**WHO/SDE/WSH/03.04/71/Rev/1**

# Acrylamide in Drinking-water

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

Rev/1: Revisions indicated with a vertical line in the left margin.

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## Preface

One of the primary goals of the World Health Organization (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 third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

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 and 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 of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, 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. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert 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 Meeting 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**

The current version of Acrylamide in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is an update of the background document originally prepared for the second edition of the Guidelines by T. Nishimura, National Institute of Health Sciences, Japan.

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

Dr J. Cotruvo, J. Cotruvo Associates, USA (*Materials and chemicals*)
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The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held in December 2011. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support throughout the review and publication process. Ms M. 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 comments are greatly appreciated.

## Acronyms and abbreviations used in the text

| | |
|---|---|
| AA | acrylamide |
| $BMDL_{10}$ | lower limit on the benchmark dose for a 10% response |
| DNA | deoxyribonucleic acid |
| FAO | Food and Agriculture Organization of the United Nations |
| GA | glycidamide |
| Gua | guanine |
| JECFA | Joint FAO/WHO Expert Committee on Food Additives |
| $LD_{50}$ | median lethal dose |
| LOAEL | lowest-observed-adverse-effect level |
| NOAEL | no-observed-adverse-effect level |
| PND | Postnatal day |
| USA | United States of America |
| Val | valine |
| WHO | World Health Organization |

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## *1. GENERAL DESCRIPTION*

### *1.1 Identity*

| | |
|---|---|
| Chemical Abstracts Service No.: | 79-06-1 |
| Molecular formula: | $C_3H_5NO$ |

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

| *Property* | *Value* |
|---|---|
| Physical state | White crystalline solid |
| Melting point | 125 °C |
| Boiling point | 1.122 g/cm$^3$ at 3.33 kPa |
| Vapour pressure | 0.009 kPa at 25 °C |
| Density | 2150 g/l at 30 °C |
| Water solubility | 2150 g/l 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/l in 24 hours 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. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE*

### *2.1 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.

### *2.2 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/l. 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/l 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 in the United States of America (USA) contained 0.024–0.041 μg of acrylamide per litre. In one study in the United Kingdom, tap water levels in the low microgram per litre range were reported (Brown & Rhead, 1979).

### *2.3 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 kilogram 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.

## *3. 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-[$^{14}$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 (tota1 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. 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 experimental 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).

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

### *4.1 Acute exposure*

Oral median lethal doses ($LD_{50}$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 $LD_{50}$ 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).

### *4.2 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).

### *4.3 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 no-observed-adverse-effect level (NOAEL) was 0.2 mg/kg of body weight per day (Burek et al., 1980).

### *4.4 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 lowest-observed-

adverse-effect level (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/El×C3H/El)$F_1$ mice were given a single intraperitoneal injection of 60 or 120 mg of acrylamide per kilogram 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 kilogram 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 hours, 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 $F_0$ and $F_1$ 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 $F_0$ males was 2.0 mg/kg of body weight per day (Tyla et al., 2000).

### *4.5 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).

### *4.6 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).

### *4.7 2010 Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluation*[1]

#### *4.7.1 Toxicological data*

Despite overt symptoms of neurotoxicity (i.e. hindlimb paralysis) at the highest oral acrylamide dose tested (44 mg/kg of body weight per day in drinking-water), a short-term study in adult male rats indicated that only minor changes were seen in messenger ribonucleic acid levels of the more than 50 genes directly related to the cholinergic, noradrenergic, γ-aminobutyric acid releasing or glutamatergic neurotransmitter systems in the striatum, substantia nigra or parietal cortex. No evidence of axonal, dendritic or neuronal cell body damage or microglial activation

[1] This section has been extracted from FAO/WHO (2011a,b). The interested reader should refer to FAO/WHO (2011b) for more information and primary references.

was found in the forebrain at acrylamide doses below 44 mg/kg of body weight per day. In addition, levels of serotonin, dopamine and their metabolites were essentially unchanged in the striatum, substantia nigra or parietal cortex. The motor deficits observed were interpreted as being caused by damage to the brain stem, spinal cord and peripheral neurons.

The effect of orally administered acrylamide on neurodevelopment in rats was investigated following exposure during gestation and postnatally in two separate studies. In one study, food-motivated behaviour, evaluated at 6–12 weeks of exposure, was significantly changed only at the highest dose tested (5 mg/kg of body weight per day).

In a second study in rats, oral acrylamide doses of 7.9 mg/kg of body weight per day and 14.6 mg/kg of body weight per day caused gait abnormalities in dams from postnatal day (PND) 18 and PND 2, respectively, to PND 21. A corresponding reduction in pup body weight occurred over the same time interval. Histopathological changes were observed in ganglion cells of the trigeminal nerves at doses of 7.9 mg/kg of body weight per day and above. Pups from untreated dams that received acrylamide intraperitoneally at a dose of 50 mg/kg of body weight 3 times a week from PND 2 to PND 21 showed similar trigeminal nerve lesions. Morphometric data of the sciatic nerve in dams but not their pups at 14.6 mg/kg of body weight per day showed a significant increase in the number of degenerated small-diameter axons and myelinated nerves. Similar lesions were found in pups treated intraperitoneally. All male pups from dams treated at 14.6 mg/kg of body weight per day and those treated intraperitoneally showed evidence of delayed spermatogenesis.

