

Sodium Dichloroisocyanurate 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 on selected chemicals in 1998 and on microbial aspects in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2005, and the second addendum to the third edition was published in 2007.

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, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the documents for the third edition and addenda.

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.

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

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The draft text was discussed at the Working Group Meeting for the second addendum to the third edition of the GDWQ, held on 15–19 May 2006. 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 in the meeting is gratefully acknowledged.

The WHO coordinator was Dr J. Bartram, Coordinator, Water, Sanitation and Health Programme, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr Robert Bos, Water, Sanitation and Health Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms Penny Ward provided invaluable administrative support at the Working Group Meeting and throughout the review and publication process. 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
DCC ⁻	dichloroisocyanurate anion
FAC	free available chlorine
FAO	Food and Agriculture Organization of the United Nations
GDWQ	<i>Guidelines for Drinking-water Quality</i>
HPLC	high-performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
NaDCC	sodium dichloroisocyanurate
NOEL	no-observed-effect level
TAC	total available chlorine
TDI	tolerable daily intake
UV	ultraviolet
WHO	World Health Organization

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This document is based on the JECFA review of sodium dichloroisocyanurate (WHO, 2004).

1. GENERAL DESCRIPTION

1.1 Identity

CAS no.:	anhydrous 2893-78-9, dihydrate 51580-86-0
Molecular formula:	anhydrous $\text{NaC}_3\text{N}_3\text{O}_3\text{Cl}_2$, dihydrate $\text{NaC}_3\text{N}_3\text{O}_3\text{Cl}_2 \cdot 2\text{H}_2\text{O}$

The IUPAC name for sodium dichloroisocyanurate, or NaDCC, is 1,3-dichloro-1,3,5-triazinane-2,4,6-trione.

1.2 Physicochemical properties (IPCS, 2004)

<i>Property</i>	<i>Value</i>
Relative molecular mass	220.96
Melting point	Decomposes below melting point at 230 °C
Relative density	>1
Water solubility (20 °C)	25 g/100 ml (dihydrate 28 g/100 ml)

1.3 Major uses and sources in drinking-water

NaDCC is the sodium salt of a chlorinated hydroxytriazine and is used as a source of free available chlorine (FAC), in the form of hypochlorous acid (HOCl), for the disinfection of water. It is widely used as a stable source of chlorine for the disinfection of swimming pools and in the food industry, since it is more stable in sunlight than most other sources of chlorine. It is also used as a means of disinfecting drinking-water, primarily in emergencies, when it provides an easy-to-use source of free chlorine.

1.4 Environmental fate

When added to water, NaDCC (anhydrous or dihydrate) rapidly hydrolyses to release FAC and establish a complex series of equilibria involving six chlorinated and four non-chlorinated isocyanurates. These equilibria are established on the order of seconds (Matte et al., 1989). The concentration of each species depends on the concentrations of total available chlorine (TAC = FAC plus “reservoir” chlorine, e.g. as DCC^-) and total isocyanurates, the pH and the values of the equilibrium constants (dependent on temperature and ionic strength). “Reservoir” chlorine refers to the bound chlorine of the various chloroisocyanurates. The latter function as reservoirs of rapidly released FAC, as FAC is depleted. Thus, if hypochlorous acid is consumed by reaction with organic material (oxidation), chloroisocyanurates will rapidly dissociate to release more hypochlorous acid.

The FAC for anhydrous NaDCC (commercial product) is 62–64%, and the dihydrate has 55–56% FAC; the FAC for elemental chlorine is 100% (Pinto & Rohrig, 2003). Therefore, development of 1 mg of FAC per litre, typical for drinking-water

treatment, requires approximately 1.6 mg of anhydrous NaDCC per litre and approximately 1.8 mg/l for the dihydrate.

The distribution of the various chemical species in aqueous solutions of NaDCC can be calculated from their hydrolysis and acid dissociation constants. As an example (OxyChem, 1997), dissolution of NaDCC to provide 1.0 mg of TAC per litre, at pH 7.0, gives the following: 48.1% TAC from hypochlorous acid, 26.8% TAC from monochlorocyanurate, 11.8% TAC from dichlorocyanurate, 12.8% TAC from hypochlorite and less than 1% from other chlorocyanurates and chlorocyanuric acids. In normal batch-type use of NaDCC, oxidative and microbiocidal demand will consume FAC until all available chlorine has been reduced, leaving only non-chlorinated isocyanurates/cyanurate (e.g. cyanuric acid). As long as NaDCC is added to water to maintain a certain level of TAC or FAC, however, the various cyanurates will be present at levels dependent on the properties of the water (i.e. pH, temperature, etc.) (Kuznesof, 2003).

