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**English only**

# Trichloroacetic Acid 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**

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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:

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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**

| | |
|---|---|
| CAS | Chemical Abstracts Service |
| CoA | coenzyme A |
| DNA | deoxyribonucleic acid |
| EPA | Environmental Protection Agency (USA) |
| IARC | International Agency for Research on Cancer |
| 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*

### *1.1 Identity*

| | |
|---|---|
| CAS No.: | 76-03-9 |
| Molecular formula: | $Cl_3CCOOH$ |

The IUPAC name for trichloroacetic acid is trichloroethanoic acid.

### *1.2 Physicochemical properties*[1] *(Verschueren, 1977; Weast, 1988; Budavari et al., 1989; HSDB, 2001)*

| *Property* | *Value* |
|---|---|
| Boiling point (°C) | 197.5 |
| Melting point (°C) | 58.0 |
| Density (g/cm$^3$) | 1.62 at 25 °C |
| Vapour pressure (kPa) | 0.02 at 25 °C<br>0.133 at 51 °C |
| p$K_a$ at 25 °C | 0.512–0.70 |
| Water solubility (g/litre) | 13 |
| Log octanol–water partition coefficient | 1.33–1.7 |

### *1.3 Organoleptic properties*

No information is available on the taste or odour threshold of trichloroacetic acid in water.

### *1.4 Major uses*

Trichloroacetic acid is used as a soil sterilizer and a laboratory intermediate or reagent in the synthesis of a variety of medicinal products and organic chemicals. Medical uses of trichloroacetic acid include application as an antiseptic and a peeling agent. Trichloroacetic acid is also used industrially as an etching and pickling agent for the surface treatment of metals and as a solvent in the plastics industry (Verschueren, 1977; Hawley, 1981; Budavari et al., 1989; Meister, 1989; HSDB, 2001).

## *2. ANALYTICAL METHODS*

The chloroacetic acids can be detected in water 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. Standard Method 6251B uses a micro liquid–liquid extraction procedure

[1] Conversion factor in air: 1 ppm = 6.68 mg/m$^3$.

combined with gas chromatography and electron capture detection. Method detection limits range from <0.1 to 0.4 µg/litre The practical quantification level for trichloroacetic acid is approximately 1 µg/litre (P. Fair, personal communication, 2002).

## *3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE*

### *3.1 Air*

Trichloroacetic acid can be formed as a combustion by-product of organic compounds in the presence of chlorine (Juuti & Hoekstra, 1998). Stack gases of municipal waste incinerators have been reported to contain trichloroacetic acid at concentrations in the range 0.37–3.7 µg/m$^3$ (Mower & Nordin, 1987). Trichloroacetic acid could be a photooxidation product of tetrachloroethylene and 1,1,1-trichloroethane in the atmosphere (Reimann et al., 1996; Sidebottom & Franklin, 1996; Juuti & Hoekstra, 1998). However, Sidebottom & Franklin (1996) suggested that atmospheric degradation of chlorinated solvents contributes only a minor amount of trichloroacetic acid to the atmosphere, based on mechanistic and kinetic evidence as well as the observed global distribution of trichloroacetic acid in precipitation.

The US National Air Toxics Information Clearinghouse reported that the annual, 8-h and 24-h time-weighted average ambient air concentrations of trichloroacetic acid in the USA were 7, 73.24 and 58.14 µg/m$^3$, respectively, when averaged across seven representative states (NATICH, 1993).

Reimann et al. (1996) reported that levels of trichloroacetic acid in rainwater ranged from 0.01 to 1 µg/litre. It can be assumed that the chlorinated acetic acids detected in rainwater are from the atmosphere. Rainwater in Germany contained 0.1–20 µg of trichloroacetic acid per litre (IARC, 1995). Sidebottom & Franklin (1996) reported that trichloroacetic acid concentrations in rainwater in remote areas (Antarctic, Arctic and sub-Arctic regions) generally ranged from 10 to 100 ng/litre.

