

## **Acrylamide 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.

## Acknowledgements

Acrylamide in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is an update of the background document published in the second edition of the Guidelines. The update was prepared by T. Nishimura, National Institute of Health Sciences, Japan, to whom special thanks are due.

The work of the following working group coordinators was crucial in the development of this document and others in the third edition:

- Mr J.K. Fawell, United Kingdom (*Organic and inorganic constituents*)
- Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)
- Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
- Dr P. Toft, Canada (*Pesticides*)
- Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
- Mr P. Jackson, WRc-NSF, United Kingdom (*Treatment achievability*)

The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

- Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
- Mr P. Callan, Water Sanitation and Health Programme, WHO Headquarters
- Mr H. Hashizume, Water Sanitation and Health Programme, WHO Headquarters

Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

### **Acronyms and abbreviations used in the text**

CAS	Chemical Abstracts Service
Hb	haemoglobin
LD <sub>50</sub>	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
USA	United States of America

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## **1. GENERAL DESCRIPTION**

### **1.1 Identity**

CAS No.:	79-06-1
Molecular formula:	C <sub>3</sub> H <sub>5</sub> NO

### **1.2 Physicochemical properties (IPCS, 1985)**

<i>Property</i>	<i>Value</i>
Physical state	White crystalline solid
Melting point	125 °C
Boiling point	1.122 g/cm <sup>3</sup> at 3.33 kPa
Vapour pressure	0.009 kPa at 25 °C
Density	2150 g/litre at 30 °C
Water solubility	2150 g/litre at 30 °C

### **1.3 Major uses**

Most of the acrylamide produced is used as a chemical intermediate or as a monomer in the production of polyacrylamide. Both acrylamide and polyacrylamide are used mainly in the production of flocculants for the clarification of potable water and in the treatment of municipal and industrial effluents. They are also used as grouting agents in the construction of drinking-water reservoirs and wells (IPCS, 1985).

### **1.4 Environmental fate**

Acrylamide is highly mobile in aqueous environments and readily leachable in soil. As it has a higher mobility and lower rate of degradation in sandy soils than in clay soils (Lande et al., 1979), it may contaminate groundwater. However, its behaviour in subsurface soil, where most grouting takes place, has not been studied.

Acrylamide is susceptible to biodegradation in both soil and surface water. Its concentration decreased from 20 to 1 µg/litre in 24 h in the effluent from a sludge dewatering process (Arimitu et al., 1975). One of the most important mechanisms for the removal of acrylamide from soils is enzyme-catalysed hydrolysis; non-biological hydrolysis may be important in natural water. Volatilization is not an important removal process. As acrylamide is both highly soluble in water and degraded by microorganisms, it is not likely to bioconcentrate significantly (Neely et al., 1974).

## **2. ANALYTICAL METHODS**

The methods used for measuring acrylamide include polarography, electron capture gas chromatography and high-performance liquid chromatography. A high-performance liquid chromatography/ultraviolet absorption detection procedure for the determination of acrylamide in water has a detection range of 0.2–100 µg/litre (Brown & Rhead, 1979).

***3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE******3.1 Air***

Because of its low vapour pressure and high water solubility, acrylamide is not expected to be a common contaminant in air. Available monitoring data are insufficient to confirm this.

***3.2 Water***

The most important source of drinking-water contamination by acrylamide is the use of polyacrylamide flocculants containing residual levels of acrylamide monomer. Generally, the maximum authorized dose of polymer is 1 mg/litre. At a monomer content of 0.05%, this corresponds to a maximum theoretical concentration of 0.5 µg of monomer per litre in water (NSF, 1988). In practice, concentrations may be lower by a factor of 2–3. This applies to both the anionic and non-ionic polyacrylamides, but residual levels from cationic polyacrylamides may be higher.

Acrylamide was detected at levels of <5 µg/litre in both river water and tap water in an area where polyacrylamides were used in the treatment of potable water. Samples from public drinking-water supply wells in West Virginia, USA, contained 0.024–0.041 µg of acrylamide per litre. In one study in the United Kingdom, tap water levels in the low µg/litre range were reported (Brown & Rhead, 1979).

