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Atrazine and Its Metabolites 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 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 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

The first draft of Atrazine and Its Metabolites in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality* (GDWQ), was prepared by Mr J.K. Fawell, United Kingdom, to whom special thanks are due. This background document is an update of the background document published in the second edition of the GDWQ.

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*)
- Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants* and *Pesticides*)
- Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
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- Professor Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
- Dr A.V. Festo Ngowi, Muhimbili University of Health and Allied Sciences, United Republic of Tanzania (*Pesticides*)
- Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held in December 2010. 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 at the Expert Consultation and 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

ADI	acceptable daily intake
DACT	diaminochlorotriazine
DEA	deethyl-atrazine
DIA	deisopropyl-atrazine
DWLOC	Drinking Water Levels of Comparison (USA)
FAO	Food and Agriculture Organization of the United Nations
GAC	granular activated carbon
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
PAC	powdered activated carbon
USA	United States of America
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization

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The atrazine drinking-water guideline prepared for the Third Edition of the WHO Guidelines for Drinking-water Quality has been revised following the recent Joint FAO/WHO Meeting on Pesticide Residues (JMPR) evaluation of atrazine and its environmental metabolites (FAO/WHO, 2007).

This background document is based on and largely extracted from this recent JMPR evaluation. Except for the critical studies on which the guidelines are based, primary references are given only for text that has not been extracted from this report. The interested reader should refer to the toxicological monograph published by FAO/WHO (2009) for more detailed information and primary references.

1. GENERAL DESCRIPTION

1.1 Identity

Chemical Abstracts Service Registry No.: 1912-24-9
Molecular formula: $C_8H_{14}ClN_5$

The International Union of Pure and Applied Chemistry name for atrazine is 6-chloro-N^2-ethyl-N^4-isopropyl-1,3,5-triazine-2,4-diamine.

1.2 Physicochemical properties

Some physical and chemical properties of atrazine that are relevant to its environmental fate are summarized in Table 1.

Table 1: Physicochemical properties of atrazine[a]

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

[a] From Meister (1989); Royal Society of Chemistry (1991); Worthing (1991).

1.3 Major uses and sources in drinking-water

Atrazine is a selective systemic herbicide of the chlorotriazine class, used for the control of annual broadleaf and grassy weeds (Worthing, 1991). Key crops in which atrazine-containing herbicides are used include maize, sorghum and sugarcane, with some other minor uses of local importance. Atrazine and its metabolites have been found in surface water and groundwater as a result of the use of atrazine as a pre-emergent or early post-emergent herbicide. The source of the residue should be considered when interpreting water monitoring data. Assessments should be based on whether diffuse sources (e.g. runoff from an agricultural field) or point sources (e.g. an accidental spill or inappropriate disposal) have contributed to a detection in water. The presence of atrazine and its metabolites in surface water is most likely to be

intermittent, particularly in flowing water, but groundwater contamination will usually be relatively persistent.

1.4 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 (USEPA, 1988). These are similar to the half-lives found under natural conditions, but longer half-lives have been seen under special conditions (Schoen & Winterlin, 1987). Degradation rates normally decrease with increasing depth, and atrazine can be fairly stable in groundwater (Burnside, Fenster & Wicks, 1963).

Atrazine's degradation products in soil include several of the chloro-*s*-triazine metabolites commonly found in water (Keller, 1978) (see section 2). 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 (Ciba-Geigy, 1986). Hydroxytriazines, however, are of low mobility (Helling, 1971) and persist for long periods in the soil (Kahn & Saidak, 1981).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Atrazine and its chloro-*s*-triazine metabolites—deethyl-atrazine (DEA), deisopropyl-atrazine (DIA) and diaminochlorotriazine (DACT)—have been found in surface water and groundwater. The metabolite hydroxyatrazine is more commonly detected in groundwater than in surface water.

A number of studies have monitored the concentrations of atrazine in groundwater and surface water over the last two decades. Recent monitoring data show declining levels and incidences of detection of atrazine and its chloro-*s*-triazine metabolites (DIA, DEA and DACT) compared with data collected in the early 1990s; this reflects restrictions on the use of atrazine that were introduced in the late 1990s and early 2000s and the introduction of good agricultural practices in the European Union, the United States of America (USA) and other parts of the world. Therefore, older monitoring data generally represent an overestimate of environmental concentrations likely to arise from current use practices.