### *3.2 Water*

Chlorinated acetic acids are formed from organic material during water chlorination (Coleman et al., 1980; IPCS, 2000). Concentrations of trichloroacetic acid measured in various water sources have been summarized by IARC (1995): in Japan, chlorinated drinking-water contained 7.5 µg of trichloroacetic acid per litre; in Germany, groundwater contained 0.05 µg of trichloroacetic acid per litre; in Australia, a maximum concentration of 200 µg/litre was found for trichloroacetic acid in chlorinated water; and chlorinated water in Switzerland contained 3.0 µg of trichloroacetic acid per litre.

Data for drinking-water supplies in the USA (US EPA, 2001, 2002a) indicate that trichloroacetic acid was detected in groundwater and surface water distribution systems at mean concentrations of 5.3 and 16 µg/litre, respectively; detected

concentrations range from <1.0 to 174 µg/litre in surface water distribution systems and from <1.0 to 80 µg/litre in groundwater systems (US EPA, 2001, 2002a).

Trichloroacetic acid has also been detected in swimming pool water. In a German study of 15 indoor and 3 outdoor swimming pools (Clemens & Scholer, 1992), trichloroacetic acid concentrations averaged 6.2 µg/litre and 94.1 µg/litre in indoor and outdoor pools, respectively. By contrast, the highest concentration of trichloroacetic acid measured in an outdoor pool was 871 µg/litre, with a mean concentration of 420 µg/litre (Kim & Weisel, 1998). The difference between this study and the lower levels reported in the German study may have been due to differences in the amounts of chlorine used to disinfect swimming pools, sample collection time relative to chlorination of the water or addition or exchanges of water in the pools.

### *3.3 Food*

As chlorine is used in food production and processing — including disinfection of chicken in poultry plants; processing seafood, poultry and red meats; sanitizing equipment and containers; cooling heat-sterilized foods; and oxidizing and bleaching in the flour industry (US EPA, 1994) — trichloroacetic acid is likely to be found as a disinfection by-product in meat and other food products (US EPA, 2002a). Trichloroacetic acid can also be taken up from cooking water (Raymer et al., 2001). In addition, there is evidence that trichloroacetic acid may be taken up by plants via the roots or by leaves via uptake from the air (Schroll et al., 1994; Sutinen et al., 1995).

Reimann et al. (1996) examined the concentrations of trichloroacetic acid and other chlorinated acetic acids in a limited number of samples from several vegetables, fruits, grains and beer. Trichloroacetic acid concentrations ranged from <0.2 to 5.9 µg/kg in vegetables and from <1.6 to 4.1 µg/kg in grains. Trichloroacetic acid was below the detection limit of 1.5 µg/kg in breads and 0.6 µg/kg in wheat flours. It was not detected in fruits or tomatoes.

### *3.4 Estimated total exposure and relative contribution of drinking-water*

Although the available data for trichloroacetic acid are sufficient to demonstrate that food and air are relevant exposure sources in addition to drinking-water, the data are not adequate to quantify the contributions of each source for an overall assessment of exposure.

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

Trichloroacetic acid is rapidly absorbed from the gastrointestinal tract in rats (Schultz et al., 1999) and by both the dermal and oral routes in humans (Kim & Weisel, 1998). Following oral and intravenous administration in rats, trichloroacetic acid appears to bind significantly to plasma proteins (Templin et al., 1993; Schultz et al., 1999; Yu et

al., 2000) and also distributes to the liver. A relatively small proportion of trichloroacetic acid is metabolized in the liver. The formation of carbon dioxide, glyoxylic acid, oxalic acid, glycolic acid and dichloroacetic acid was observed in rats and mice following oral administration of 20 or 200 mg of radiolabelled trichloroacetic acid per kg of body weight. The authors suggested that trichloroacetic acid was metabolized by reductive dehalogenation to dichloroacetic acid (Larson & Bull, 1992). Further reductive dehalogenation of dichloroacetic acid to monochloroacetic acid and ultimately to thiodiglycolate has been proposed as a metabolic pathway (Bull, 2000).