Cyanuric acid is considered to be not readily biodegradable in laboratory studies (OECD, 1999). However, it does biodegrade in the environment, in both soil and ambient water systems, in which it degrades to carbon dioxide and ammonia so that it does not accumulate in the environment (Saldick, 1975; Jessee et al., 1983; de Souza et al., 1998; Ghosh & Philip, 2006; Satsuma, 2006; Shiomi et al., 2006).

2. EXPOSURE IN DRINKING-WATER

Where NaDCC is used for the disinfection of drinking-water, exposure will be to both the chlorinated species and residual cyanuric acid, which is highly stable in water. In a flow-through system, the concentrations will directly relate to the quantities added (i.e. the quantities sufficient to achieve adequate disinfection). When used to disinfect water in a container, the concentration of cyanuric acid will depend on whether the concentrations are topped up, because the concentrations of cyanuric acid will continue to increase; however, there will be a limit to this if a free chlorine level is to be achieved, because the increasing levels of cyanuric acid would affect the equilibrium (see below).

3. TOXICOLOGICAL SUMMARY¹

In contact with saliva of about pH 7.0, chlorinated isocyanurates react extremely rapidly, such that, at the concentrations required to deliver FAC at the levels typically used in drinking-water, no detectable chlorinated isocyanurate remains. The material that reaches the gastrointestinal tract is, therefore, the unchlorinated cyanuric acid. The relevant toxicological studies cited refer to this compound.

3.1 Metabolism and toxicity

In studies in which ¹⁴C-labelled sodium cyanurate was administered in multiple doses of 5 mg/kg of body weight to rats, the sodium cyanurate was extensively absorbed and excreted unchanged in the urine, mainly within about 6 h. Only 5% of the administered dose was detected in the faeces, and the radiolabel was not exhaled as

¹ After WHO (2004).

¹⁴CO₂. In a similar study in dogs, between 2% and 13% of ¹⁴C-labelled sodium cyanurate was excreted unchanged in the faeces and the remainder in the urine, mainly within 12 h. In two human volunteers given a solution of cyanuric acid of unspecified concentration, >98% of the cyanurate was recovered unchanged in the urine after 24 h. The elimination half-life was 40–60 min in the rat, 1.5–2.0 h in the dog and about 3 h in humans.

Both NaDCC and sodium cyanurate have low acute oral toxicity.

In 13-week studies in mice given drinking-water containing sodium cyanurate at a concentration of up to 5375 mg/l (equivalent to 1500 mg/kg of body weight per day), the only compound-related effect reported was the occurrence of bladder calculi in males receiving the highest dose. In a similar study in Charles River rats, 1/28 males in the group receiving sodium cyanurate at a concentration of 1792 mg/l (equivalent to 145 mg/kg of body weight per day) and 7/28 males in the group receiving the highest dose (equivalent to 95 mg/kg of body weight per day) showed epithelial hyperplasia of the bladder.

In a 2-year study, Charles River CD1 rats were given drinking-water containing sodium cyanurate at a dose estimated as 26, 77, 154 or 371 mg/kg of body weight per day, with control groups receiving drinking-water containing an equivalent amount of sodium hippurate or untreated drinking-water. Survival was slightly lower in the group receiving the highest dose compared with the control group receiving untreated drinking-water, but not the control group receiving sodium hippurate. There was no substance-related increase in tumour incidence. Multiple lesions of the urinary tract (calculi and hyperplasia, bleeding and inflammation of the bladder epithelium, dilated and inflamed ureters and renal tubular nephrosis) and cardiac lesions (acute myocarditis, necrosis and vascular mineralization) were reported in males that died during the first year of the study and that were receiving a dose of 371 mg/kg of body weight per day. No toxicologically significant treatment-related effects were observed at 154 mg/kg of body weight per day, which was considered to be the NOEL in this study. In a similar 2-year study in which B6C3F1 mice received a dose of sodium cyanurate equivalent to 30, 110, 340 or 1523 mg/kg of body weight per day, survival was similar in all groups, and there were no treatment-related changes in the incidence of tumours or other histopathological lesions. There were no signs of toxicity in adult animals and no effects reported in the offspring of groups of Charles River COB and CD rats given sodium cyanurate at doses of 0, 200, 1000 or 5000 mg/kg of body weight per day, by gavage, on days 6–15 of gestation.