In surface water, the concentrations of the chlorotriazine metabolites of atrazine are generally less than those of atrazine itself, whereas the concentrations of these metabolites in rural wells are more similar to those of atrazine. The relative order of concentrations in rural wells in the USA was generally as follows: atrazine ~ DEA ~ DACT > DIA > hydroxyatrazine. However, concentrations of DEA that are several-fold higher than those of the parent compound have been reported.

Monitoring carried out in a number of countries indicates that concentrations of atrazine and its chloro-*s*-triazine metabolites in groundwater and surface water rarely exceed 2 µg/l and are commonly well below 0.1 µg/l, although concentrations may be higher in agricultural areas where large amounts of atrazine are used. In the past, its

use for weed control on non-crop land, such as railway lines and paved areas, gave rise to contamination of groundwater in particular, although this use has largely disappeared worldwide. The concentration of atrazine in public water supplies in the USA does not exceed the United States Environmental Protection Agency's (USEPA) Drinking Water Levels of Comparison (DWLOC)—the maximum concentrations in drinking-water that, when considered together with dietary exposure, do not exceed a level of concern—for any age group These DWLOCs, which account for atrazine plus its three chloro-*s*-triazine metabolites, range from 12.5 to 68 µg/l for intermediate (seasonal) or chronic (annual) exposure. Concentrations of atrazine in drinking-water in the United Kingdom are less than 0.1 µg/l, based on data measured when atrazine was registered and when good agricultural practices had been adopted. In Canada, concentrations of atrazine and its chloro-*s*-triazine metabolites did not exceed the interim guideline level (5 µg/l, includes metabolites) in any samples of drinking-water from 10 Canadian treatment plants in the cereal-growing regions of Ontario and Quebec (from groundwater and surface water). Levels of atrazine were below 0.83 µg/l, concentrations of DEA were below 0.35 µg/l, and DIA and DACT were found less often and at lower levels in treated surface water. Total chloro-*s*-triazine concentrations from raw water were below 0.5 µg/l in groundwater and well below 0.68 µg/l in surface water (Tauber, 2006).

It is expected that exposure of the public will be primarily through drinking-water.

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

After oral administration to rats, ^{14}C-labelled atrazine was rapidly and almost completely absorbed, independent of dose and sex. Radioactivity was widely distributed throughout the body. Excretion was more than 93% of the administered dose within 7 days, primarily via the urine (approximately 73%) and to a lesser extent via the faeces (approximately 20%; approximately 7% via bile), with more than 50% being excreted within the first 24 h. The elimination half-life of radiolabel from the whole body was 31.3 h in rats; this prolonged half-life was caused by covalent binding of atrazine to cysteine sulfhydryl groups in the β-chain of rodent haemoglobin. Seven days after administration of a single low dose (1 mg/kg body weight), tissue residues represented 6.5–7.5% of the dose, with the highest concentrations in erythrocytes (≤0.63 mg/kg), liver (≤0.50 mg/kg) and kidneys (≤0.26 mg/kg).

Atrazine was extensively metabolized; more than 25 metabolites have been identified in rats. The major metabolic pathways were stepwise dealkylation via either DIA or DEA to DACT, the major metabolite. Dechlorination involving conjugation with glutathione was a minor pathway. The biotransformation of atrazine in rats and humans was qualitatively similar.

4. TOXICOLOGICAL SUMMARY

4.1 Atrazine

Atrazine was of low acute toxicity in rats exposed orally (median lethal dose [LD_{50}] 1870–3090 mg/kg body weight), dermally (LD_{50} >2000 mg/kg body weight) or by

inhalation (median lethal concentration [LC_{50}] >5.8 mg/l). Atrazine was not a skin irritant or an eye irritant in rabbits.

In short-term studies of toxicity in rats, dogs and rabbits, the consistent toxic effects noted across species included reduced body weight gain and food intake and a slight decrease in erythrocyte parameters. Also, liver weights and splenic haemosiderin deposition were increased in rats, whereas there was marked cardiac toxicity in dogs.

Atrazine was tested for genotoxicity in a large number of studies covering an adequate range of end-points. JMPR agreed that it is unlikely that atrazine is genotoxic.