***3.3 Food***

Acrylamide has been found in certain foods (particularly starchy foods) that have been cooked and processed at high temperatures. Based on the data available in June 2002, food was estimated to make a significant contribution to the total exposure of the general public to acrylamide. Average intakes for the general population were estimated to be in the range of 0.3–0.8 µg of acrylamide per kg of body weight per day (FAO/WHO, 2002). Polyacrylamide is also used in the refining of sugar, and small amounts of acrylamide may remain in the final product.

***4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS***

Acrylamide is readily absorbed by ingestion, by inhalation and through the skin (IPCS, 1985) and is then widely distributed in body fluids. It can cross the placental barrier. The tissue distribution following intravenous injection of 1-[<sup>14</sup>C]acrylamide (100 mg/kg of body weight) into male Porton strain rats was highest (up to 1360 µmol/g of tissue) in blood; progressively lower amounts were present in kidney, liver, brain, spinal cord, sciatic nerve and plasma (Hashimoto & Aldridge, 1970).

In rats, biotransformation of acrylamide occurs through glutathione conjugation and decarboxylation. At least four urinary metabolites have been found in rat urine. *N*-

Acetyl-S-(3-amino-3-oxypropyl) cysteine accounted for 48% of the oral dose, and unmetabolized acrylamide (2%) and three non-sulfur-containing metabolites (total 14%) were also present. Acrylamide and its metabolites are accumulated (protein-bound) in both nervous system tissues and blood, where they are bound to haemoglobin (Hb). Accumulation in the liver and kidney as well as in the male reproductive system has also been demonstrated (Miller et al., 1982).

The results of animal studies indicate that acrylamide is largely excreted as metabolites in urine and bile. Because of the enterohepatic circulation of biliary metabolites, faecal excretion is minimal. Two-thirds of the absorbed dose is excreted with a half-life of a few hours. However, protein-bound acrylamide or acrylamide metabolites in the blood, and possibly in the central nervous system, have a half-life of about 10 days. Acrylamide has been identified in rat milk during lactation (Miller et al., 1982).

There are no data indicating any major differences in acrylamide metabolism between humans and other mammals (IPCS, 1985).

## ***5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS***

### ***5.1 Acute exposure***

Oral LD<sub>50</sub>s for acrylamide were reported to range from 100 to 270 mg/kg of body weight in various strains of mice and rats. The dermal LD<sub>50</sub> in rats was reported to be 400 mg/kg of body weight (Fullerton & Barnes, 1966; Paulet & Vidal, 1975; Tilson & Cabe, 1979; Hashimoto et al., 1981).

### ***5.2 Short-term exposure***

Studies have shown convincingly that acrylamide is a cumulative neurotoxin. Rats, cats and dogs receiving 5–30 mg/kg of body weight per day in the diet for 14–21 days exhibited weakness and ataxia in hind limbs, which progressed to paralysis with continued exposure (Leswing & Ribelin, 1969; Thomann et al., 1974). Other characteristic symptoms were testicular atrophy and degeneration of germinal epithelium (McCollister et al., 1964).

### ***5.3 Long-term exposure***

Signs of acrylamide toxicity in animals exposed for longer periods of time (several months to 1 year) are generally the same as those in animals exposed for shorter periods, but average daily doses as low as 1 mg/kg of body weight sometimes produce effects. When male and female F344 rats were exposed to 0, 0.05, 0.2, 1.5 or 20 mg/kg of body weight per day in drinking-water for 90 days, definite peripheral nerve and spinal cord lesions and testicular atrophy were observed in the group receiving 20 mg/kg of body weight per day; although 1.5 mg/kg of body weight per day caused no external signs of toxicity, histological evidence of neuropathy was noted. The NOAEL was 0.2 mg/kg of body weight per day (Burek et al., 1980).

#### **5.4 Reproductive and developmental toxicity**

Male Long-Evans rats exposed to acrylamide doses of up to 5.8 mg/kg of body weight per day for 10 weeks in their drinking-water experienced increased pre-implantation and post-implantation loss after mating (Smith et al., 1986). The LOAEL and NOAEL in this study were 2.8 and 1.5 mg/kg of body weight per day, respectively. Another series of experiments carried out by the same authors suggested that acrylamide could affect the spermatid–spermatozoa stages (Sublet et al., 1986).