Significantly increased incidences of neurotoxicity, measured as peripheral nerve (sciatic) axon degeneration by microscopic histopathology, were observed in a 2-year United States National Center for Toxicological Research/National Toxicology Program (NCTR/NTP) bioassay (Beland, 2010) with F344 rats treated with acrylamide in drinking-water. The NOAELs were 0.67 mg/kg of body weight per day in males and 1.88 mg/kg of body weight per day in females.

*4.7.2 Genotoxicity*

In accord with the previously reported findings, the new in vitro genotoxicity studies indicate that acrylamide in the absence of activation is a weak mutagen but an effective clastogen. In contrast, glycidamide is a mutagen and clastogen. Assays of mutagenicity in vivo have demonstrated that administration of acrylamide or glycidamide in the drinking-water increases mutant frequencies in lymphocyte *Hprt* and liver and lung *cII* genes of adult Big Blue mice by inducing primarily G:C to T:A transversions. Similarly, acrylamide and glycidamide (approximately 3–5 mg/kg of body weight per day) are mutagenic in thyroid, but not liver or mammary gland, of male and female Big Blue rats. In addition, glycidamide, but not acrylamide, was found to be a deoxyribonucleic acid (DNA)-reactive mutagen in neonatal Tk mice at *Hprt* and *Tk* loci. In mice treated with acrylamide for 28 days, there was a linear increase in the number of micronuclei that achieved significance at 6 mg/kg of body

weight per day in erythrocytes and at 4 mg/kg of body weight per day in reticulocytes. Use of an internal marker of acrylamide exposure, such as concentrations of haemoglobin adducts (glycidamine–valine, or GA-Val; acrylamide–valine, or AA-Val) or DNA adducts (N7-glycidamine–guanine, or N7-GA-Gua), gave a better fit than the external dose for modelling micronuclei frequency. The fitted model gave a threshold at adduct levels equivalent to an external dose of 1–2 mg/kg of body weight per day.

*4.7.3 Carcinogenicity*

In the recently completed 2-year NCTR/NTP studies in which mice and rats were treated with acrylamide in drinking-water (Beland, 2010), the sites of tumours (thyroid and mammary gland, peritesticular mesothelium) induced in male and female F344 rats at a dose range up to 2.78 mg/kg of body weight per day in males and 4.09 mg/kg of body weight per day in females were concordant with those found in previous 2-year studies in rats. Additional tumour sites observed in the new study were heart schwannomas and pancreatic islet tumours in males. A notable absence in the new study was the lack of significantly elevated incidences of brain and spinal cord tumours of glial origin. The new study also reported the tumorigenesis of acrylamide in multiple tissues of male and female B6C3F1 mice (lung, Harderian gland, forestomach, mammary, ovary) using the same drinking-water concentrations as used in the rat study. The achieved acrylamide doses in mice were up to 9.11 mg/kg of body weight per day for males and 9.97 mg/kg of body weight per day for females. These findings were further supported by results from parallel groups of animals that were treated with equimolar concentrations of glycidamide in drinking-water. Most tumour sites at which the incidence was significantly elevated in rats and mice exposed to acrylamide were also significantly increased by glycidamide, with glycidamide-induced tumour incidences being either similar or higher. The only exceptions were ovarian benign granulosa cell tumours in female mice and pancreatic adenomas and carcinomas in male rats. Tumours in other tissues were observed to be significantly increased in glycidamide-treated rats and mice, including skin in mice and oral cavity and mononuclear cell leukaemia in rats. The concordance of tumour sites and glycidamide internal dosimetry from physiologically based pharmacokinetic modelling modelling between acrylamide- and glycidamide-treated rodents provides strong support for the hypothesis that glycidamide is the ultimate carcinogenic species derived from metabolism of acrylamide. Additional support for the tumorigenicity of glycidamide, but not acrylamide, was observed in livers of male Tk mice treated neonatally on PNDs 1, 8 and 15 and evaluated after 1 year of life.

## *5. 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 hours and seizures after 9 hours. 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, haemoglobin adduct with acrylamide (acrylamide adducted in the *N*-terminal of valine in haemoglobin 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 haemoglobin 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/l, and that of valine adducts was 13.4 nmol/g of haemoglobin. 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).