Other investigators have suggested that metabolism to dichloroacetic acid may have been over-reported in earlier studies due to analytical artefacts (Lash et al., 2000). In F344 rats given intravenous injections of radiolabelled trichloroacetic acid at doses of 0, 6.1, 61 or 300 μmol/kg of body weight (approximately 0, 1, 10 or 50 mg/kg of body weight), as much as 84% of the administered radioactivity was excreted in the urine within 24 h of dosing; high-performance liquid chromatographic analyses of plasma, urine and liver homogenate did not detect any oxalate, glyoxalate, glycolate or dichloroacetic acid, suggesting that trichloroacetic acid was poorly metabolized by the rats (Yu et al., 2000).

The primary route of excretion is via the urine (Templin et al., 1993; Schultz et al., 1999; Yu et al., 2000). Approximately 40% of the clearance of trichloroacetic acid from blood following a single intravenous dose of 500 μmol/kg of body weight (approximately 80 mg/kg of body weight) to male F344 rats was accounted for by renal clearance; excretion in faeces was negligible (Schultz et al., 1999). In light of the minimal metabolism observed, the authors suggested that the remaining 54% of the trichloroacetic acid dose was removed from blood primarily by tissue sequestration. In rats exposed to 82 mg/kg of body weight via the intravenous route, the elimination half-life of trichloroacetic acid was 8 h (Schultz et al., 1999). Some limited data on comparative excretion rates in rats and humans are available, based on a study of the inhalation of tetrachloroethylene, which is metabolized to trichloroacetic acid (Volkel et al., 1998). The mean elimination half-life of trichloroacetic acid in urine was 45.6 h in humans, compared with 11.0 h in rats, suggesting that elimination of trichloroacetic acid in rats is more rapid. It is possible, however, that the observed differences may be due to differences in tetrachloroethylene metabolism.

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

### *5.1 Acute exposure*

Oral $LD_{50}$s of 3320 and 4970 mg/kg of body weight for trichloroacetic acid have been reported in rats and mice, respectively (Woodard et al., 1941). Dosed animals quickly passed into a state of narcosis or semi-narcosis and, within 36 h, either recovered completely or died in the narcotic state.

### *5.2 Short-term exposure*

Groups of male B6C3F$_1$ mice were given 0, 0.1, 0.5 or 2.0 g of trichloroacetic acid per litre in drinking-water (0, 25, 125 or 500 mg/kg of body weight per day) for 3 or 10 weeks and evaluated for oxidative DNA damage in the liver. After 3 weeks, liver weight was increased in the two highest dose groups, accompanied by increased 12-hydroxylation of lauric acid. After 10 weeks, effects included increased absolute and relative liver weights in the two highest dose groups, a dose-related increase in cyanide-insensitive palmitoyl-coenzyme A (CoA) oxidase activity, increased 12-hydroxylation of lauric acid and increased peroxisome proliferation. Based on these liver effects, the NOAEL was 25 mg/kg of body weight per day (Parrish et al., 1996).

Groups of male Sprague-Dawley rats were exposed to trichloroacetate in drinking-water at a concentration of 5 g/litre (about 312 mg/kg of body weight per day) for 10, 20 or 30 days. No treatment-related changes in body weight, organ weights, gross necropsy or histopathology were found. The NOAEL for this study was 312 mg/kg of body weight per day (Parnell et al., 1988).

Six male F344 rats and eight male B6C3F$_1$ mice were given trichloroacetic acid by gavage at 500 mg/kg of body weight per day for 10 days. In both species, relative liver weights and cyanide-insensitive palmitoyl-CoA oxidation were increased. There was no effect on relative kidney weights. The LOAEL for liver effects in this study was 500 mg/kg of body weight per day for both rats and mice (Goldsworthy & Popp, 1987).