Long-term studies of toxicity and carcinogenicity were conducted in mice and rats. As in short-term studies, reduced body weight gain and food intake and a decrease in erythrocyte parameters were noted consistently. Additionally, reduced survival of females and cardiovascular effects (atrial thrombi) in both sexes were observed in mice at high doses.

In three studies of carcinogenicity in mice, no treatment-related carcinogenic effects were observed at dietary concentrations up to about 386 and 483 mg/kg body weight per day in males and females, respectively. Overall, the no-observed-adverse-effect level (NOAEL) was 1.2 mg/kg body weight per day, on the basis of lower body weight/body weight gain at 38.4 mg/kg body weight per day and greater.

In one study of carcinogenicity in Fischer 344 rats fed diets containing atrazine at concentrations up to about 20 mg/kg body weight per day, there was no effect at any dose on the onset or incidence of tumours. The NOAEL was about 3.5 mg/kg body weight per day, on the basis of decreased body weight.

In seven studies of carcinogenicity in Sprague-Dawley rats fed diets containing atrazine at concentrations up to about 42 and 65 mg/kg body weight per day in males and females, respectively, an increased incidence of mammary tumours (adenomas, carcinomas, fibroadenomas) with or without an earlier onset (relative to controls) was observed in four studies, whereas there was an earlier onset of mammary tumours without any increase in their overall lifetime incidence in two studies. An earlier onset of pituitary tumours was also observed in one study, with no increase in incidence at term. Overall, the NOAEL for mammary carcinogenicity was 1.5 mg/kg body weight per day, on the basis of a statistically significant increased incidence in mammary tumours at 3.1 mg/kg body weight per day.

In a study of carcinogenicity in ovariectomized Sprague-Dawley rats, neither increases in mammary gland proliferative changes nor mammary tumours were seen at dietary concentrations up to about 21 mg/kg body weight per day, suggesting that the carcinogenic mode of action of atrazine in Sprague-Dawley rats is related to ovarian function.

In a study designed to evaluate the effects of atrazine on the pre-ovulatory luteinizing hormone (LH) surge and on the estrous cycle, groups of 90 female Sprague-Dawley (Crl:CD BR) rats received diets containing atrazine (purity, 97.1%) at a concentration of 0, 25, 50 or 400 mg/kg (equal to 0, 1.8, 3.65 and 29.44 mg/kg bw per day) for

26 weeks. Attenuation of the LH surge and subsequent disruption of the estrous cycle (characterized by an increase in days in estrus) were observed at and above 3.65 mg/kg body weight per day, with a NOAEL of 1.8 mg/kg body weight per day (Morseth, 1996). The NOAEL and lowest-observed-adverse-effect level (LOAEL) for these effects were comparable to those found in the studies of carcinogenicity. The effects on the LH surge and disruption of the estrous cycle were further supported by a number of short-term mechanistic studies. Additional experiments suggested that the effects of atrazine on LH and prolactin secretion are mediated via a hypothalamic site of action.

The postulated mode of action for atrazine-induced mammary tumours in female Sprague-Dawley rats involved disruption of the hypothalamic–pituitary–ovary axis. Atrazine modifies catecholamine function and the regulation of gonadotropin-releasing hormone pulsatility in the rat hypothalamus, with the consequence that the pulse of LH released from the pituitary gland is of insufficient amplitude or duration to trigger ovulation. The failure to ovulate results in persistent secretion of estrogen, which provides a feedback to the pituitary, leading to increased secretion of prolactin. As a result, atrazine accelerates the normal reproductive ageing process in female Sprague-Dawley rats, whereby reproductive senescence is characterized by persistent exposure to estrogen and prolactin. In contrast, women respond to reduced levels of LH by reductions in levels of estrogen. Thus, JMPR considered that the mode of carcinogenic action in certain susceptible rat strains is not relevant for human risk assessment.

Investigations of other modes of action did not provide any evidence that atrazine had intrinsic estrogenic activity or that it increased aromatase activity in vivo.

JMPR concluded that atrazine is not likely to pose a carcinogenic risk to humans.

