What is WHO's Position on Use of the Chlorinated Isocyanurates in Drinking Water?

The World Health Organization (WHO) standards for drinking water are given in their "Guidelines for Drinking-water Quality". See http://www.who.int/water_sanitation_health/dwq/guidelines/en/index.html. Section 16 in Volume 2, Heath criteria and other supporting information (Second Edition, 1996), discusses disinfectants and disinfectant by-products but did not mention chlorinated isocyanurates.

The WHO periodically updates these guidelines via the "Rolling Revision of WHO Guidelines for Drinking-Water Quality". Section 7 of the 1997 version of the "Rolling Revision" indicated that evaluation of NaDCC was a high priority because of its use as a drinking water disinfectant in emergency situations.

In 1998-1999, the WHO attempted to revise the section on NaDCC in the "Rolling Revision". A review was conducted and changes were recommended. However, approval of NaDCC was blocked in committee by critics of the chlorinated isocyanurates.

In 2002, the WHO requested another review of the use of NaDCC as a disinfectant for drinking water. This review was conducted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). JECFA is an international expert scientific committee, administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the WHO. It has been meeting since 1956 to evaluate the safety of food additives, contaminants, and residues of veterinary drugs in food.

As part of the JECFA review, three documents were prepared:
1. a Toxicological Monograph
2. a Specifications Monograph
3. a Chemical and Technical Assessment (CTA)

The Isocyanurate Industry Ad Hoc Committee (IIAHC) provided a considerable amount of data to the people preparing these documents and had the opportunity to comment on the drafts.

The 61st Meeting of JECFA was held in Rome on June, 2003. At this meeting, they recommended that the TDI (tolerable daily intake) applicable for intake from drinking water treated with NaDCC for the purpose of disinfection be set at 0 – 2.0 mg of anhydrous NaDCC/kg of body weight/day. The Summary and Conclusions for this meeting is available at: ftp://ftp.fao.org/es/esn/jecfa/jecfa61sc.pdf. The evaluation of NaDCC is on page 8, section 6.

On a mg/day basis, this TDI translates to:
For a 77 kg adult: 2 mg/kg x 77 kg = 154 mg/day of NaDCC
For a 29 kg child: 2 mg/kg x 29 kg = 58 mg/day of NaDCC
Note: the adult and child weights used above were the ones used in EPA's risk assessment.

This gives the maximum dose (using EPA's standard water consumption rates) of:
For an adult: 154 mg/day / 2 L/day = 77 mg/L of NaDCC or 47.7 mg/L of available chlorine
For a child: 58 mg/day / 1 L/day = 58 mg/L of NaDCC or 36.0 mg/L of available chlorine
The maximum dose for both an adult and a child are higher than any of the directions for use on the label.

The toxicological review was published in the "Evaluation of Certain Food Additives and Contaminants, Sixty-first report of the Joint FAO/WHO Expert Committee on Food Additives", WHO Technical Report Series No. 922 (ISBN 92-4-120922-4, date 2004). A printed edition can be ordered (for US$31.50) from WHO (http://www.who.int/bookorders/anglais/search1.jsp?sesslan=1, search in "Series" for "Technical Report Series"). A copy of the toxicological review is attached.

The Specifications Monograph for NaDCC (anhydrous and dihydrate) was published in the "Compendium of food additives specifications", FOA Food and Nutrition Paper 52 addendum 11, pages 69-72 (ISBN 92-5-105002-3, date 2003) which can be obtained (for US$20) from FAO publications (use the interactive catalog at: http://www.fao.org/publishing/, click on Food and Nutrition, then choose FAO Food and Nutrition Papers, scroll down to Compendium of food additives specifications, Addendum 11). A copy of the Specifications Monograph (attached below) can be found at:

http://apps3.fao.org/jecfa/additive_specs/foodad-q.jsp (search for sodium dichloroisocyanurate, CAS No. 2893-78-9).