Acrylamide was administered to pregnant Porton rats either as a single intravenous dose (100 mg/kg of body weight) on day 9 of gestation or in the diet as a cumulative dose of either 200 or 400 mg/kg of body weight between days 0 and 20 of gestation. Apart from a slight decrease in the weight of individual fetuses from rats dosed with 400 mg/kg of body weight, no fetal abnormalities were seen, even at doses that induced neuropathy in the dams (Edwards, 1976).

When fertilized chicken eggs were injected with 0.03–0.6 mg of acrylamide on day 5, 6 or 7 of incubation, embryonic mortality increased and leg deformities were observed in hatched chicks (Parker et al., 1978).

Male (102/EI×C3H/EI)F<sub>1</sub> mice were given a single intraperitoneal injection of 60 or 120 mg of acrylamide per kg of body weight. The frequency of aneuploid sperm was investigated by fluorescence *in situ* hybridization 22 days after injection. No significant effects were found (Schmid et al., 1999).

The induction of chromosomal aberrations in mouse zygotes was investigated in male germ cells in first-cleavage zygote metaphases following intraperitoneal administration of 5 × 50 mg of acrylamide per kg of body weight to male mice. High levels of chromosomally defective zygotes were detected after mating at all post-meiotic stages (20- to 190-fold,  $P < 0.001$ ) (Marchetti et al., 1997).

Female Fischer 344 rats were given 2 or 15 mg/kg of body weight per day for 2 or 7 days by gavage. After 24 h, hormone analysis of blood and histopathological examination of selected tissues were performed. There were no toxicity-related deaths, no clinical signs of toxicity, no significant difference in the mean body weight and no lesions of pathological significance. There were no significant changes in the levels of hormones in plasma. However, there was a slight dose-dependent increase in plasma thyroxine and a slight dose-dependent decrease in plasma thyroid stimulating hormone. Thyroid gland morphometry showed a significant decrease ( $P < 0.05$ ) in the colloid area and a significant increase ( $P < 0.05$ ) in the follicular cell height of treated rats compared with controls (Khan et al., 1999).

In a two-generation study, Fischer 344 weanling rats were administered acrylamide in drinking-water at doses of 0, 0.5, 2.0 or 5.0 mg/kg of body weight. The NOAEL for adult systemic toxicity was 0.5 mg/kg of body weight per day. Reproductive indices in the F<sub>0</sub> and F<sub>1</sub> generations were unaffected, although reduced pup survival and

embryotoxicity were apparent at 5.0 mg/kg of body weight per day. The NOAEL for the dominant lethal assay using the F<sub>0</sub> males was 2.0 mg/kg of body weight per day (Tyla et al., 2000).

### ***5.5 Mutagenicity and related end-points***

Acrylamide does not cause mutations in bacterial test systems but does cause chromosome damage to mammalian cells both *in vitro* and *in vivo* (Shiraishi, 1978; Bull et al., 1984; IPCS, 1985).

### ***5.6 Carcinogenicity***

Male and female Fischer 344 rats were given acrylamide at 0, 0.01, 0.02, 0.5 or 2 mg/kg of body weight per day in drinking-water for 2 years. In male rats receiving doses of 0.5 or 2 mg/kg of body weight per day, there was an increase in the frequency of scrotal, thyroid and adrenal tumours. In female rats receiving 2 mg/kg of body weight per day, there was an increased incidence of malignant tumours of the mammary gland, central nervous system, thyroid and uterus (Johnson et al., 1986).

Eight-week-old A/J male and female mice given oral acrylamide doses of 6.3, 12.5 or 25.0 mg/kg of body weight 3 times per week for 3 weeks or intraperitoneal doses of 1, 3, 10, 30 or 60 mg/kg of body weight 3 times per week for 8 weeks showed a dose-dependent increased incidence of lung adenomas at 9 and 8 months of age, respectively (Bull et al., 1984).

