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Brominated Acetic Acids in Drinking-water

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

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

The first draft of Brominated Acetic Acids in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, was prepared by Dr D. Wong, US Environmental Protection Agency, to whom special thanks are due. The document is based on the US Environmental Protection Agency's *Drinking Water Criteria Document for Brominated Acetic Acids* (US EPA, 2003) and WHO's *Disinfectants and Disinfectant By-products* monograph (IPCS, 2002).

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

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

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

The WHO coordinators were as follows:

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

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

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

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

Acronyms and abbreviations used in the text

CAS	Chemical Abstracts Service
CoA	coenzyme A
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency (USA)
GST	glutathione-*S*-transferase
IgM	immunoglobulin M
IUPAC	International Union of Pure and Applied Chemistry
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
TDI	tolerable daily intake
USA	United States of America

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1. GENERAL DESCRIPTION

The chemicals addressed here are those for which at least a minimal number of toxicity data are available.

1.1 Identity

Compound	*CAS No.*	*Molecular formula*
Monobromoacetic acid	79-08-3	$BrCH_2COOH$
Dibromoacetic acid	631-64-1	$Br_2CHCOOH$
Bromochloroacetic acid	5589-96-8	BrClCHCOOH

The IUPAC names for these compounds are monobromoethanoic acid, dibromoethanoic acid and bromochloroethanoic acid.

1.2 Physicochemical properties (Windholz et al., 1996; Lide, 1999)

Property	*Monobromoacetic acid*[1]	*Dibromoacetic acid*[2]	*Bromochloroacetic acid*[3]
Molecular weight	138.95	217.84	173.39
Appearance	hygroscopic crystal	hygroscopic crystal	hygroscopic crystal
Density (g/ml)	1.93	nd[4]	1.98
Melting point (°C)	49–51	49	27.5–31.5
Solubility in water	miscible	very soluble	nd
Log *P*	0.41[5]	1.22[6]	1.08[6]

[1] Conversion factor in air: 1 ppm = 5.68 mg/m^3.
[2] Conversion factor in air: 1 ppm = 8.91 mg/m^3.
[3] Conversion factor in air: 1 ppm = 7.09 mg/m^3.
[4] nd = no data.
[5] Log *P* is the log octanol–water partition coefficient derived experimentally, as presented in Hansch et al. (1995).
[6] Log *P* is the calculated log octanol–water partition coefficient in the un-ionized form, as presented in Schultz et al. (1999).

1.3 Organoleptic properties

No information is available on the taste or odour thresholds of brominated acetic acids in water.

1.4 Major uses

Monobromoacetic acid has been used in commercial letterpress printing, in the production of plastics and in medical and surgical hospitals. There is no reported industrial use of dibromoacetic acid or bromochloroacetic acid (NIOSH, 1990).

2. ANALYTICAL METHODS

The brominated acetic acids can be determined by EPA Method 552.1, EPA Method 552.2 or Standard Method 6251B (APHA et al., 1998). In EPA Method 552.1, the haloacetic acids are extracted on a miniature anion exchange column and converted to methyl esters in the eluant prior to analysis. EPA Method 552.2 involves a liquid–liquid extraction procedure, after which the acetic acids are converted to methyl esters (US EPA, 1995). Both EPA methods use gas chromatography and electron capture detection. Method detection limits for EPA Method 552.2 are 0.204 µg/litre for monobromoacetic acid, 0.066 µg/litre for dibromoacetic acid and 0.251 µg/litre for bromochloroacetic acid (US EPA, 1995). Standard Method 6251B uses a micro liquid–liquid extraction procedure combined with gas chromatography and electron capture detection. Method detection limits for Standard Method 6251B are 0.087 µg/litre for monobromoacetic acid, 0.065 µg/litre for dibromoacetic acid and 0.04 µg/litre for bromochloroacetic acid (APHA et al., 1998). The practical quantification level for the brominated acetic acids in all of the above methods is approximately 1 µg/litre (US EPA, 1996).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Water