Although carcinogenicity in humans was not a concern owing to the rat-specific mode of action, alterations in neurotransmitter and neuropeptide function regulating LH and secretion of prolactin may potentially induce adverse effects during critical periods of development (as found in special studies showing pregnancy loss, delayed puberty in males and females, and decreased suckling-induced prolactin release in lactating dams). Unlike the carcinogenic effects, the developmental effects do not appear to be specific to certain strains of rats, and JMPR therefore considered these effects to be relevant for risk assessment in humans.

In special studies of reproductive toxicity, exposure of rats during early pregnancy (i.e. the LH-dependent period) caused increased pre-implantation or post-implantation losses, including full-litter resorptions. Effects were seen at doses of ≥50 mg/kg body weight per day after treatment on days 6–10 of gestation, with a NOAEL of 25 mg/kg body weight per day. In contrast, exposure on days 11–15 of gestation (after the LH-dependent period of pregnancy) at a dose of 200 mg/kg body weight per day did not induce full-litter resorptions.

Suppression of the suckling-induced prolactin release in lactating rats was seen with atrazine at doses of ≥25 mg/kg body weight per day, with a NOAEL of 12.5 mg/kg body weight per day. Treatment of lactating rats on postnatal days 1–4 affected the development of tuberoinfundibular dopaminergic neurons in the pups (presumably

due to the lack of prolactin derived from the dam's milk), with the consequence of impaired regulation of prolactin secretion, hyperprolactinaemia prior to puberty and prostatitis in the adult male offspring.

A delay in sexual development was observed in female rats after exposure on postnatal days 21–46 at doses of ≥30 mg/kg body weight per day, with a NOAEL of 10 mg/kg body weight per day, and in male rats after exposure on postnatal days 23–53 at doses of ≥12.5 mg/kg body weight per day, with a NOAEL of 6.25 mg/kg body weight per day.

In a standard two-generation study of reproduction (conducted according to earlier guidelines, which did not include end-points such as estrous cyclicity and sexual development) in rats, there was no effect on fertility at 36.1 mg/kg body weight per day, the highest dose tested. The NOAEL for parental toxicity was 3.6 mg/kg body weight per day, on the basis of decreased body weight gains and food consumption. The NOAEL for reproductive toxicity was 3.6 mg/kg body weight per day, on the basis of decreased body weights of male pups at postnatal day 21.

In two studies of prenatal developmental toxicity in rats given atrazine on days 6–15 of gestation, the NOAELs for maternal toxicity were 10 or 25 mg/kg body weight per day on the basis of decreased body weight gain and food intake at 70 or 100 mg/kg body weight per day, respectively. The NOAELs for developmental toxicity were 10 or 25 mg/kg body weight per day on the basis of incomplete ossification at several sites at 70 or 100 mg/kg body weight per day, respectively. In a study of prenatal developmental toxicity in rabbits given atrazine on days 7–19 gestation, the NOAEL for maternal toxicity was 5 mg/kg body weight per day on the basis of clinical signs, abortion and decreased food intake and body weight gain at 75 mg/kg body weight per day. The NOAEL for developmental toxicity was 5 mg/kg body weight per day on the basis of increased resorptions, reduced litter size and incomplete ossification at 75 mg/kg body weight per day. In rats and rabbits, the developmental effects were observed only at maternally toxic doses.

JMPR concluded that atrazine was not teratogenic.

Studies using a variety of test systems in vitro and in vivo indicated that modulation of the immune system occurs after exposure to atrazine. However, effects suggestive of impaired function of the immune system were observed only at doses greater than those shown to affect neuroendocrine function, leading to disruption of the estrous cycle or developmental effects.

A range of epidemiological studies (including cohort studies, case–control studies, and ecological or correlational studies) assessed possible relationships between atrazine or other triazine herbicides and cancer in humans. For some cancer types, such as prostate or ovarian cancer and non-Hodgkin lymphoma, the increased risks reported in single studies either could be explained by the methodology used or had not been confirmed in more reliable studies. Thus, the weight of evidence from the epidemiological studies did not support a causal association between exposure to atrazine and the occurrence of cancer in humans.

4.2 Metabolites of atrazine

*4.2.1 Chloro-*s*-triazine metabolites*

The toxicity profiles and mode of action of the chloro-*s*-triazine metabolites were similar to those of atrazine; the potency of these metabolites with regard to their neuroendocrine-disrupting properties appeared to be similar to that of the parent compound.