In a study in which Fischer 344 rats were administered acrylamide in their drinking-water at concentrations providing doses of 0, 0.1, 0.5 or 2.0 mg/kg of body weight per day in males and 0, 1.0 or 3.0 mg/kg of body weight per day in females for 106 weeks, there was no clinical indication of neurotoxicity, although sciatic nerve degeneration was observed in the high-dose groups of both males and females. Mesotheliomas of the testicular tunic showed a significant increase in the high-dose group, and the incidence of combined mammary tumours was increased in females at both dose levels. There was also an increased incidence of thyroid follicular cell adenomas and adenocarcinomas in both sexes at the high dose level and in females at the lower dose level (Friedman et al., 1995).

## ***6. EFFECTS ON HUMANS***

Subacute toxic effects were experienced by a family of five exposed through the ingestion and external use of well water contaminated with 400 mg of acrylamide per litre as the result of a grouting operation (Igisu et al., 1975). Symptoms of toxicity developed about a month later and included confusion, disorientation, memory disturbances, hallucinations and truncal ataxia. The family recovered fully within 4 months.

A 23-year-old female survived after intentionally ingesting 18 g of acrylamide crystals. Hallucinations and hypotension were observed after 5 h and seizures after 9

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h. Gastrointestinal bleeding, adult respiratory distress syndrome, hepatotoxicity and peripheral neuropathy were observed on day 3 (Donovan & Pearson, 1987).

Many other cases of human exposure to acrylamide have been reported, generally the result of the dermal or inhalation exposure of workers in grouting operations or factories manufacturing acrylamide-based flocculants (Auld & Bedwell, 1967; Garland & Patterson, 1967; Fullerton, 1969; Davenport et al., 1976). Typical clinical symptoms were skin irritation, generalized fatigue, foot weakness and sensory changes, which reflect dysfunction of either the central or peripheral nervous system.

In a study in China, Hb adduct with acrylamide (acrylamide adducted in the *N*-terminal of valine in Hb protein) was determined in 41 workers who were exposed to acrylamide by inhalation for 1 month to 11.5 years in an acrylamide synthesis room. The adduct of acrylamide was found to be 0.3–34 nmol/g of Hb in exposed workers but was not found in controls (Bergmark et al., 1993).

Free acrylamide in plasma as an indicator of neurotoxicity was studied in the same group of workers as described above. The average level of free acrylamide in plasma was 1.8 mmol/litre and that of valine adducts was 13.4 nmol/g of Hb. There were significant differences in the frequency of signs and symptoms of neurotoxicity and differences in vibration sensitivity and electroneuromyographic measurements between the exposed group of workers and the control group (Calleman et al., 1994).

### **7. GUIDELINE VALUE**

In mutagenicity assays, acrylamide does not cause mutations in bacterial test systems but does cause chromosome damage to mammalian cells *in vitro* and *in vivo*. In a long-term carcinogenicity study in rats exposed via drinking-water, it induced tumours at various sites (Johnson et al., 1986). IARC (1994) has placed acrylamide in Group 2A (probably carcinogenic to humans).

New data on acrylamide exposure through food has led to a re-examination of the mechanism of carcinogenicity and the cancer risk associated with exposure from all sources. Controlling acrylamide exposure through drinking-water is relatively easy. A non-threshold approach was used to define safe concentrations that can be readily achieved. The upper-bound risks determined using the linearized multistage model do not equate to actual population risks through drinking-water or other routes of exposure. On the basis of combined mammary, thyroid and uterine tumours observed in female rats in a drinking-water study (Bull et al., 1984) and using the linearized multistage model, guideline values associated with upper-bound excess lifetime cancer risks of  $10^{-4}$ ,  $10^{-5}$  and  $10^{-6}$  are estimated to be 5, 0.5 and 0.05 µg/litre, respectively.

The most important source of drinking-water contamination by acrylamide is the use of polyacrylamide flocculants that contain residual acrylamide monomer. The practical quantification level for acrylamide is generally of the order of 1 µg/litre. However, acrylamide concentrations in drinking-water are controlled by limiting

either the acrylamide content of polyacrylamide flocculants or the dose used, or both. In the event of acrylamide being present in raw water, acrylamide concentrations can be reduced by ozonation (Mallevialle et al., 1984) or treatment with potassium permanganate (Ma et al., 1994). Conventional treatment processes do not remove acrylamide.

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