In studies in pregnant rabbits, either Dutch belted or New Zealand White, in which a sodium cyanurate dose of 0, 50, 200 or 500 mg/kg of body weight per day was administered by gavage on days 6–18 of gestation, a small reduction in body weight gain was observed in the groups receiving the two highest doses on days 12–19 of gestation in New Zealand White rabbits only, but compensatory body weight gains were made by the end of the study. An increased incidence of post-implantation loss, which was within the historical control range, was also observed in this strain at 500 mg/kg of body weight per day. JECFA considered that these effects were not significant, and there were no other effects that were considered to be related to treatment.

Three generations of Charles River CD rats were given drinking-water containing sodium cyanurate at an estimated dose of 26, 77 or 100 mg/kg of body weight per day, with control groups receiving untreated drinking-water or sodium hippurate. There were no treatment-related effects on reproductive parameters in the P0, F1 and F2 generations or on offspring of the F1, F2 or F3 generations. Sodium cyanurate was not genotoxic in four different tests.

3.2 Evaluation

JECFA concluded that studies of the toxicity of sodium cyanurate were appropriate for assessing the safety of NaDCC, because any residues of intact NaDCC in drinking-water would be rapidly converted to cyanuric acid on contact with saliva. Sodium cyanurate did not induce any genotoxic, carcinogenic or teratogenic effects. The NOEL for sodium cyanurate derived from the 2-year study in rats was 154 mg/kg of body weight per day, equivalent to 220 mg/kg of body weight per day as anhydrous NaDCC. With the application of an uncertainty factor of 100, a TDI of 0–2.0 mg/kg of body weight per day for intake of anhydrous NaDCC from drinking-water treated with NaDCC for the purpose of disinfection was determined by JECFA.

4. PRACTICAL ASPECTS

4.1 Analytical methods and analytical achievability

The main concern with NaDCC is monitoring the concentration of its decomposition product, sodium cyanurate (or “cyanuric acid”).

The commonest technique for determination of cyanuric acid is HPLC. Analysis by HPLC with UV detection at 225 nm gave a limit of detection of 0.1 mg/l in swimming pool water (Briggle et al., 1981). Reverse-phase liquid chromatography with UV detection at 213 nm was used to analyse water samples and gave a detection limit of 0.05 mg/l for concentrations in the range 0.5–125 mg/l (Cantú et al., 2000). Similar results were obtained using two different HPLC columns (Cantú et al., 2001).

Limits of detection of 1 and 90 µg/l were reported using derivatization followed by gas chromatography with flame thermionic specific detection and mass spectrometry selective ion monitoring, respectively (Fiamegos et al., 2003). Solvent extraction followed by electrospray mass spectrometry gave a detection limit of 130 µg/l (Magnuson et al., 2001).

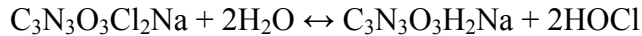
Differential pulse polarography gave a detection limit of approximately 1 mg/l (Struys & Wolfs, 1987).

For application in the field, various types of test kit are available — typically marketed for swimming pool applications. Test kits with detection limits of 1 mg/l or lower are available.

4.2 Treatment and control methods and technical achievability

When NaDCC is added to water, it is rapidly hydrolysed, releasing FAC (HOCl). A complex series of equilibria is set up involving six chlorinated and four non-

chlorinated isocyanurates (Kuznesof, 2003). However, for the sake of simplicity, the overall hydrolysis reaction can be considered as:



producing sodium cyanurate and hypochlorous acid.

The FAC content of pure NaDCC is 64.5% and of the dihydrate is 55.5% (Pinto & Rohrig, 2003); the FAC of elemental chlorine is 100% by definition.² Thus, to produce 1 mg of available chlorine per litre requires 100/64.5 = 1.55 mg of NaDCC per litre. Figure 1 shows the dose of NaDCC required to achieve a given chlorine dose and the corresponding concentration of sodium cyanurate produced. (The required chlorine dose will depend on the chlorine demand of the water and the desired chlorine residual concentration.)