Like atrazine, the chloro-*s*-triazine metabolites were of moderate or low acute oral toxicity in rats; LD_{50}s were 1110, 1240 and 2310–5460 mg/kg body weight for DEA, DIA and DACT, respectively.

Like atrazine, its chloro-*s*-triazine metabolites delayed sexual development of male rats exposed on postnatal days 23–53 at atrazine molar equivalent doses of ≥25 mg/kg body weight per day (DEA, DIA) and ≥12.5 mg/kg body weight per day (DACT), with NOAELs of 12.5 and 6.25 mg/kg body weight per day, respectively. Exposure of female rats to DACT on postnatal days 22–41 delayed sexual development at atrazine molar equivalent doses of ≥50 mg/kg body weight per day, and the NOAEL was 25 mg/kg body weight per day. Doses at which these effects occurred were similar to those observed for parent atrazine.

In short-term feeding studies in rats, the main effects of the chlorinated metabolites were similar to those of atrazine and included reduced body weight gain and decreased erythrocyte parameters and also, for DACT, disruption of the estrous cycle. The NOAELs were 3.2 mg/kg body weight per day for DEA and DIA and 7.6 mg/kg body weight per day for DACT.

In a 29/52-week study with DACT in Sprague-Dawley rats, effects comparable to those observed with atrazine (attenuation of the LH surge, increased incidences of mammary tumours) were seen at 270 mg/kg diet; the NOAEL was 48 mg/kg diet, equal to 3.4 mg/kg body weight per day. No long-term studies were performed with DEA or DIA.

In short-term feeding studies in dogs, the main effects of the chlorinated metabolites were similar to those of atrazine and included reduced body weight gain and decreased erythrocyte parameters, whereas DEA and DACT showed cardiac toxicity. The NOAELs were 3.7, 3.8 and 3.5 mg/kg body weight per day for DEA, DIA and DACT, respectively.

DEA, DIA and DACT did not show genotoxicity in an adequate range of tests in vitro and in vivo.

In studies of prenatal developmental toxicity in rats, the chlorinated metabolites induced increased incidences of fused sternebrae and/or incomplete ossification at doses of 25–100 mg/kg body weight per day; the NOAELs for developmental toxicity were 25, 5 and 2.5 mg/kg body weight per day for DEA, DIA and DACT, respectively. The effects were seen only at doses that also produced maternal toxicity.

4.2.2 Hydroxyatrazine

The metabolite hydroxyatrazine does not have the same mode of action or toxicity profile as atrazine and its chlorometabolites. The main effect of hydroxyatrazine was kidney toxicity (owing to its low solubility in water, resulting in crystal formation and a subsequent inflammatory response), and there was no evidence that hydroxyatrazine has neuroendocrine-disrupting properties. Also, the acute oral toxicity of hydroxyatrazine in rats (LD_{50} >5050 mg/kg body weight) was lower than that of atrazine or its chlorometabolites.

In short-term feeding studies, the main effects of hydroxyatrazine in rats included reduced body weight gain, increased water consumption, changes in clinical chemistry and urine analysis parameters, and kidney lesions. The overall NOAEL was 6.3 mg/kg body weight per day. In dogs, effects included reduced body weight gain and food consumption, changes in clinical chemistry and urine analysis parameters, and kidney lesions; the NOAEL was 5.8 mg/kg body weight per day.

In a 2-year study of toxicity and carcinogenicity in rats, the effects of hydroxyatrazine included clinical signs and increased mortality, reduced body weight gain and food consumption, increased water consumption, changes in haematological, clinical chemistry and urine analysis parameters, and kidney lesions. The NOAEL was 1.0 mg/kg body weight per day. There was no evidence of carcinogenicity (Chow & Hart, 1995).

Hydroxyatrazine did not show genotoxicity in an adequate range of tests in vitro and in vivo.

In a study of prenatal developmental toxicity in rats, the effects of hydroxyatrazine consisted of reduced food consumption and body weight gain in dams and increased incidences of incomplete and absent ossification in fetuses at 125 mg/kg body weight per day; the NOAEL was 25 mg/kg body weight per day for maternal and developmental toxicity. Exposure of female rats on postnatal days 22–41 at atrazine molar equivalent doses up to 200 mg/kg body weight per day did not delay sexual development.