Brominated acetic acids are formed during disinfection of water that contains bromide ions and organic matter (Jacangelo et al., 1989; Pourmoghaddas et al., 1993). Bromide ions occur naturally in surface water and groundwater and exhibit seasonal fluctuations in levels. Bromide ion levels can increase due to saltwater intrusion resulting from drought conditions or due to pollution (IPCS, 2000). Data for drinking-water supplies in the USA (US EPA, 2000) indicate that monobromoacetic acid is present in groundwater and surface water distribution systems at mean concentrations of 0.16 and 0.25 µg/litre, respectively. Dibromoacetic acid was detected in groundwater and surface water distribution systems at mean concentrations of 0.82 and 1.09 µg/litre, respectively, and bromochloroacetic acid was detected in groundwater and surface water distribution systems at mean concentrations of 1.47 and 3.61 µg/litre, respectively (US EPA, 2000). In a survey of 20 drinking-waters prepared from different source waters in the Netherlands, haloacetic acids were found in all drinking-waters prepared from surface water, whereas they could not be detected in drinking-waters prepared from groundwater. Brominated acetic acids accounted for 65% of the total haloacetic acid concentration (IPCS, 2000).

4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

4.1 Monobromoacetic acid

No studies of the absorption, distribution, metabolism or excretion of monobromoacetic acid have been identified in the literature.

4.2 Dibromoacetic acid

Following gavage exposure in rats, the concentration of dibromoacetic acid in blood peaked within 1 h after dosing, suggesting rapid intestinal absorption. The oral bioavailability of dibromoacetic acid was estimated to be 30%. Following intravenous dosing, dibromoacetic acid did not bind significantly to plasma proteins or accumulate in blood cells. Dibromoacetic acid is not lipophilic at physiological pH, indicating a low propensity to accumulate in fat; however, the extent of tissue distribution is not known (Schultz et al., 1999). Limited *in vitro* data (Schultz et al., 1998; Tong et al., 1998a,b) and a single kinetics study (Schultz et al., 1999) suggest that dibromoacetic acid is metabolized to glyoxylic acid via a recently identified class of glutathione-*S*-transferase (GST) isoenzymes (GST-zeta), in a manner similar to dichloroacetic acid (Kennedy et al., 1993). Downstream metabolites of glyoxylic acid may include glycolate, oxalate, glycine and carbon dioxide (Stacpoole et al., 1998). It is not clear whether the parent compound or a metabolite is the active toxicological moiety. Dibromoacetic acid metabolites appear to be rapidly excreted, and dibromoacetic acid does not exhibit evidence of bioaccumulation. The urine and faeces were minimal contributors to overall blood clearance, suggesting that biotransformation was responsible for the rapid disappearance of dibromoacetic acid from blood. In rats, dibromoacetic acid crossed the placenta and was detected in fetal plasma, but not in maternal milk, at concentrations similar to those observed in maternal plasma (Christian et al., 2001).

4.3 Bromochloroacetic acid

Bromochloroacetic acid was systemically absorbed following gavage dosing, with peak concentrations in blood occurring 1.5 h after dosing. The oral bioavailability was estimated to be 47%. Following intravenous dosing, bromochloroacetic acid did not appear to bind significantly to plasma proteins or accumulate in blood cells. The extent of tissue distribution is not known; however, bromochloroacetic acid is not lipophilic at physiological pH, suggesting a low tendency to accumulate in fat (Schultz et al., 1999). Similar to other dihaloacetic acids, bromochloroacetic acid appears to be metabolized to glyoxylic acid via GST-zeta (Tong et al., 1998a,b); however, no metabolic studies have been conducted. Bromochloroacetic acid was rapidly cleared from the blood following a single intravenous dose (Schultz et al., 1999). The urine and faeces were minimal contributors to overall blood clearance, suggesting that biotransformation was responsible for the rapid disappearance of bromochloroacetic acid from blood. Based on analogy to dichloroacetic acid, it has been suggested that bromochloroacetic acid is eliminated via conversion to carbon dioxide (Schultz et al., 1999).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Monobromoacetic acid

5.1.1 Acute exposure

The oral LD_{50} of monobromoacetic acid in rats was reported as 177 mg/kg of body weight, with a 95% confidence limit range of 156–226 mg/kg of body weight (Linder et al., 1994a). Observed clinical symptoms included excess drinking-water intake, hypomobility, laboured breathing and diarrhoea.

5.1.2 Long-term exposure

No long-term toxicity studies were identified for any exposure route.

