triazine, 2-chloro-4-ethylamino-6-amino-1,3,5-triazine, 2-chloro-4-amino-6-amino-1,3,5-triazine, 2-hydroxy-4-ethylamino-6-isopropylamino-1,3,5-triazine, and 2-hydroxy-4-amino-6-isopropylamino-1,3,5-triazine (the main metabolite) (*7*). Unsubstituted amino metabolites and triazine are formed later and may be mineralized completely. Atrazine and its dealkylated metabolites are moderately to very mobile in sandy, silt, and clay soils (*8*). Hydroxytriazines, however, are of low mobility (*9*) and persist for long periods in the soil (*10*).

ANALYTICAL METHODS

Atrazine is determined by extraction with pentane followed by gas chromatography with nitrogen–phosphorus detection. The detection limit in tapwater and river water is about 0.1 µg/litre.

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

Evaporation tests in fields treated with atrazine have shown a loss of about 0.2% of the dose per day. It is found in precipitation just after spraying (*11*) and may then also be expected to be found in air.

Water

In many countries, after application in agricultural areas, atrazine has been found in groundwater at levels of 0.01–6 µg/litre. It has also been detected in drinking-water in several countries at levels of 0.01–5 µg/litre (*11,12*).

Food

Hydroxy metabolites of atrazine have been found in plants grown in soil treated with it (*10*), but atrazine itself has not been found on crops. When sprayed on maize, it is quickly transformed by the plant into its hydroxy metabolites (*13*).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Atrazine appears to be readily absorbed from the gastrointestinal tract. In a study of rats given a single dose by gavage, at least 80% of the dose was absorbed. Within 3 days, 66% of the dose was excreted in the urine, 14% was retained in tissues, mainly the blood cells, and only 0.1% was found in the expired air (*14*). Doses given orally are retained mainly in erythrocytes, liver, spleen, and kidney. Most of the metabolites found in soil can also be found as degradation products in rats, with 2-chloro-4,6-diamino-1,3,5-triazine being the major compound present in urine (*15*). Absorption through skin is limited, amounting to less than 2% after a 10-h exposure (*16*).

EFFECTS IN LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

When technical atrazine (97% active ingredient) was administered to very young rats (<7 weeks), LD_{50}s of 1900–2300 mg/kg of body weight were found, whereas LD_{50}s in the range 670–740 mg/kg of body weight were found for 3-month-old rats (*17*). LD_{50}s of 1750–4000 mg/kg of body weight were established in mice (*18*).
Atrazine causes moderate irritation to rabbit skin but is not appreciably irritating to the rabbit eye. It causes dermal sensitization in the guinea-pig. The dermal LD_{50} was reported to be higher than 3100 mg/kg of body weight in the rat (*19*).

Short-term exposure

A 2-week study on female rats on oral toxicity and hormonal effects showed that 100 mg/kg of body weight per day influenced the serum concentration of estrogen, luteinizing hormone, prolactin, and progesterone. These effects may be important in the development of breast cancer in rats (*20*).

Long-term exposure

In a 1-year oral study on beagle dogs with technical atrazine (97% active ingredient) at doses of 0, 0.5, 5, or 34 mg/kg of body weight per day, the heart was the main target organ. Dogs given 34 mg/kg of body weight per day showed ECG alterations and clinical signs referable

to cardiac toxicity after only 17 weeks. Treatment-related changes in haematological values were also reported in males of this group. Slight decreases in total serum protein and albumin were reported for males at 34 mg/kg of body weight per day. The NOAEL in this study was 5 mg/kg of body weight per day (*21*).

Technical atrazine (98.9% active ingredient) was fed to Sprague-Dawley rats for 2 years at 0, 10, 70, 500, or 1000 mg/kg in the diet. At 500 and 1000 mg/kg, there was a significant decrease in mean body weights of both sexes and decreased food consumption. At 1000 mg/kg, females were found to have a consistent reduction in red blood cell count, haemoglobin and haematocrit, and glucose levels were depressed in both females and males during the first 12 months. The NOAEL in this study was 70 mg/kg (equivalent to 3.5 mg/kg of body weight per day) based on non-neoplastic effects as well as reduced body weight and food consumption (*22*).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a two-generation rat study utilizing technical atrazine (97% active ingredient) in doses of 0, 0.5, 2.5, or 25 mg/kg of body weight per day, pup weights in the second generation at the two highest doses were statistically significantly lower than those of the control group. Both parental animals had significant decreases in body weight, body weight gain, and food consumption at 25 mg/kg of body weight per day. In addition, a statistically significant increase in relative testis weight was seen in both generations at this dose level. Thus, the reproductive NOAEL was 0.5 mg/kg of body weight per day, and the parental NOAEL 2.5 mg/kg of body weight per day (*23*).

No teratogenic response was found in New Zealand white rabbits that received atrazine by gavage on days 7–19 of gestation at dose levels of 1, 5, or 75 mg/kg of body weight per day. Maternal toxicity, in the form of decreased body weight gain and food consumption, was seen in the mid- and high-dose groups. Fetotoxicity was demonstrated only at 75 mg/kg of body weight per day by an increased resorption rate, reduced fetal weights, and delay of ossification. The embryotoxic NOAEL appears to be 5 mg/kg of body weight per day, and the maternal NOAEL is 1 mg/kg of body weight per day (*24*).

Mutagenicity and related end-points

Atrazine has been tested in several systems, but there is no convincing evidence that it has any significant genotoxic action. However, deficiencies exist with respect to certain of the tests performed, and some evidence of genotoxic effects *in vivo* needs confirmation (*25–28*).

Carcinogenicity

In the study in which technical atrazine (98.9% active ingredient) was fed to Sprague-Dawley rats for 2 years at 0, 10, 70, 500, or 1000 mg/kg in the diet, a significant increase in the incidence of mammary tumours in females was seen at the three highest doses (*22*). The doses in the middle of the range (70 and 500 mg/kg) showed 95% significance for the occurrence of adenocarcinomas and carcinosarcomas, suggesting that atrazine interferes with hormonal regulation in male rats. The effect of atrazine on rat hormones confirms this hypothesis (*20*). The NOAEL in this study was 10 mg/kg, equivalent to 0.5 mg/kg of body weight per day. Studies on mice have not shown any signs of tumours (*29*).

EFFECTS ON HUMANS

In an epidemiological study in northern Italy, an increased relative risk of ovarian neoplasia was found among women exposed to triazine herbicides (*30*). An 80% formulation of atrazine did not cause skin sensitization on repeated application to humans.

GUIDELINE VALUE

The weight of evidence from a wide variety of genotoxicity assays indicates that atrazine is not genotoxic. There is some evidence that it can induce mammary tumours in rats as a result of hormonal changes, but it is highly probable that the mechanism for this process is non-genotoxic. No significant increase in neoplasia has been observed in mice. IARC has concluded that atrazine is not classifiable as to its carcinogenicity in humans (Group 3) (*31*).

A TDI approach can therefore be used to calculate a guideline value. Based on a NOAEL of 0.5 mg/kg of body weight per day in a carcinogenicity study in the rat (*22*) and using an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 to reflect potential neoplasia), a TDI of 0.5 µg/kg of body weight can be calculated. With an allocation of 10% of the TDI to drinking-water, the guideline value is 2 µg/litre (rounded figure).

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