Male Sprague-Dawley rats (10 per dose) received trichloroacetic acid in drinking-water at 0, 0.05, 0.5 or 5.0 g/litre (0, 4.1, 36.5 or 355 mg/kg of body weight per day) for 90 days. At the two highest dose levels, decreased absolute spleen weight and increased relative liver and kidney weights were observed. At the highest dose, there was focal hepatocellular enlargement, intracellular hepatic swelling, hepatic glycogen accumulation and increased hepatic peroxisomal β-oxidation activity. The NOAEL for this study was 36.5 mg/kg body weight per day (Mather et al., 1990).

Male B6C3F$_1$ mice were given trichloroacetic acid in their drinking-water at 0, 0.3, 1.0 or 2.0 g/litre (0, 75, 250 or 500 mg/kg of body weight per day, based on strain-specific default values for water intake and body weight) for 14 days. A dose-related increase in liver weight was observed, beginning at 0.3 mg/litre and becoming statistically significant at 1.0 g/litre. Based on these effects, the NOAEL was 75 mg/kg of body weight per day (Sanchez & Bull, 1990).

Male Wistar rats (5–6 per dose) were given water containing 0 or 0.025 g of trichloroacetic acid per litre (0 or 3.8 mg/kg of body weight per day) for 10 weeks. Effects included decreased body weight, changes in serum markers of lipid and carbohydrate metabolism (increased succinate dehydrogenase activity, increased glycogen accumulation and decreased liver triglyceride and cholesterol levels) and decreased kidney glutathione levels. No changes in relative liver weight, serum liver enzyme activity or liver glutathione levels were observed (Acharya et al., 1995). In a

follow-up study using the same experimental protocol and dose level, mild liver and kidney histopathology were noted (Acharya et al., 1997). Based on these effects, the single dose tested, 3.8 mg/kg of body weight per day, was a minimal LOAEL (Acharya et al., 1995, 1997).

### *5.3 Long-term exposure*

Decreased body weight and increased relative liver weights were associated with administration of trichloroacetic acid to female $B6C3F_1$ mice in drinking-water at concentrations of 0, 0.33, 1.1 or 3.3 g/litre (0, 78, 262 or 784 mg/kg of body weight per day, based on US EPA [1988] conventions for drinking-water intake and body weight for $B6C3F_1$ mice) for 51 or 82 weeks. Based on significantly increased relative liver weights at 262 mg/kg of body weight per day and above, the NOAEL for this study is 78 mg/kg of body weight per day (Pereira, 1996).

Groups of male F344 rats were given trichloroacetate in drinking-water at 0, 0.05, 0.5 or 5.0 g/litre (0, 3.6, 32.5 or 364 mg/kg of body weight per day) for 2 years. At 364 mg/kg of body weight per day, effects observed included decreased body weight, decreased absolute (but not relative) liver weight, increased serum alanine aminotransferase activity, increased cyanide-insensitive palmitoyl-CoA oxidase activity and increased severity of hepatic necrosis. No changes in kidney, spleen or testis weights were observed. There was no evidence of increased hepatocellular proliferation, as measured by radiolabelled thymidine incorporation rates. At 32.5 mg/kg of body weight per day, a significant decrease in serum aspartate aminotransferase activity was observed. This effect was not considered by the authors to be adverse. Based on non-neoplastic effects, the NOAEL for this study was 32.5 mg/kg of body weight per day (DeAngelo et al., 1997).

### *5.4 Reproductive and developmental toxicity*

Groups of pregnant Long-Evans rats were given trichloroacetic acid by gavage at doses of 0, 330, 800, 1200 or 1800 mg/kg of body weight per day on gestation days 6–15. At 800 mg/kg of body weight per day and higher, effects included decreased maternal body weight gain, dose-related increases in maternal spleen and kidney (but not liver) weights and increased resorptions. At 330 mg/kg of body weight per day and higher, fetal weight and length were significantly reduced, and an increase in the incidence of soft tissue malformations, primarily involving the cardiovascular and renal systems, was observed. Skeletal malformations of the orbit and hydronephrosis were also noted. The maternal LOAEL was 330 mg/kg of body weight per day, based on decreased body weight gain. The developmental LOAEL was 330 mg/kg of body weight per day, based on teratogenic and fetal growth effects; no developmental NOAEL was identified (Smith et al., 1989).