5.1.3 Reproductive and developmental toxicity

No adverse reproductive effects were observed in a spermatotoxicity study in which male Sprague-Dawley rats (eight per dose) were given a single gavage dose of 0 or 100 mg of monobromoacetic acid per kg of body weight and sacrificed either 2 or 14 days after dosing (Linder et al., 1994a). Measures of male reproductive toxicity included reproductive organ weights, sperm counts, sperm morphology and motility and histopathological examination of the seminiferous tubules. In a similar but repeated-dose study, male rats (eight per dose) receiving monobromoacetic acid by gavage at 0 or 25 mg/kg of body weight per day for 14 days did not exhibit adverse reproductive effects (Linder et al., 1994a).

5.1.4 Mutagenicity and related end-points

Monobromoacetic acid was mutagenic in *Salmonella typhimurium* (NTP, 2000a). Monobromoacetic acid was positive with microsomal activation and negative without microsomal activation in the Ames fluctuation test using *S. typhimurium* strain TA100 (Giller et al., 1997). Monobromoacetic acid produced DNA strand breaks in L-1210 mouse leukaemia cells (Stratton et al., 1981) but did not induce DNA repair in the SOS chromotest (Giller et al., 1997). Chromosomal damage was not observed in a newt micronucleus test in which 15 larvae per dose group were exposed to a range of concentrations of monobromoacetic acid, in the absence of microsomal activation, for 12 days (Giller et al., 1997).

5.2 Dibromoacetic acid

5.2.1 Acute exposure

The oral LD_{50} of dibromoacetic acid in rats was reported as 1737 mg/kg of body weight, with a 95% confidence limit range of 1411–1952 mg/kg of body weight. Observed clinical symptoms included excess drinking-water intake, hypomobility, laboured breathing, diarrhoea and ataxia. Histopathological examination of

epididymal sperm in surviving animals showed the presence of misshapen and degenerating sperm and abnormal retention of Step 19 spermatids (Linder et al., 1994a).

5.2.2 Short-term exposure

Male B6C3F_1 mice (six per dose) given dibromoacetic acid in drinking-water at 0, 0.1, 0.5 or 2.0 g/litre (0, 25, 125 or 500 mg/kg of body weight per day) for 3 weeks showed an increase in absolute and relative liver weights in the two highest dose groups (Parrish et al., 1996).

In four related, but independent, immunotoxicity studies, female B6C3F_1 mice (eight per dose) drank water containing dibromoacetic acid at 0, 0.125, 0.250, 0.5, 1.0 or 2.0 g/litre (0, 14–20, 33–39, 68–73, 132–150 or 236–285 mg/kg of body weight per day) for 28 days. Selected immunological end-points, as well as body and organ weights, haematology and gross pathology, were evaluated (NTP, 1999). Exposure to dibromoacetic acid resulted in body and organ weight changes and alterations in several indicators of immunological response. Body weight gain and thymus weights were decreased in the highest dose group, liver weights were increased at all doses tested and kidney weights were elevated in the four highest dose groups. At 0.5 g/litre and above, the number of spleen macrophages was increased in a dose-dependent manner, indicative of immunotoxicity, and there was a significant dose-dependent reduction in spleen IgM antibody-forming cell responses to sheep erythrocytes, representing a decrease in humoral immunity. In this study, a NOAEL for immunotoxicity was identified as 38 mg/kg of body weight per day (NTP, 1999).

As part of a series of experiments investigating the toxicity of brominated disinfection by-products, dibromoacetic acid was administered to male B6C3F_1 mice in their drinking-water at concentrations ranging from 0.2 to 3 g/litre (Bull & DeAngelo, 1995). The principal target organ was identified as the liver; observed effects included hepatomegaly, glycogen accumulation and cytomegaly. The severity of these effects was less for dibromoacetic acid than for bromochloroacetic acid. Dibromoacetic acid was also reported to produce increases in cyanide-insensitive acyl CoA activity in the liver, suggesting that it is an inducer of peroxisome proliferation.

5.2.3 Long-term exposure

No long-term toxicity studies for any exposure route were identified.