The CTA was scheduled to be published in Oct, 2004, but so far is not yet available. The draft version of the CTA is attached. Go to the following site for updates on WHO's work on NaDCC: http://www.who.int/water_sanitation_health/dwq/chemicals/sodiumdichlor/en/index.html

In September, 2004, the WHO published Volume 1 of the Third Edition of the "Guidelines for Drinking-water Quality", see the news release at: http://www.who.int/mediacentre/news/releases/2004/pr67/en/. Go to: http://www.who.int/water_sanitation_health/dwq/gdwq3/en/ for the full text of the Third Edition of Volume 1. Disinfection is discussed in Section 8.4, pages 171-173. However, there is no mention of NaDCC here. A draft addition to the Rolling Revisions for NaDCC in currently in progress, as noted at: http://www.who.int/water_sanitation_health/dwq/drafts/en/index.html under "Aspects of chemical quality".

The original request from WHO only asked JECFA to review NaDCC for use in drinking water. However, the toxicological review on NaDCC concluded that:

1. In contact with saliva, chlorinated isocyanurates react rapidly such that no detectable chlorinated material remains. The material that reaches the gastrointestinal tract is unchlorinated cyanuric acid.
2. The NOEL for sodium cyanurate is 154 mg/kg of body weight per day. This value was used to calculate the TDI (tolerable daily intake) for NaDCC.

These conclusions apply to TCCA (trichloroisocyanuric acid) as well. The summary makes it clear that the JECFA analysis would be identical for TCCA since the essential part of the toxicity review was for cyanuric acid. The corresponding TDI for TCCA would also be the same at 2.0 mg/kg bw/day. Therefore, even though the JECFA review did not specifically discuss TCCA, it is clear that the results of the toxicity review also apply to TCCA.

Note that the WHO has also published international norms on recreational water use. A revision of "WHO's Guidelines for Safe Recreational Water Environments, Volume 2: Swimming pools and spas" will be available at: http://www.who.int/water_sanitation_health/bathing/en/. This document does discuss chlorinated isocyanurates. The Chlorine Chemistry Council has provided comments on this revision, which is expected to be available by the end of 2006.

(TK 10/6/04, revised 3/10/06)

WHO Technical Report Series
922

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Sixty-first report of the
Joint FAO/WHO Expert Committee on
Food Additives

World Health Organization
Geneva 2004

6. Disinfectant for drinking-water

6.1 Sodium dichloroisocyanurate

Sodium dichloroisocyanurate (NaDCC) is the sodium salt of a chlorinated hydroxytriazine and is used as a source of free available chlo-

rine (in the form of hypochlorous acid, HOCl) for the disinfection of drinking-water. NaDCC can be manufactured either as the anhydrous salt or as the dihydrate. It has not been evaluated previously by the Committee. At its present meeting, the Committee considered the safety of NaDCC in relation to its possible use as a disinfectant for drinking-water in emergency situations, and for routine use in some water supplies. When NaDCC is added to water, it is rapidly hydrolysed to release free available chlorine, establishing a complex series of equilibria involving six chlorinated and four non-chlorinated isocyanurates. As free available chlorine is consumed by reaction with organic material in the water, chloroisocyanurates will rapidly dissociate and continue to release free chlorine. Conventional chlorination of drinking-water with elemental chlorine gives rise to a number of by-products as a result of the reaction of free available chlorine with natural organic matter. The safety of these by-products has been addressed by WHO, with the development of guidelines for drinking-water quality. The use of NaDCC as a source of free available chlorine is not expected to lead to greater production of such by-products than does the use of elemental chlorine.