5. PRACTICAL ASPECTS

5.1 Analytical methods and analytical achievability

Atrazine is determined by gas chromatography with nitrogen–phosphorus detection following extraction with pentane or ethyl acetate. The detection limit in tap water and river water is about 0.1 µg/l (Yokley & Cheung, 2000).

Atrazine is determined by gas chromatography/mass spectrometry with solid-phase extraction. The detection limit in raw water and drinking-water is 10 ng/l (Bruzzoniti et al., 2006). Extraction of the metabolites can be achieved using styrene-divinylbenzene sorbents. Detection limits for triazines determined by capillary gas chromatography with nitrogen thermionic specific detection and high-performance liquid chromatography with photodiode array absorption detection following extraction with styrene-divinylbenzene sorbents and elution with acetone were lower

than 5 ng/l (Drevenkar et al., 2002). Atrazine is also determined by isotope dilution gas chromatography/mass spectrometry with solid-phase extraction. The method detection limit in surface water is 1 ng/l (Planas et al., 2006). In the case of a large-volume injection approach using 50 µl of the 40-fold concentrated extract, the detection limit in river water is 2 ng/l (Schellin & Popp, 2007). Using a liquid chromatography/mass spectrometry method utilizing online solid-phase extraction (Koivunen et al., 2006) or ultra-performance liquid chromatography combined with tandem mass spectrometry (Gervais et al., 2008), the limit of quantification is 50 ng/l or 12 ng/l, respectively.

Other methods are included in the USEPA's (2009) document on *Analytical Methods Approved for Drinking Water Compliance Monitoring of Organic Contaminants*.

5.2 Treatment and control methods and performance

Coagulation and filtration are ineffective at removing atrazine. Only 7% removal was achieved with ferric chloride dosed with iron at at 14 mg/l, with an atrazine concentration of 0.84 µg/l (Normann, Haberer & Oehmichen, 1987). Aluminium sulfate (aluminium dose of 2 mg/l at pH 8) was also completely ineffective at reducing an atrazine concentration of 66 µg/l (Miltner et al., 1989). In laboratory tests, atrazine at 3 µg/l in river water was treated with aluminium sulfate (up to 10 mg/l as aluminium) or ferric sulfate (up 40 mg/l as iron), but no removal was observed (Jiang & Adams, 2006). Lime soda softening was also ineffective. Results from other studies also suggest that conventional coagulation-based water treatment processes are ineffective at reducing atrazine concentrations (Foster, Rachwal & White, 1991; Van Hoof, Ackermans & Celens, 1992).

A full-scale granular activated carbon (GAC) plant treating river water with an atrazine concentration of 0.3–2 µg/l, with an empty bed contact time of 15–20 min, treated 20 000 bed volumes before 0.1 µg/l was reached in the effluent (Normann, Haberer & Oehmichen, 1987). Results from other treatment works incorporating GAC have shown that the atrazine concentration can be reduced to 0.1 µg/l (contact times 19–20 min, bed lifetimes 20–24 months, initial atrazine concentrations 0.16–0.27 µg/l) (Croll, Chadwick & Knight, 1991). One study found that the adsorption capacity of GAC varied between 0.04 and 0.22 mg/g carbon, depending on the type of GAC used (Duguet, 1994). The same study also found that the concentration of natural organic matter present greatly affected the capacity of the carbon to adsorb atrazine (e.g. 20 mg of atrazine per gram carbon for distilled water, reduced to 0.6–0.15 mg/g for dissolved organic carbon in range 2–8 mg/l as carbon). GAC has been applied successfully to pesticide removal (including atrazine) using slow sand filtration, as a layer 75–200 mm thick, sandwiched between conventional sand media. Contact times are 30–60 min (Anon, 1994).

Powdered activated carbon (PAC) has been used to remove atrazine from surface waters, with only a seasonal requirement to reduce pesticide concentrations. A dose of 5 mg/l with 40 min contact in a PAC reactor (coupled with coagulation) reduced the influent concentration of atrazine (0.53 µg/l) to 0.08 µg/l; there was a further reduction to <0.05 µg/l in the final water due to the remaining capacity in the PAC once it was separated at the filtration stage (Haist-Gulde, Baldauf & Brauch, 1993). Tests with a batch reactor showed that PAC (3.3 mg/l) reduced the initial

concentration of atrazine (22.5 µg/l) by 60% after 75 min contact (Qi, 1994). Atrazine spiked into water at 5 µg/l was treated with two PACs at pH 7.5. At a PAC dose of 10 mg/l in deionized water, both achieved ~100% removal. In river water, the removals were reduced to ~95% and ~90%, respectively (Jiang & Adams, 2006). In the same study, desethylatrazine was also ~100% removed from deionized water. In river water, the removals were reduced to ~85% and ~70%, respectively.