Pregnant Sprague-Dawley rats were given trichloroacetic acid in drinking-water at concentrations of 0 or 2.73 g/litre (0 or 290 mg/kg of body weight per day) on gestation days 1–22. A significant decrease in body weight gain was observed in treated dams relative to controls. Reproductive effects included increased resorptions

and increased cardiac soft tissue malformations. Based on decreased maternal weight gain, the LOAEL for maternal toxicity is the only dose tested, 290 mg/kg of body weight per day, which is also a LOAEL for reproductive and developmental toxicity (Johnson et al., 1998).

Trichloroacetic acid was not observed to exhibit teratogenic potential in a non-mammalian developmental toxicity screening assay with *Hydra attenuata* (Fu et al., 1990).

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

Trichloroacetic acid was not mutagenic in *Salmonella typhimurium* strain TA100 without metabolic activation (Rapson et al., 1980), but it gave positive results in three *in vivo* chromosomal aberration assays in mice: the bone marrow assay, the micronucleus test and the sperm head abnormality assay (Bhunya & Behera, 1987); the results were time- and route-dependent (oral gavage or intraperitoneal injection) but did not demonstrate a dose–response. In modified Ames *S. typhimurium* assays, mixed results have been reported (DeMarini et al., 1994; Giller et al., 1997). In the SOS chromotest (an inducible error-prone repair system), trichloroacetic acid did not show evidence of genotoxicity with or without metabolic activation (Giller et al., 1997). Trichloroacetic acid showed weakly positive mutagenic activity in a mouse lymphoma cell assay and was considered to be one of the least potent mutagens among a range of chemical compounds evaluated in this test system (Harrington-Brock et al., 1998). Mixed results were observed in DNA strand break tests (Nelson & Bull, 1988; Chang et al., 1991), and no chromosomal damage was noted in cultured human peripheral lymphocytes (Mackay et al., 1995). Recent evidence suggests that trichloroacetic acid-induced clastogenicity is secondary to pH changes and not a direct effect of trichloroacetic acid exposure (Mackay et al., 1995).

Although the data are somewhat conflicting, the weight of evidence suggests that trichloroacetic acid has neither significant mutagenic potential nor any structural alerts for mutagenicity. This conclusion is supported by the results from carcinogenicity bioassays in two species (negative in rats, liver tumours only in mice), discussed in the next section.

### *5.6 Carcinogenicity*

Male B6C3$F_1$ mice received trichloroacetic acid in drinking-water at concentrations of 0, 1.0 or 2.0 g/litre (approximately 0, 178 or 319 mg/kg of body weight per day, based on the study authors' calculations) for 37 or 52 weeks. An increase in the incidence of hepatocellular carcinomas was seen in males in both dose groups. No increases in tumours were noted in females in either dose group (Bull et al., 1990).

Male B6C3$F_1$ mice (50 per dose group) received 0, 0.05, 0.5 or 5 g of trichloroacetic acid per litre (0, 8, 71 or 595 mg/kg of body weight per day) in drinking-water for 60 weeks. At the two highest doses, a significant increase in the incidences of combined hepatocellular tumours (adenomas and carcinomas) was observed relative to controls

(37.9% and 55.2% in mice receiving 71 and 595 mg/kg of body weight per day, respectively, compared with 13.3% in controls) (US EPA, 1991). In a second experiment, a significantly increased incidence of combined hepatocellular adenomas/carcinomas was also observed in male and female $B6C3F_1$ mice (50 males and 55 females) given 4.5 g of trichloroacetic acid per litre (583 mg/kg of body weight per day) in drinking-water for 94 weeks (US EPA, 1991).

No evidence of carcinogenicity was observed in groups of male F344 rats (50 per dose group) administered trichloroacetic acid in their drinking-water at concentrations of 0, 0.05, 0.5 or 5.0 g/litre (0, 3.6, 32.5 or 364 mg/kg of body weight per day) for 104 weeks (DeAngelo et al., 1997).