A typical concentration of free available chlorine used for the treatment of drinking-water is 1.0 mg/l. As anhydrous NaDCC contains about 63% free available chlorine, 1.6 mg/l NaDCC (or 1.8 mg/l of the dihydrate) is equivalent to 1 mg/l free available chlorine. Drinking-water becomes increasingly unpalatable as concentrations of free chlorine increase above this level. However, to overcome initial chlorine demand, disinfection using NaDCC might require higher initial doses, but not greater than double these quantities (i.e. 3.2 mg/l), according to WHO estimates. The default upper-percentile drinking-water intake rates currently used by WHO are 2 litres per day for adults, 1 litre per day for a 10-kg child, and 0.75 litres per day for a 5-kg bottle-fed infant. WHO also recognizes that higher intake rates may occur in some tropical countries. These intakes include water consumed in the form of juices and other beverages containing tap water (e.g. coffee). Thus, the daily intake of the dissociation products of NaDCC from the consumption of water by adults, children and infants, assuming a maximum application of 3.2 mg NaDCC per litre, would be equivalent to 6.4, 3.2, and 2.4 mg/person per day, expressed as NaDCC, respectively. Given that 1 mole of NaDCC corresponds to 1 mole of cyanuric acid (the ultimate end-product of the application of NaDCC), ingestion of cyanuric acid is estimated to be 0.06 mg/kg of body weight for adults, 0.19 mg/kg of body weight for children, and 0.28 mg/kg of body weight for a bottle-fed infant.

In contact with saliva of about pH 7.0, chlorinated isocyanurates react extremely rapidly such that, at the concentrations required to deliver free available chlorine 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.

In studies in which ^{14}C-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 hours. Only 5% of the administered dose was detected in the faeces and the radiolabel was not exhaled as ^{14}C-carbon dioxide. In a similar study in the dog, between 2% and 13% of ^{14}C-labelled sodium cyanurate was excreted unchanged in the faeces and the remainder in the urine, mainly within 12 hours. In two human volunteers given a solution of cyanuric acid of unspecified concentration, greater than 98% of the cyanurate was recovered unchanged in the urine after 24 hours. The elimination half-life was 40–60 minutes in the rat, 1.5–2.0 hours in the dog and about 3 hours in humans.

Both NaDCC and sodium cyanurate have low acute oral toxicity.

In 13-week studies in mice given up to 5375 mg/l of sodium cyanurate (equivalent to 1500 mg/kg of body weight per day) in drinking-water, 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 out of 28 males in the group receiving 1792 mg/l (equivalent to 145 mg/kg of body weight per day) and 7 out of 28 males in the group receiving the highest dose (equivalent to 495 mg/kg of body weight per day) showed epithelial hyperplasia of the bladder.

In a 2-year study, Charles River CD-1 rats were given sodium cyanurate in the drinking-water at doses estimated as 26, 77, 154 or 371 mg/kg of body weight, 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 to 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. No toxicologically significant treatment related effects

were observed at 154 mg/kg of body weight, which was considered to be the NOEL in this study. In a similar 2-year study in which B6C3F$_1$ mice received doses 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 of pregnant rabbits, either Dutch belted or New Zealand White, in which 0, 50, 200 or 500 mg/kg of body weight per day of sodium cyanurate 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 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 in the group given a dose of 500 mg/kg. The Committee 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 doses estimated to be 26, 77 or 100 mg/kg of body weight sodium cyanurate in their drinking-water, with control groups receiving untreated drinking-water or sodium hippurate. There were no treatment-related effects on reproductive parameters in the P_0, F_1 and F_2 generations or on offspring of the F_1, F_2 or F_3 generations.

Sodium cyanurate was not genotoxic in four different tests.

The Committee concluded that studies of the toxicity of sodium cyanurate were appropriate for assessing the safety of sodium dichloroisocyanurate, 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 anhydrous NaDCC/kg of body weight per day. With the application of an uncertainty factor of 100, a tolerable daily intake (TDI) of 0–2.0 mg anhydrous NaDCC/kg of body weight per day was determined by the Committee for intake from drinking-water treated with NaDCC for the purpose of disinfection.

A toxicological monograph and a chemical and technical assessment (CTA) were prepared and new specifications were established to cover both anhydrous NaDCC and the dihydrate.

SODIUM DICHLOROISOCYANURATE (ANHYDROUS and DIHYDRATE)

New specifications prepared at the 61st JECFA (2003), published in FNP 52 Add 11 (2003). An ADI of 2.0 mg/kg bw for the anhydrous form was established at the 61st JECFA (2003).