At a waterworks, ozonation produced removals of 29% and 42% for concentrations of 0.17 µg/l and 0.19 µg/l, respectively (Brauch & Kuhn, 1988). Ozonation conditions, such as dissolved ozone concentration, contact time and applied ozone dose, affect removal efficiency, as well as factors influencing the decomposition of ozone to form hydroxyl radicals (e.g. pH, temperature, organic matter content and bicarbonate concentration) (Duguet, 1994). A combination of ozone and either ultraviolet (UV) radiation or hydrogen peroxide improves removal efficiency and results in bed life extension if associated with GAC adsorption (Duguet, 1994). At full scale, one treatment works achieved a reduction of approximately 40% (initial concentration 100–600 ng/l) with ozone alone (15 min contact, dose approximately 2.2 mg/l); for the same ozone dose, in combination with hydrogen peroxide (H_2O_2/O_3 = 0.4 by mass), there was an 80% reduction in atrazine concentration (Duguet, 1992). For the treatment of atrazine at 1 mg/l to below 0.1 µg/l, the life of the GAC bed was doubled by ozonation alone and increased nearly 6-fold by the combination of oxidants. Other studies have found removals of 60% using ozone at 2.2 mg/l with a contact time of 5 min on a solution containing atrazine at 3 µg/l (Meijers, Van der Veer & Kruithof, 1993). Pilot plant trials have achieved removals of atrazine between 30% and 60% with ozone doses of 2–4 mg/l and 5–15 min contact time (Foster, Rachwal & White, 1991). In a 9-month pilot study, raw water atrazine concentrations of 7–80 ng/l were hardly affected by aluminium sulfate coagulation treatment but were reduced by 66–96% when ozonation (1.5–2 mg/l, 20 min contact) was applied (Hua, Bennett & Letcher, 2006). A combination of bankside storage, ozonation and finally GAC filtration reduced the concentration of atrazine in river water from 0.32 µg/l to 0.11, 0.09 and <0.01 µg/l, respectively (Haist-Gulde, Baldauf & Brauch, 1993).

Membrane filtration using ultrafiltration techniques does not remove atrazine, but nanofiltration is more successful; one study indicated that removals of between 66% and 98% were achieved for atrazine at an initial concentration of 3–5 µg/l (Hofman, 1992). With nanofiltration, rejection rates varied between 75% and 100% for atrazine (influent atrazine 1 µg/l, combined with five other pesticides); the specific membrane type was an important factor in determining rejection rates. Pilot plant trials involving membrane filtration have achieved removals between 79% and 99% for atrazine (Hofman et al., 1993). Atrazine (10 µg/l) was 85–95% removed by a nanofiltration membrane (Chen et al., 2004). Atrazine (concentration not stated) was 80–85% removed by different nanofiltration membranes and 96% removed by a polyamide reverse osmosis membrane (Kosutic et al., 2005). A concentration of 0.5–1.5 mg/l was 98% and 68% removed by two polyvinyl alcohol/polyamide nanofiltration membranes, but only 15% and 11% removed by two polyethersulfone nanofiltration membranes (Kiso et al., 2000). Removals of 82%, 83% and 84% from a 150–300 µg/l solution were reported for three different nanofiltration membranes (Plakas et al., 2006); fouling of the membrane by calcium and humic acid worsened the performance. A full-scale (140 000 m^3/day) nanofiltration plant at Méry-sur-Oise, France, reduced a concentration of 850 ng/l to <50 ng/l (Cyna et al., 2002). In a pilot

plant study, DEA was spiked at 1 µg/l into distilled water, sand-filtered water and GAC-filtered water, then subjected to nanofiltration through composite polyamide membranes. Removals of 62–95% and 62–75% were obtained with two nanofiltration membranes (Boussahel, Baudu & Montiel, 2001). In another study (Boussahel et al., 2000), one of the membranes gave ~90% removal from a 1 µg/l solution, and the other gave ~70% removal. With both membranes, adsorption onto the membrane accounted for about 35% removal.