Female $B6C3F_1$ mice were given trichloroacetate in drinking-water at concentrations of 0, 0.3, 1.1 or 3.3 g/litre (approximately 0, 78, 262 or 784 mg/kg of body weight per day) for 51 or 82 weeks. After 51 weeks at 784 mg/kg of body weight per day, 25% of animals had liver carcinomas, compared with none in the other groups. After 82 weeks, mice in this group exhibited significantly increased incidences of altered hepatocellular foci, adenomas and carcinomas. After 82 weeks at 262 mg/kg of body weight, significant increases in altered foci and carcinomas were also observed. Staining showed that these lesions were predominantly basophilic or mixed basophilic/eosinophilic, lacked expression of glutathione-*S*-transferase-pi and were consistent with peroxisome proliferation involvement in tumorigenesis (Pereira, 1996).

No treatment-related effects on the mutation patterns of the K- and H-*ras* proto-oncogenes were observed in trichloroacetic acid-induced liver tumours in male $B6C3F_1$ mice, suggesting to the authors that trichloroacetic acid is a tumour promoter, not a tumour initiator (Ferreira-Gonzalez et al., 1995).

In a number of recent mechanistic studies, trichloroacetic acid promoted liver tumours in mice pretreated with *N*-methyl-*N*-nitrosourea, a tumour-initiating agent (Pereira & Phelps, 1996; Tao et al., 1996; Latendresse & Pereira, 1997).

## *6. EFFECTS ON HUMANS*

Trichloroacetic acid has been used clinically in chemical skin-peeling treatments for years, at concentrations of 16.9–50%. This procedure results in a slight erythema and swelling for the first few days post-operatively and is followed by exfoliation of dead skin. Histologically, trichloroacetic acid-induced skin damage is characterized by epidermal loss, early inflammatory response and collagen degeneration (Moy et al., 1996; Tse et al., 1996). Marked erythema and tenderness in the vulvar vestibule area, lasting for 2–15 weeks, have been reported in two cases in which trichloroacetic acid was used for the topical treatment of genital warts (Nunns & Mandal, 1996).

## *7. GUIDELINE VALUE*

Trichloroacetic acid has been shown to induce tumours in the liver of mice. It has given mixed results in *in vitro* assays for mutations and chromosomal aberrations and has been reported to cause chromosomal aberrations in *in vivo* studies. IARC (2002) has classified trichloroacetic acid in Group 3, not classifiable as to its carcinogenicity to humans. US EPA (1994) classified trichloroacetic acid as C, possible human carcinogen, in accordance with the 1986 EPA Guidelines for Carcinogen Risk Assessment (US EPA, 1986). Under the 1999 US EPA Draft Guidelines for Carcinogen Risk Assessment (US EPA, 1999), there is suggestive evidence of trichloroacetic acid carcinogenicity, but the data are not sufficient to assess human carcinogenicity (US EPA, 2002a).

The weight of evidence indicates that trichloroacetic acid is not a genotoxic carcinogen. A TDI of 32.5 µg/kg of body weight was calculated, based on a NOAEL of 32.5 mg/kg of body weight per day from a study in which decreased body weight, increased liver serum enzyme activity and liver histopathology were seen in rats exposed to trichloroacetate in drinking-water for 2 years (DeAngelo et al., 1997), and incorporating an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for database deficiencies, including the absence of a multigeneration reproductive study, the lack of a developmental study in a second species and the absence of full histopathological data in a second species).

On the basis of the TDI of 32.5 µg/kg of body weight per day, and assuming a 60-kg body weight, drinking-water consumption of 2 litres/day and an allocation of 20% of the TDI to drinking-water, a guideline value of 200 µg/litre (rounded figure) can be calculated for trichloroacetic acid. This guideline value is achievable using commonly available analytical methods.

It is noted that this guideline value is the same as would have been calculated from the TDI established by IPCS (2000), based on the Pereira (1996) study. The DeAngelo et al. (1997) study used to establish the guideline value has better dose definition, evaluated more non-cancer end-points and conducted a full histopathological examination of tissues.

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