SYNONYMS Anhydrous: NaDCC; sodium dichloro-*s*-triazinetrione

Dihydrate: NaDCC dihydrate; sodium dichloro-*s*-triazinetrione dihydrate

DEFINITION NaDCC (anhydrous/dihydrate) is prepared by first reacting elemental chlorine with cyanuric acid in aqueous alkaline slurry to produce dichloroisocyanuric acid monohydrate. The latter is converted to the dihydrate of NaDCC, which may be heated to yield the anhydrous material. Both the dihydrate and the anhydrous material are produced as dry powders that can be granulated and packaged.

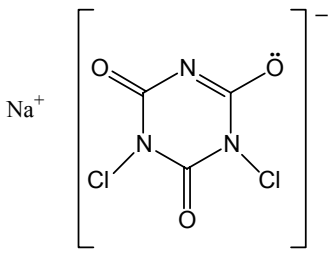
Chemical names 1,3-dichloro-1,3,5-triazine-2,4,6(1H,3H,5H)-trione, sodium salt
Triazine, 2,4,6(1H,3H,5H)-trione, 1,3-dichloro-, sodium salt

1,3-dichloro-1,3,5-triazine-2,4,6(1H,3H,5H)-trione, sodium salt, dihydrate
Triazine, 2,4,6(1H,3H,5H)-trione, 1,3-dichloro-, sodium salt, dihydrate

C.A.S. number Anhydrous: 2893-78-9
Dihydrate: 51580-86-0

Chemical formula Anhydrous: $NaC_3N_3O_3Cl_2$
Dihydrate: $NaC_3N_3O_3Cl_2 \cdot 2H_2O$

Structural formula



(anhydrous form)

Formula weight Anhydrous: 219.95
Dihydrate: 255.98

Assay Available chlorine: not less than 62.0% (anhydrous) and 55.0% - 57.0% (dihydrate)
Not less than 98% of NaDCC on the dried basis for both anhydrous and the dihydrate

DESCRIPTION Hygroscopic white crystalline powder or granules with a slight chlorine odour.

FUNCTIONAL USES Antimicrobial agent for use in drinking water systems

CHARACTERISTICS

IDENTIFICATION

Solubility (FNP 5) Soluble in water, slightly soluble in acetone

Melting range (FNP 5) 240° (decomposes)
Infrared spectrum (FNP 5) The infrared spectra of anhydrous NaDCC and NaDCC dihydrate obtained using a diamond anvil compression cell are given in the Appendix.
Sodium (FNP 5) Passes test

PURITY

pH (FNP 5)	6.0 - 7.0 (1 % soln)
Sodium chloride	Not more than 2 %. See description under TESTS
Loss on drying (FNP 5)	Anhydrous: not more than 3.0% (127°, 1.5 h) Dihydrate: between 11.0% and 14.0% (127°, 1.5 h)
Lead (FNP 5)	Not more than 2 mg/kg Determine using an atomic absorption technique appropriate to the specified level. The selection of sample size and method of sample preparation may be based on the principles of the methods described in FNP 5, "Instrumental Methods."

TESTS

PURITY TESTS

Sodium chloride

Principle:
Chloride ion is determined using a chloride-specific electrode.

Apparatus:
- Ion-selective electrode meter
- Chloride ion electrode
- Reference electrode

Reagents:
(Note: Use only distilled water. Do not use de-ionized water.)
Sodium nitrate, 5 M: Dissolve 42.5 g of reagent-grade material in 100 ml of water.
Chloride standards for calibration of the ion-selective electrode meter:
- *Stock solution (1000 mg/l):* Transfer 1.650 g of reagent grade sodium chloride to a 1-litre volumetric flask. Add ca. 500 ml of water to dissolve the salt and dilute to volume. Mix well.
- *Chloride standard (20 mg/l):* Pipette 10 ml of the stock solution into a 500-ml volumetric flask, dilute to volume and mix.
- *Chloride standard (2 mg/l):* Pipette 10 ml of the 20 mg/l chloride standard into a 100-ml volumetric flask, dilute to volume and mix.