5.2.4 Reproductive and developmental toxicity

Histopathological examination of the reproductive organs of male Sprague-Dawley rats (five per dose) administered a single gavage dose of 0 or 1250 mg of dibromoacetic acid per kg of body weight demonstrated the occurrence of treatment-related adverse effects on caput sperm count, sperm morphology and sperm motility, but only marginal changes in reproductive organ weights (Linder et al., 1994a). In contrast, male Crl:CD(SD)BR rats given single gavage doses of 0, 600 or 1200 mg of

dibromoacetic acid per kg of body weight did not exhibit changes in sperm motility, sperm morphology or cell membrane permeability; however, mild testes histopathology (the presence of basophilic bodies) was observed in both dose groups (Vetter et al., 1998).

In male Sprague-Dawley rats (eight per dose) given 14 daily gavage doses of dibromoacetic acid at 0, 10, 30, 90 or 270 mg/kg of body weight per day, a variety of male reproductive tract end-points were adversely affected (Linder et al., 1994b). At 270 mg/kg of body weight per day, testis and epididymis weights and testicular sperm head counts were reduced relative to control values. At 90 mg/kg of body weight per day and above, there was a significant decrease in cauda sperm count and sperm motility and a significantly increased frequency of abnormal cauda sperm morphology. At 10 mg/kg of body weight per day and above, effects included decreased caput sperm count and histopathological evidence of altered spermiation, including delayed release of Step 19 spermatids and atypical acrosomal development of Step 15 spermatids. The severity of these spermiation effects increased with increasing dose. The LOAEL for this study was the lowest dose tested, 10 mg/kg of body weight per day (Linder et al., 1994b).

In another study, male Sprague-Dawley rats (10 per dose) administered 0 or 250 mg of dibromoacetic acid per kg of body weight per day by gavage for 42 days were paired with unexposed females 3 times during treatment (study days 8–14, 15–21 and 30–37) and 3 times during recovery (study days 49–56, 65–71 and 199–213) and permitted to mate naturally (Linder et al., 1995). Dosing was terminated on day 42 due to onset of overt toxicity, including laboured breathing, light tremor, difficulty moving the hind limbs and severe weight loss. During treatment, fertility was significantly decreased in a time-dependent manner, as measured by the number of copulations, number of litters and number of implants and fetuses per litter. No litters resulted from mating during study days 15–21 and 30–37. Following cessation of treatment, fertile matings occurred only during the final pairing (study days 199–213) in three of nine males that sired five litters.

Artificial insemination of unexposed females with sperm from treated males showed a significant effect on the reproductive competence of females inseminated with sperm from males treated for 16 or 31 days, but not for 9 days. Consistent with these reproductive outcomes, measures of sperm motility were significantly reduced after 16 or more days of treatment. No developmental toxicity was observed in fetuses conceived during treatment.

In a second study employing the same protocol, male rats (10 per dose) were given daily gavage doses of dibromoacetic acid at 0, 2, 10 or 50 mg/kg of body weight per day for up to 79 days. The rats were mated naturally during study days 30–37 and 49–56 with one female per male and during study days 65–71 with two females per male (Linder et al., 1995). No treatment-related effects on the number of fertile males, litter size, number of implants per litter or fetal body weights were observed. During the final mating period, there was a dose-dependent decrease in the number of males siring two litters; this was significant only at the highest dose tested. Effects on

mating behaviour were similar at 10 and 50 mg/kg of body weight per day, but there was no clear dose–response. At 10 mg/kg of body weight per day, non-significant decreases in the number of copulating pairs, inseminations, copulatory plugs and multiple litters were observed, but the only significant effect was a decrease in the number of copulating pairs in the study days 65–71 group. No significant effects on reproductive outcomes were observed in unexposed females artificially inseminated with sperm from males administered dibromoacetic acid at daily gavage doses of 0, 2, 10 or 50 mg/kg of body weight and sacrificed after 31 or 79 days of treatment (Linder et al., 1995). Necropsy results reported by Linder et al. (1997) showed histopathology indicative of delayed or altered spermiation at 10 mg/kg of body weight per day and above. Based on histological evidence for changes in seminiferous tubule staging of altered spermatid development, the NOAEL was 2 mg/kg of body weight per day (Linder et al., 1997).