UV radiation was effective at reducing atrazine concentrations during laboratory studies. With an irrradiation time of 5 min, the atrazine concentration was reduced by almost 90%. With a longer duration of radiation, there was only a small further decrease in the atrazine concentration (Cermak & Cermakova, 1992). UV irradiation, at pilot plant scale, was found to be effective in decomposing atrazine in a chalk borehole water, up to 70% removal being achieved with UV doses of up to 700 Wh/m^3. Removal efficiency was constant over an influent concentration range of 0.1–0.5 µg/l (Bourgine et al., 1995). UV irradiation causes substantial photodecomposition but not complete mineralization (Le Brun et al., 1993).

A laboratory comparison of UV, hydrogen peroxide, ozone, ozone/UV, ozone/hydrogen peroxide, hydrogen peroxide/UV and ozone/hydrogen peroxide/UV demonstrated that all processes destroyed atrazine (hydrogen peroxide only at pH >10) and that UV/hydrogen peroxide gave the fastest degradation rate (Prado & Esplusgas, 1999). Treatment of 3 µg/l solutions of atrazine and DEA with 2 mg/l free chlorine and a 30 min contact time gave no removal (Jiang & Adams, 2006).

A number of point-of-use and point-of-entry water treatment systems based on activated carbon are available and are suitable for treating water that may be contaminated with atrazine. These systems should be used only on microbially safe drinking-water, they should be well flushed before each use and the filters should be changed frequently. Point-of-use and point-of-entry reverse osmosis systems could also be used for removal of atrazine.

Although specific published data on the removal of the atrazine metabolites are limited, what data there are suggest that these will behave in a manner similar to atrazine.

6. GUIDELINE VALUES

Drinking-water may contain metabolites of atrazine as well as atrazine itself. The chloro-*s*-triazine metabolites DEA, DIA and DACT share the same mode of action as atrazine and have a similar toxicological profile. Hence, JMPR decided to establish a group acceptable daily intake (ADI). Hydroxyatrazine, the plant and soil degradate, was not included because its mode of action and toxicological profile are different from those of atrazine and its chloro-*s*-triazine metabolites.

JMPR established a group ADI of 0–0.02 mg/kg body weight based on the NOAEL for atrazine of 1.8 mg/kg body weight per day identified on the basis of LH surge suppression and subsequent disruption of the estrous cycle seen at 3.6 mg/kg body weight per day in a 6-month study in rats, using a safety factor of 100 for interspecies and intraspecies variation. JMPR considered that this NOAEL is protective for the

consequences of neuroendocrine and other adverse effects caused by prolonged exposure to atrazine and its chloro-*s*-triazine metabolites.

Applying this group ADI to a 60 kg adult drinking 2 litres of water per day and allocating 20% of the total daily intake to drinking-water, a guideline value of 0.1 mg/l can be derived for atrazine and its chloro-*s*-triazine metabolites in drinking-water. JMPR was not able to assess the source allocation of atrazine to drinking-water. As such, the default 20% allocation was chosen, as it will be very conservative in most countries, and in addition it is expected that exposure of the public will be primarily through drinking-water.

For hydroxyatrazine, JMPR established an ADI of 0–0.04 mg/kg body weight based on the NOAEL of 1.0 mg/kg body weight per day identified on the basis of kidney toxicity (caused by low solubility in water, resulting in crystal formation and a subsequent inflammatory response) at 7.8 mg/kg body weight per day in a 24-month study in rats, and using a safety factor of 25. A modified safety factor on the basis of kinetic considerations was deemed appropriate, as the critical effect of hydroxyatrazine is dependent on its physicochemical properties, and the interspecies variability for such effects is lower than for effects dependent on the area under the curve.

Applying this ADI to a 60 kg adult drinking 2 litres of water per day and allocating 20% of the total daily intake to drinking-water, a guideline value of 0.2 mg/l can be derived for hydroxyatrazine in drinking-water. Again, this default 20% allocation will be very conservative in most countries, as it is expected that exposure of the public will be primarily through drinking-water.

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