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Diquat 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

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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
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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

ADI	acceptable daily intake
CAS	Chemical Abstracts Service
FAO	Food and Agriculture Organization of the United Nations
IPCS	International Programme on Chemical Safety
IUPAC	International Union of Pure and Applied Chemistry
JMP	Joint Meeting on Pesticides
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
NOAEL	no-observed-adverse-effect level
TOPPS	1,2,3,4-tetrahydro-1-oxopyrido[1,2a]-5-pyrazinium ion
WHO	World Health Organization

Table of contents

1. GENERAL DESCRIPTION

1.1 Identity

	Ion	*Dibromide*
CAS No.:	2764-72-9	85-007
Molecular formula:	$C_{12}H_{12}N_2$	$C_{12}H_{12}Br_2N_2$

The IUPAC name for diquat is 9,10-dihydro-8a,10a-diazoniaphenanthrene ion. Diquat is sold as diquat dibromide and is usually formulated as an aqueous solution (270 g of diquat ion per litre) (FAO/WHO, 1995).

1.2 Physicochemical properties (FAO/WHO, 1995)

Physicochemical properties for the pure active ingredient (diquat dibromide) are as follows:

Property	*Value*
Vapour pressure	$<10^{-8}$ kPa at 25 °C
Melting point	325 °C
Log octanol–water partition coefficient	-4.6 at 20 °C
Water solubility	718 g/litre
Specific gravity	1.61 g/cm^3
Hydrolysis	pH 5–7, stable; pH 9, slight hydrolysis

1.3 Major uses

Diquat is a non-selective contact herbicide and crop desiccant. On a global basis, pre-harvest desiccation to aid the harvesting of seed and fodder crops accounts for the use of two-thirds of the global volume of diquat, whereas one-third of the diquat sold is used as a weed killer. The regions of North America, Europe, Australia and Japan consume 90% of the diquat used for herbicidal and crop desiccation purposes. Diquat may also be used (at or below 1 mg/litre) as an aquatic herbicide for the control of free-floating and submerged aquatic weeds in ponds, lakes and irrigation ditches (FAO/WHO, 1995).

1.4 Environmental fate

Diquat is strongly adsorbed to soil, is not taken up by plant roots and is not metabolically degraded by plants. The rate of degradation in soil, although slow, was found to be sufficient to ensure that diquat residues would not accumulate indefinitely in soil but would reach a plateau level when the amount degraded each year was equal to the amount of new addition. In the presence of sunlight, rapid and extensive photochemical degradation occurs. Diquat does not bioaccumulate in food.

The potential for diquat to leach into potable water was tested using a model pond–soil–aquifer system (an extremely sandy soil with low adsorption capacity was used as the soil in the system). No diquat (<0.003 mg/litre) was found in any aquifer sample.

Photodegradation of diquat is extensive in water. The major degradation product is 1,2,3,4-tetrahydro-1-oxopyrido[1,2a]-5-pyrazinium ion (TOPPS). Diquat monopyridone is formed to only a limited extent. On further irradiation, TOPPS is degraded to picolinamide, picolinic acid, formic acid, oxalic acid, carbon dioxide and other volatile fragments. Picolinamide in water is also known to undergo bacterial oxidation with ring opening to form maleic and fumaric acids.

When diquat is added to surface waters to control aquatic weeds, residues in the water rapidly decline, owing mainly to the absorption of diquat into the aquatic plants, where it is firmly bound until the decaying weeds disintegrate into the bottom mud. The diquat is then irreversibly bound to the soil particles, leaving the water free of diquat residues. Half-lives of diquat in natural waters are generally less than 48 h (FAO/WHO, 1995).

2. ANALYTICAL METHODS

Analytical methods are based on extraction of diquat by acid hydrolysis and cleanup and concentration by ion exchange chromatography followed by reduction and measurement of the diquat reduction products by gas–liquid chromatography with a nitrogen–phosphorus detector. The limits of determination are 4 µg/litre in water, 0.01 mg/kg in soil and 0.02 mg/kg in animal tissues and food crops (FAO/WHO, 1995). In other methods, diquat residues have been determined spectrophotometrically, with a limit of detection of 1 µg/litre in water (Earl & Boseley, 1988).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Because of diquat's extremely low vapour pressure, levels in air are expected to be low. After spraying, diquat levels decreased from 0.6 mg/m^3 in the immediate spray area (tractor cabin) to 0.06 mg/m^3 in a treated field 10 min after spraying; diquat was not detectable 20 min after spraying. No diquat was detected at a distance of 400 m from the treated field (IPCS, 1984).