Female Holtzman rats were given gavage doses of dibromoacetic acid at 0, 62.5, 125 or 250 mg/kg of body weight per day on gestation days 1–8 and sacrificed on gestation day 9 or 20 (Cummings & Hedge, 1998). No treatment-related changes in body weight, reproductive organ weights, number of implantation sites, number of resorptions, number of corpora lutea, preimplantation losses or serum levels of progesterone and luteinizing hormone were observed. The only effect was a 170% increase in serum 17β-estradiol at 250 mg/kg of body weight per day. Based on this end-point, the NOAEL was 125 mg/kg of body weight per day (Cummings & Hedge, 1998).

Male and female Crl:CD Sprague-Dawley rats (10 per sex per group) were given drinking-water containing dibromoacetic acid at 0, 0.125, 0.250, 0.5 or 1.0 g/litre beginning 14 days prior to cohabitation and continuing through gestation and lactation (63–70 days of treatment) (Christian et al., 2001). The average daily doses of dibromoacetic acid varied, depending on the phase of reproduction. An exposure-dependent reduction in water consumption, paralleled by a reduction in food intake, was observed at all concentrations of dibromoacetic acid and was attributed to taste aversion. No effects on estrous cycling, pre- and post-implantation losses, live litter sizes, pup gross external morphology or sex ratio were noted. The only observed reproductive effect was a slight reduction in mating performance in the 1.0 g/litre group, as evidenced by a small but non-significant increase in the number of days of cohabitation and a similar decrease in the number of mated pairs. An exposure-related decrease in pup body weights was observed, but insufficient information was provided to assess the significance of this effect. The parental NOAEL for this study was the highest dose tested, estimated at 66 mg/kg of body weight per day for males and not less than 60 mg/kg of body weight per day for females (Christian et al., 2001). A NOAEL for developmental toxicity could not be determined.

A two-generation reproduction study has recently been conducted with male and female Crl SD rats administered 0, 0.05, 0.25 or 0.65 g of dibromoacetic acid per litre in drinking-water (Chlorine Chemistry Council, 2001); the results of this study are under review by the US EPA.

Dibromoacetic acid did not exhibit teratogenic potential in the frog embryo teratogenesis assay — *Xenopus* (Gardner & Toussant, 1999).

5.2.5 Mutagenicity and related end-points

Dibromoacetic acid was mutagenic in *S. typhimurium* (NTP, 2000c) and in the Ames fluctuation test with *S. typhimurium* tester strain TA100, with and without metabolic activation (Saito et al., 1995; Giller et al., 1997), but not in *S. typhimurium* tester strain TA98 (Saito et al., 1995). Dibromoacetic acid induced DNA repair in the SOS chromotest, with and without metabolic activation, but did not increase the number of erythrocytes with micronuclei in the newt micronucleus test (Giller et al., 1997). DNA damage secondary to the production of oxidative stress, as measured by increased levels of 8-hydroxydeoxyguanosine adducts in liver DNA and thiobarbituric acid-reactive substances, has been reported (Austin et al., 1996) and was not due to peroxisome proliferation (Parrish et al., 1996).

5.3 Bromochloroacetic acid

5.3.1 Short-term exposure

No treatment-related differences in body weight, body weight gain, food and water consumption, clinical observations or mortality were reported in male and female Sprague-Dawley rats (six per sex per group) exposed for 14 days to drinking-water containing bromochloroacetic acid at concentrations of 0, 0.03, 0.1, 0.3 or 0.5 g/litre (0, 3, 10, 28 or 41 mg/kg of body weight per day). The NOAEL for this study was the highest dose tested, 41 mg/kg of body weight per day (NTP, 1998).

As part of a series of experiments investigating the toxicity of brominated disinfection by-products, bromochloroacetic acid was administered to male $B6C3F_1$ mice in their drinking-water at concentrations ranging from 0.2 to 3 g/litre (Bull & DeAngelo, 1995). The principal target organ in mice was identified as the liver. The observed effects included hepatomegaly, glycogen accumulation and cytomegaly, and these effects were more prominent than similar effects induced by dibromoacetic acid. Bromochloroacetic acid also produced only small and inconsistent effects on cyanide-insensitive acyl CoA activity in the liver, suggesting that it was not a potent inducer of peroxisome proliferation.