Procedure:
Calibrate the ion-selective electrode meter according to the manufacturer's instructions.
Weigh 0.30 g of the sample. Quantitatively transfer the sample to a 500-ml volumetric flask. Add about 300 ml of water and shake the flask until the sample has completely dissolved. Dilute to volume and mix. Transfer 100 ml of the solution to a 150-ml beaker and, *via* pipette, add 2 ml of 5 M sodium nitrate. Stir the solution slowly. Introduce the electrodes into the solution. Record the concentration of chloride ion, C (mg/l), directly from the meter display. (Note: If the concentration reading is above 20 mg/l (i.e., 20 ppm), repeat the analysis, decreasing the sample weight as necessary.) Remove the electrodes from the solution, rinse them with water and blot dry. Store the electrodes in a beaker of water until needed.

Calculations:

$$\% \text{ sodium chloride} = C \times 0.0824/W$$

where
W = sample weight (g)
0.0824 = 500/(10000 × FWCl/FWNaCl), and FWCl/FWNaCl is the ratio of the formula weight of chlorine to that of sodium chloride.

METHOD OF ASSAY

Principle:

The sample is dissolved in a solution of potassium iodide. The chlorine of the sample oxidizes iodide to free iodine, which is titrated against sodium thiosulfate. "Available chlorine" is calculated from the titration result. The sample purity on the dried basis is calculated from the available chlorine and the loss on drying.

Procedure*:*

Add 200 ml of freshly boiled and cooled distilled water to a 500 ml iodine flask with stirring bar. Add 25 ml of potassium iodide TS. Accurately weigh about 0.23 g - 0.26 g of sample. Transfer to the flask; stir until dissolved. Add either 10 ml of a 1:3 sulfuric acid solution or 10 ml of glacial acetic acid. Titrate with standardized 0.1 N sodium thiosulfate solution (FNP 5) until the solution turns yellow. Add 1 ml of starch TS and continue with the titration until the blue colour just disappears. Record the volume (ml) of titrant used (V). The percent available chlorine (%AvCl) is:

$$\%AvCl = 100 \times V \times N \times 0.03546 / W.$$

where

N =	normality of the titrant
W =	weight of the sample (g)
0.03546 =	molecular weight of chlorine divided by 1000

(Note: For the dihydrate, to ensure the absence of free water, the material is normally dried to slightly less than the theoretical water content, i.e., to < 2:1 water:NaDCC. In this case, the %AvCl can be slightly higher than the theoretical available chlorine, TAC, of 55.40%.)

The content of sodium dichloroisocyanurate is:

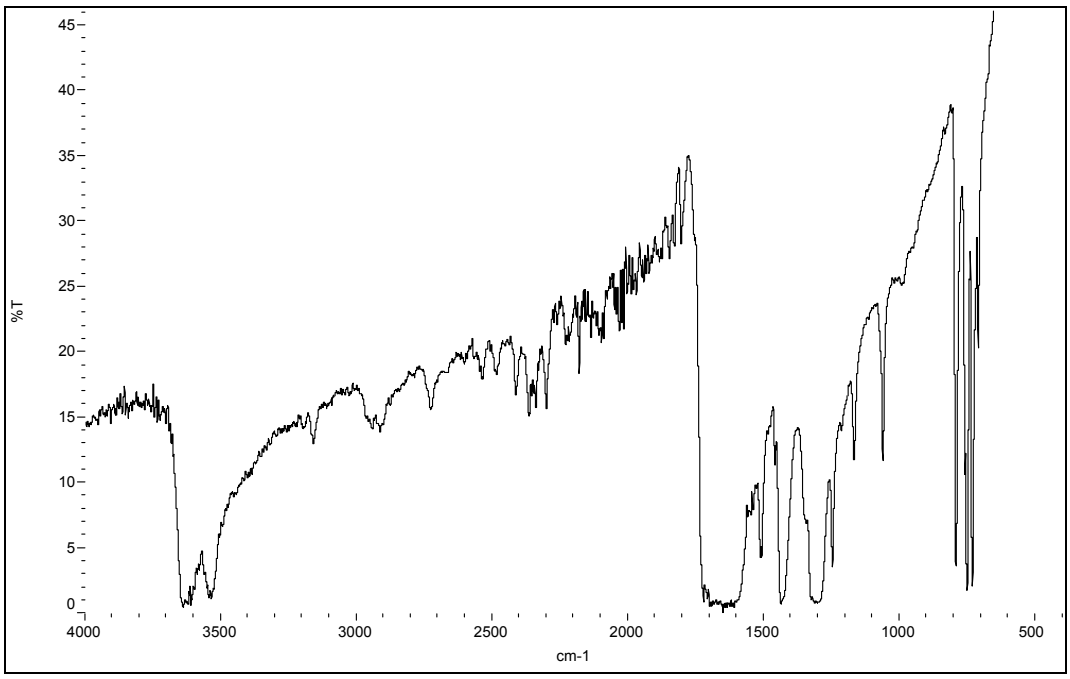
$$\%\ NaDCC\ (dried\ basis) = 100 \times [\ \%AvCl\ /64.47] \times [100\ /(100 - LOD]$$