3.2 Water

Groundwater was analysed for diquat at two sites in Japan where the product had been used commercially for 5 and 15 years. No diquat was detected in the water, the limit of detection being 0.1 mg/litre (FAO/WHO, 1995).

Following its use as an aquatic herbicide at normal application rates, diquat residues in water have been found to decrease rapidly to essentially undetectable levels within 7–14 days (IPCS, 1984).

3.3 Food

When diquat is used as a herbicide to control weeds, no residues (<0.05 mg/kg) are found in the harvested crop. When diquat is used as a desiccant, the product is sprayed directly onto the crop, and significant residues are present in the crop at harvest. Diquat concentrations of <0.02–0.7 mg/kg have been reported in beans, lentils, peas, potatoes and other food crops harvested 3–21 days after spraying (FAO/WHO, 1995).

3.4 Estimated total exposure and relative contribution of drinking-water

Because of diquat's rapid degradation in water and strong adsorption onto sediments, the contribution of drinking-water to total exposure is expected to be low. Major sources of exposure are expected to be air in the occupational setting and food for the general population.

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS[1]

When administered orally, [^{14}C]diquat is poorly absorbed from the gastrointestinal tract of rats, cows and goats and mainly eliminated via the faeces during the first 24 h, the small part absorbed being principally eliminated via the urine. The total percentages of administered doses eliminated via the faeces were 94, 91 and 94 for the rat, cow and goat, respectively; 3.1% and 0.4% were eliminated in the urine of the rat and the cow, respectively, and very small percentages of radioactivity were found in cow's and goat's milk (0.004% and 0.0175%, respectively).

After oral administration of [^{14}C]diquat to rats (45 mg of ion per kg of body weight), the major excreted product was diquat in both urine (5% of dose) and faeces (>57% of dose); diquat monopyridone was the main metabolite in the faeces (5% of dose), but a minor one in the urine. In another oral study in rats (100 mg of ion per kg of body weight), small amounts of diquat dipyridone and picolinic acid were found in addition to the monopyridone. After subcutaneous injection (10 mg of ion per kg of body weight) in the rat, 75% of the dose was present in the urine as diquat, about 3% as the monopyridone and 6% as the dipyridone.

Unlike paraquat, diquat is not actively taken up by lung slices, and lung toxicity is not characteristic of diquat poisoning.

[1] This section has been taken from FAO/WHO (1994).

5. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS[2]

The acute oral toxicity of diquat varies with species, but is between 125 and 250 mg of ion per kg of body weight in rodents. Diquat is classified by WHO (2001) as "moderately hazardous."

In a 90-day feeding study in rats, using dietary concentrations of 0, 20, 100 or 500 mg/kg, the NOAEL was 100 mg/kg, equal to 8.5 mg of ion per kg of body weight per day, based upon reduction in body weight gain, food consumption and reduced plasma protein at the next higher dose.

In a 1-year feeding study, dogs received doses of 0, 0.5, 2.5 or 12.5 mg/kg of body weight per day. The NOAEL was 0.5 mg of ion per kg of body weight per day based upon lens opacity in females at the next dose.

Two long-term toxicity/carcinogenicity studies were conducted in mice. The first (80 weeks) used dietary concentrations of diquat ion of 0, 30, 150 or 500 mg/kg. The NOAEL was 30 mg/kg, equivalent to 4.5 mg of ion per kg of body weight per day, based upon reduced growth rates at the next higher dose together with hepatic vacuolation in males. In a 2-year study in mice, in which dietary concentrations of 0, 30, 100 or 300 mg/kg were used, the NOAEL was 30 mg/kg, equal to 3.6 mg of ion per kg of body weight per day, based on reduction in body weight gain and increased relative kidney weights at the next higher dose. There was no evidence of carcinogenicity in mice.

Two 2-year feeding studies in rats have been conducted. In the first study, diquat dibromide was administered in the diet at concentrations of 0, 5, 15, 75 or 375 mg/kg. The NOAEL was 5 mg/kg, equal to 0.19 mg of ion per kg of body weight per day, based upon cataract formation in the 15 mg/kg group. In the second study, dietary concentrations of 0, 15, 25 or 75 mg of diquat ion per kg were used. The NOAEL was 25 mg/kg (equivalent to 1.3 mg of ion per kg of body weight per day), based on cataract formation at the next higher dose. There was no evidence of carcinogenicity in rats.