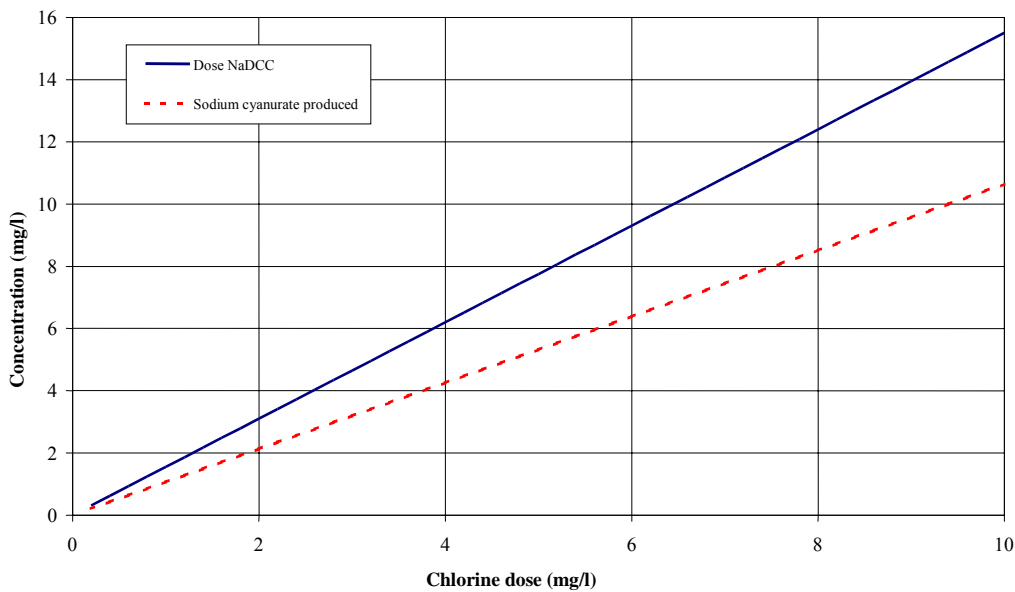


Figure 1: Dose of NaDCC and concentration of sodium cyanurate produced

According to Figure 1, at very high chlorine doses (up to 10 mg/l), the sodium cyanurate concentration would be below 11 mg/l, which is not injurious to health (see section 5).

However, it is possible that in emergency situations, “topping-up” might be done in an attempt to maintain a free chlorine residual.³ In this case, it would be possible for the sodium cyanurate concentration to build up to undesirable levels. In such cases, it would be desirable to monitor the concentration of sodium cyanurate. Various types of test kit are available for measuring sodium cyanurate (or “cyanuric acid”) concentrations — typically for swimming pool applications. Some of these will not be

² In calculating the FAC content, it has to be borne in mind that when chlorine hydrolyses, $\text{Cl}_2 + \text{H}_2\text{O} \leftrightarrow \text{HOCl} + \text{HCl}$, only one chlorine atom ends up as available chlorine (HOCl), whereas with NaDCC, both chlorine atoms are available to form available chlorine.

³ This practice should be discouraged. Because equilibrium is established between free chlorine and the various chloroisocyanurates, if hypochlorous acid is consumed, then chloroisocyanurates will rapidly dissociate to release more hypochlorous acid.

sufficiently sensitive for drinking-water applications, but test kits with a limit of detection of 1 mg/l or lower are available.

5. GUIDELINE VALUE

The TDI determined by JECFA (WHO, 2004) was 0–2.0 mg/kg of body weight as dichloroisocyanuric acid. This was derived from a long-term study on sodium cyanurate in rats for which the NOEL was 154 mg/kg of body weight per day (equivalent to 220 mg/kg of body weight per day as anhydrous NaDCC) using an uncertainty factor of 100. The guideline value for NaDCC for use in drinking-water would be 50 mg/l (rounded value), assuming that a 60-kg adult drinks 2 litres of water and allowing 80% of the TDI (using the unrounded value of 2.2 mg/kg of body weight for anhydrous NaDCC) to come from drinking-water. However, the controlling factors would be the level of free chlorine and the residue of cyanuric acid, particularly if there was topping up of chlorine in a static system under emergency conditions. The concentration of free chlorine should normally be such that it should not give rise to unacceptable tastes and should not normally exceed the guideline value of 5 mg/l for free chlorine (see background document on chlorine: WHO, 2003).

The unrounded TDI for cyanuric acid from the same study is 1.54 mg/kg of body weight. Assuming a 60-kg adult drinking 2 litres of water per day and allocating 80% of the TDI to drinking-water, the guideline value is 40 mg/l (rounded value).