where

64.47 =	percent TAC for anhydrous NaDCC
LOD	percent loss on drying previously determined.

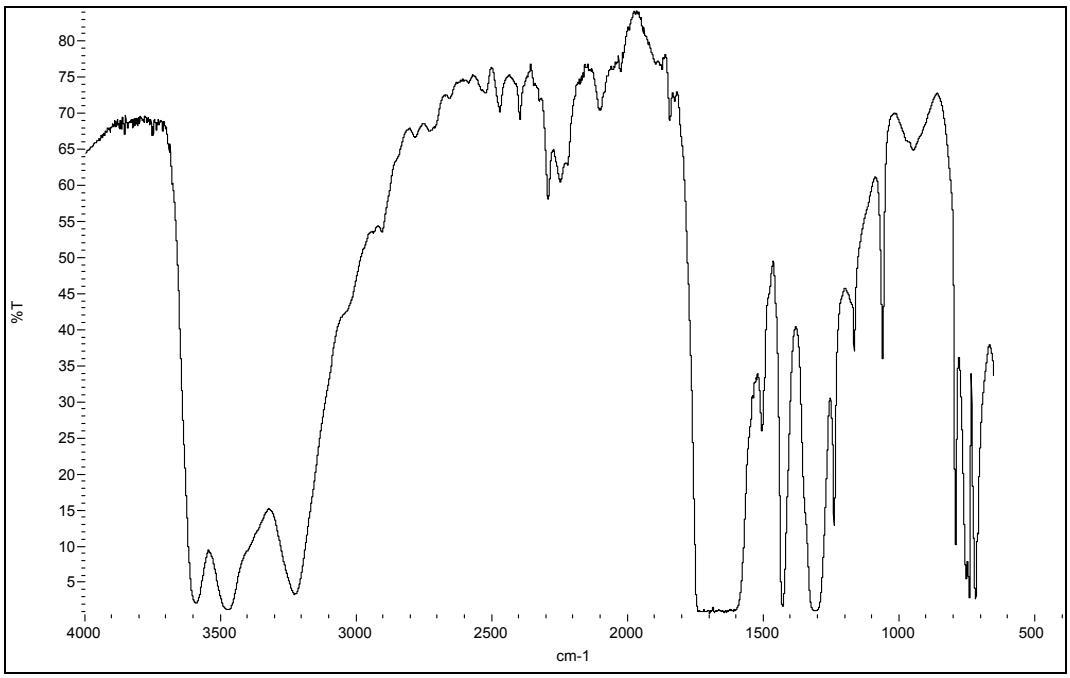
IR Spectrum of NaDCC in Diamond Cell

Peaks at: 3636, 3533, 2910, 2725, 2536, 2482, 2411, 2362, 2297, 1647, 1508, 1433, 1310, 1243, 1164, 1057, 788, 748, 728, 706 cm-1



IR Spectrum of NaDCC Dihydrate in Diamond Cell:

Peaks at: 3592, 3472, 3225, 2898, 2699, 2466, 2288, 2052, 1841, 1717, 1502, 1427, 1309, 1235, 1163, 1057, 789, 752, 739, 717 cm-1

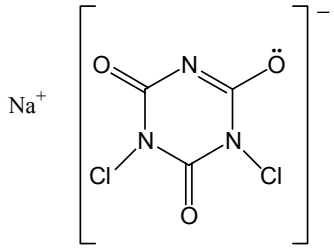


Source: Occidental Chemical Corp., 2003

DRAFT

(9 May 2003)

SODIUM DICHLOROISOCYANURATE
(NaDCC – anhydrous and dihydrate)



Chemical and Technical Assessment

61st JECFA
10-19 June 2003, Rome

Paul M. Kuznesof, Ph.D.