Numerous teratogenicity studies have been conducted. NOAELs could not be determined in two mouse studies. There were three teratogenicity studies in rats. In the first study, dietary concentrations of 0, 125 or 500 mg of diquat ion per kg were used. A dose-related increase in subcutaneous fetal haemorrhages compared with the controls was observed. A NOAEL could not be derived from this study. In the second study, diquat was administered at oral doses of 0, 4, 12, 24 or 40 mg of ion per kg of body weight per day. For fetal toxicity, the NOAEL was 24 mg of ion per kg of body weight per day, but maternal toxicity was observed in all test groups (reduced weight gain and food consumption). In the third study, diquat was administered by gavage at doses of 0, 4, 12 or 40 mg of ion per kg of body weight per day. The NOAEL for both

[2] This section has been taken from FAO/WHO (1994).

maternal and fetal toxicity was 12 mg of ion per kg of body weight per day, based in the case of the dams on reduced body weight and food consumption and in the case of the fetuses on reduced fetal weight and defects in fetal ossification at the highest dose.

In a study in rabbits, diquat was given orally at doses of 0, 1.3, 2.5 or 5.0 mg of ion per kg of body weight per day. There was no evidence of any effects on embryonic or fetal development. The NOAEL was 2.5 mg of ion per kg of body weight per day based on mild maternal toxicity at the highest dose. In a second study in rabbits, doses of 0, 1, 3, 7 or 10 mg of ion per kg of body weight per day were administered by gavage. Doses of 3 mg of ion per kg of body weight per day or above were associated with maternal toxicity as manifested by weight loss or reduced weight gain and reduced food intake. No evidence of fetotoxicity was observed. The NOAEL was 1 mg of ion per kg of body weight per day based upon maternal toxicity. In a third study in rabbits, doses of 0, 1, 3 or 10 mg of ion per kg of body weight per day were given by gavage. The NOAEL was 1 mg of ion per kg of body weight per day based upon maternal toxicity (reduced weight gain and food consumption) and skeletal effects in the fetuses at doses of 3 mg of ion per kg of body weight per day.

Two multigeneration reproduction studies were conducted in rats. In the first study, diquat was given at dietary concentrations of 0, 125 or 500 mg/kg. This study did not exhibit a NOAEL, since there was decreased weight gain in F_0 and F_1 animals at the lowest dose, but the effects observed at this dose (125 mg/kg, equivalent to 6.3 mg of ion per kg of body weight per day) were trivial. In the second study, rats were fed diquat at dietary concentrations of 0, 16, 80 or 400 mg/kg. The NOAEL was 16 mg/kg (equivalent to 0.8 mg/kg of body weight per day), based upon a low incidence of partial cataract formation at 80 mg/kg.

Diquat has been adequately tested in a series of genotoxicity assays *in vitro* and *in vivo*. Chromosomal aberrations were induced *in vitro*, but there was no other evidence of genotoxicity. The Meeting concluded that diquat was not genotoxic.

6. CONCLUSIONS

In 1993, JMPR established an ADI of 0.002 mg of diquat ion per kg of body weight based on a NOAEL of 0.19 mg of diquat ion per kg of body weight per day (based on cataract formation at the next higher dose) identified in a 2-year study in rats and using an uncertainty factor of 100 (FAO/WHO, 1994). Issues relevant to the establishment of a guideline value for diquat in drinking-water were addressed by JMP (FAO/WHO, 1996). JMP concluded that the ADI established by JMPR was relevant for the establishment of a drinking-water guideline value and that a more accurate determination of potential dietary exposure would be useful in setting a drinking-water guideline.

A health-based value of 6 µg/litre can be derived for the diquat ion, assuming a 60-kg person consumes 2 litres of drinking-water per day and allocating 10% of the JMPR ADI to drinking-water. However, diquat is not expected to occur in drinking-water (although it may be used as an aquatic herbicide for the control of free-floating and

submerged aquatic weeds in ponds, lakes and irrigation ditches), and it is therefore not necessary to establish a guideline value for diquat in drinking-water.

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