It should be noted that the amounts of NaDCC used should be the lowest consistent with adequate disinfection and that the concentrations of cyanuric acid should be managed to be kept as low as is reasonably possible.

6. REFERENCES

- Briggle TV et al. (1981) High performance liquid chromatographic determination of cyanuric acid in human urine and pool water. *Journal of the Association of Official Analytical Chemists*, 64(5):1222–1226.
- Cantú R et al. (2000) An HPLC method with UV detection, pH control, and reductive ascorbic acid for cyanuric acid analysis in water. *Analytical Chemistry*, 72(23):5820–5828.
- Cantú R et al. (2001) HPLC determination of cyanuric acid in swimming pool waters using phenyl and confirmatory porous graphitic carbon columns. *Analytical Chemistry*, 73(14):3358–3364.
- de Souza ML et al. (1998) Molecular basis of a bacterial consortium: interspecies catabolism of atrazine. *Applied Environmental Microbiology*, 64(1):178–184.
- Fiamegos YC, Konidari CN, Stalikas CD (2003) Cyanuric acid trace analysis by extractive methylation via phase-transfer catalysis and capillary gas chromatography coupled with flame thermoionic and mass-selective detection. Process parameter studies and kinetics. *Analytical Chemistry*, 75(16):4034–4042.
- Ghosh PK, Philip L (2006) Environmental significance of atrazine in aqueous systems and its removal by biological processes: an overview. *Global NEST Journal*, 8(2):159–178.
- IPCS (2004) *Sodium dichloroisocyanurate*. Geneva, World Health Organization, International Programme on Chemical Safety (International Chemical Safety Card 0437).

Jessee JA et al. (1983) Anaerobic degradation of cyanuric acid, cysteine and atrazine by a facultative anaerobic bacterium. *Applied Environmental Microbiology*, 45:97–102.

Kuznesof PM (2003) *Sodium dichloroisocyanurate (NaDCC — anhydrous and dihydrate)*. Prepared for the 61st meeting of the Joint FAO/WHO Committee on Food Additives, 10–19 June 2003, Rome.

Magnuson ML, Kelty CA, Cantú R (2001) Stable association complex electrospray mass spectrometry for the determination of cyanuric acid. *Journal of the American Society for Mass Spectrometry*, 12(10):1085–1091.

Matte D et al. (1989) Étude cinétique de la *N*-chloration de la diméthylamine et de la diéthylamine en phase aqueuse. *Canadian Journal of Chemistry*, 67:786–791.

OECD (1999) *SIDS initial assessment report for 9th SIAM: isocyanuric acid*. Paris, Organisation for Economic Co-operation and Development, SIDS Initial Assessment Meeting, Screening Information Dataset for High Production Volume Chemicals (108-80-5; <http://www.inchem.org/documents/sids/sids/108805.pdf>).

OxyChem (1997) *Chemistry of the chlorinated isocyanurates*. Unpublished report, submitted by T. Kuechler (Occidental Chemical Corporation) to P.M. Kuznesof, 8 April 2003.

Pinto G, Rohrig B (2003) Use of chloroisocyanurates for disinfection of water. *Journal of Chemical Education*, 80(1):41–44.

Saldick J (1975) Biodegradation of cyanuric acid. *Applied Microbiology*, 28(6):1004–1008.

Satsuma K (2006) Characterisation of new strains of atrazine-degrading *Nocardioides* sp. Isolated from Japanese riverbed sediment using a naturally derived river ecosystem. *Pest Management Science*, 62(4):340–349.

Shiomi N et al. (2006) Degradation of cyanuric acid in soil by *Pseudomonas* sp. NRRL B-12227 using bioremediation with self-immobilization system. *Journal of Bioscience and Bioengineering*, 102(3):206–209.

Struys J, Wolfs PM (1987) Determination of cyanuric acid in swimming pool water by differential pulse polarography. *Analytica Chimica Acta*, 199:173–176.

WHO (2003) *Chlorine in drinking-water. Background document for preparation of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/03.04/45).

WHO (2004) *Evaluation of certain food additives and contaminants*. Sixty-first report of the Joint FAO/WHO Committee on Food Additives. Geneva, World Health Organization (WHO Technical Report Series 922; http://whqlibdoc.who.int/trs/WHO_TRS_922.pdf).