More recently, JECFA evaluated the effects of acrylamide on humans, which were summarized as follows (FAO/WHO, 2011a,b)[1]:

> The updated analyses of workers exposed to acrylamide by inhalation revealed considerably lower relative risks for mortality from pancreatic cancer than in previous analyses of the same cohorts, and the results were not statistically significant. The updated analyses are based upon comparisons with mortality in the general population as well as comparisons of different levels of acrylamide exposure within the cohort, with control for smoking history. Taken together, in spite of high acrylamide exposure in some workers, results for these two cohorts do not provide support for any relationship between acrylamide exposure at the workplace and cancer mortality.
>
> The potential association between dietary exposure to acrylamide and cancer has been assessed in five prospective studies. Without taking into account subgroup analyses (i.e. different histological types of tumour in a particular organ, different stage at diagnosis, stratified analysis by smoking), these cohorts provided 23 estimates of relative risk for 16 tumour sites. No statistically significant associations were found between dietary acrylamide exposure and the following cancers: breast (four studies), ovary (two), endometrium (two), prostate (two), urinary bladder, colon and rectum (two), stomach, oesophagus, pancreas, lung (men), brain, oral cavity, pharynx, larynx and thyroid. Statistically significant associations were found in some studies for some cancers, including renal

[1] The interested reader should refer to FAO/WHO (2011b) for more information and primary references.

cell cancer, when adjusted for smoking, and for ovarian and endometrial cancers among non-smokers. A significant increase in risk was also reported for cancer of the oral cavity, but this was restricted to female non-smokers. For lung cancer, there was a significant inverse association among women; this association was stronger among non-smokers and for adenocarcinomas. To date, none of these associations between acrylamide exposure and cancer at particular sites have been confirmed.

No association was found between concentrations of the biomarker AA-Val haemoglobin adduct and prostate cancer in a population-based case–control study. In a prospective study, no association between AA-Val/GA-Val concentrations and risk of breast cancer in postmenopausal women was found. However, a significantly increased risk was reported in smokers after adjusting for duration and intensity of smoking. This effect was even stronger when the analysis was restricted to cases with ER+ [estrogen receptor positive] tumours. These associations were found for AA-Val adducts but not for GA-Val adducts.

Overall, the epidemiological studies do not provide any consistent evidence that occupational exposure or dietary exposure to acrylamide is associated with cancer in humans. Although some studies indicate an association with some tumour types, particularly the hormone-related cancers in women, this needs confirmation. While the epidemiological investigations have not shown an increased cancer risk from acrylamide exposure, the statistical power and potential for misclassification of acrylamide dietary exposure in these studies are of concern. The reviewed studies, including those with a relatively large sample size, had low power (always below 50%) to detect an increased risk of small magnitude. Data from FFQs [food frequency questionnaires], which are used to estimate the extent of dietary exposure to acrylamide in population-based studies, have been shown to correlate poorly with biomarkers of acrylamide and glycidamide exposure. Dietary exposure estimates derived from FFQs cannot readily capture the inherent variability of acrylamide concentrations in individual foods…. Consequently, epidemiological studies that use FFQs have a limited ability to detect an association between the surrogate measure of dietary acrylamide exposure and a modest increase in cancer risk.

## *6. PRACTICAL CONSIDERATIONS*

### *6.1 Analytical methods and achievability*

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/l (Brown & Rhead, 1979). A newly developed method involving gas chromatography with mass spectrometric detection has a detection limit of 0.008 µg/l and can be used with concentrations typically up to 0.5 µg/l (Environment Agency, 2009).

### *6.2 Treatment methods and performance*

Acrylamide concentrations in drinking-water are usually controlled by limiting either the acrylamide content of polyacrylamide flocculants or the dose used, or both. However, advances in analytical techniques are beginning to allow control by direct measurement.

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.

## *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 have led to a re-examination of the mechanism of carcinogenicity and the cancer risk associated with exposure from all sources. 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, the guideline value associated with an upper-bound excess lifetime cancer risk of $10^{-5}$ is estimated to be 0.5 µg/l.

JECFA reconsidered acrylamide in order to take into account new data (FAO/WHO, 2011a,b). When average and high dietary exposures were compared with the lower limit on the benchmark dose for a 10% response ($BMDL_{10}$) of 0.31 mg/kg of body weight per day for the induction of mammary tumours in rats, the margins of exposure were 310 and 78, respectively. For Harderian gland tumours in mice, the $BMDL_{10}$ was 0.18 mg/kg of body weight per day, and the margins of exposure were 180 and 45 for average and high exposures, respectively. There were also concerns regarding the neurotoxicity of acrylamide. JECFA concluded that although there were uncertainties with regard to extrapolating the risks in laboratory animal studies to humans (epidemiological studies of occupationally exposed populations do not show the expected incidence of cancer), exposure should be reduced to as low a level as technically achievable (FAO/WHO, 2011a,b).

The guideline value of 0.5 µg/l is therefore retained, with the additional proviso that exposure should be reduced to as low a level as technically achievable.

The most important source of drinking-water contamination by acrylamide is the use of polyacrylamide flocculants that contain residual acrylamide monomer. Acrylamide concentrations in drinking-water are usually controlled by limiting either the acrylamide content of polyacrylamide flocculants or the dose used, or both. However, advances in analytical techniques are beginning to allow control by direct measurement. Every effort should be made to limit free acrylamide monomer in polyacrylamide used for water treatment, and water suppliers should also make every effort to ensure that residual acrylamide in drinking-water is kept as low as is technically feasible. In particular, if acrylamide is controlled by limiting the amount dosed, overdosing should always be avoided.

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