5.3.2 Long-term exposure

No long-term toxicity studies for any exposure route were identified.

5.3.3 Reproductive and developmental toxicity

Male and female Sprague-Dawley rats were given drinking-water containing bromochloroacetic acid at concentrations of 0, 0.06, 0.2 or 0.6 g/litre (0, 5, 15 or 39 mg/kg of body weight per day for males; 0, 6, 19 or 50 mg/kg of body per day for females) for various periods during a 35-day study (NTP, 1999). No treatment-related

effects on clinical pathology, organ weights, sperm count, sperm morphology, sperm motility or histopathology were reported in two groups of males, exposed on study days 6–31 or 6–35. No effects were observed on the mating index, pregnancy index or fertility index in two groups of females given bromochloroacetic acid on study days 1–34 and cohabited with treated males on study days 13–18. Statistically significant decreases in the number of live fetuses per litter and the total number of implants per litter were observed in the combined female groups at 50 mg/kg of body weight per day compared with controls. A number of other reproductive outcomes were reported to be adversely affected but were not significantly different from controls, possibly due to the small number of pregnancies evaluated. In another group, untreated females cohabiting with treated males on study days 1–5 and subsequently given drinking-water containing bromochloroacetic acid at concentrations of 0, 0.06, 0.2 or 0.6 g/litre (0, 10, 25 or 61 mg/kg of body weight per day) on gestation day 6 through parturition did not differ from controls in maternal body weight, food and water consumption, the number of uterine implantations, the number, weight and anogenital distance of pups and fetal heart and brain soft tissue malformations. A non-significant increase in post-implantation losses and total resorptions was observed at all doses. Based on decreased implants and decreased number of live fetuses per litter observed in the first two groups of treated females, the NOAEL was 50 mg/kg of body weight per day (NTP, 1999).

5.3.4 Mutagenicity and related end-points

Bromochloroacetic acid was mutagenic in *S. typhimurium* in the standard Ames assay (NTP, 2000b). DNA damage secondary to the production of oxidative stress, as measured by increased levels of 8-hydroxydeoxyguanosine adducts in the liver and thiobarbituric acid-reactive substances, has been reported (Austin et al., 1996) and was not associated with peroxisome proliferation (Parrish et al., 1996).

6. CONCLUSIONS

IPCS (2000) established a TDI of 20 µg/kg of body weight per day for dibromoacetic acid, based on a 79-day male reproductive toxicity study (Linder et al., 1995, 1997) showing altered spermiation at daily gavage doses of 10 mg/kg of body weight per day and higher, with a NOAEL of 2 mg/kg of body weight per day. A total uncertainty factor of 100 was used (10 each for inter- and intraspecies differences). With an allocation of 20% of the TDI to drinking-water and assuming a 60-kg adult consuming 2 litres of drinking-water per day, a health-based value of 100 µg/litre (rounded figure) may be derived. However, the Linder et al. (1995, 1997) study examined only reproductive end-points in male rats. The database for dibromoacetic acid is considered inadequate for the development of a TDI, because there are no systemic toxicity studies of subchronic duration or longer. In addition, the database lacks suitable toxicokinetic studies, a carcinogenicity study, a developmental study in a second species and a multigeneration reproductive toxicity study (one has been conducted but is currently being evaluated by the US EPA). In the current assessment, this database is considered to be inadequate for derivation of a guideline value for dibromoacetic acid.

Data on the oral toxicity of monobromoacetic acid and bromochloroacetic acid are also limited. The results of a single toxicokinetic study show that bromochloroacetic acid is rapidly absorbed from the gastrointestinal tract, rapidly cleared from the blood, almost completely metabolized and minimally excreted in the urine and faeces. However, little information is available on tissue distribution, metabolism or primary excretion pathways. Limited mutagenicity and genotoxicity data give mixed results for monobromoacetic acid and generally positive results for bromochloroacetic acid. Because monobromoacetic acid and bromochloroacetic acid have not been tested in subchronic or chronic toxicity studies, the available data are considered inadequate to establish guideline values for these chemicals. Other data gaps for these chemicals include the absence of multigeneration reproductive toxicity studies, standard developmental toxicity studies and carcinogenicity studies.

7. REFERENCES

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