SODIUM DICHLOROISOCYANURATE (NaDCC – anhydrous and dihydrate)

Chemical and Technical Assessment (CTA)

First draft prepared by Paul M. Kuznesof, Ph.D.
Office of Food Additive Safety, Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration, College Park, Maryland, USA

1. Summary

NaDCC (anhydrous: CAS no. 2893-78-9; dihydrate: CAS no. 51580-86-0) was placed on the agenda of the 61st JECFA at the request of the WHO Unit on Water, Sanitation, and Health for an evaluation of its safe use to purify drinking water. NaDCC is produced as a white crystalline powder or in granular form and elicits a slight odor of chlorine. Dissolution in water produces a series of complex equilibria among a variety of chlorinated and non-chlorinated isocyanurates and free available chlorine (FAC) in the form of hypochlorous acid (HOCl). The latter is widely used for treating potable water, wastewater, water in swimming pools and spas, and many industrial water systems. Elemental chlorine, sodium hypochlorite solution, and calcium hypochlorite are other commonly used sources of FAC. Regardless of the source of FAC, HOCl is the active antimicrobial agent, effective against a wide range of bacteria, fungi, algae, viruses and other microorganisms. Cyanuric acid, the end product from use of chloroisocyanurates in bleaching, sanitizing, and disinfection applications, is unusually stable to hydrolysis, only slowly hydrolyzing in hot aqueous alkali; it is virtually inert to acid hydrolysis.

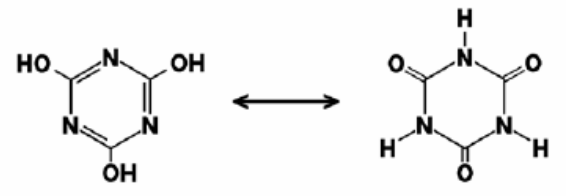
NaDCC is manufactured in a multi-step process. Pyrolysis of urea produces crude cyanuric acid. A slurry of cyanuric acid (dihydrate), previously purified (> 99%) by digestion with a strong mineral acid, is made alkaline with strong base (sodium hydroxide). This slurry is exposed to elemental chlorine. Dichloroisocyanuric acid monohydrate (DCCA) precipitates and is separated by filtration. DCCA monohydrate is reslurried and treated with strong base to form NaDCC dihydrate, which can be recovered as such for commercial purposes or be subjected to heating to produce anhydrous NaDCC. Anhydrous NaDCC is marketed at > 97% and the dihydrate at > 99%, based on analyzed deliverable FAC. On a dry basis, both products meet an assay of > 98%. The principal impurity in NaDCC is sodium chloride.

A typical value of FAC for effectiveness in drinking water is about 1 mg/L. Above about 25 mg/L, water becomes unpalatable; consumption of heavily chlorinated (> 90 mg/L) water produces throat constriction and irritation of the throat and mouth. Approximately 1.6 mg NaDCC (anhydrous) delivers about 1 mg FAC per liter of water. Assuming a daily intake of water of 2 L/person/day, the daily intake of "NaDCC" would be 3.2 mg. Given that cyanuric acid is the ultimate end-product of application of NaDCC, ingestion of 3.2 mg "NaDCC" per day leads to an exposure estimate for cyanuric acid of 1.9 mg/person/day. With regard to ingested FAC, essentially all is rapidly reduced to chloride ion in the saliva and the stomach. Therefore, little FAC would be available in the stomach to undergo chlorination reactions, such as reactions with proteins and amino acids to form N-chlorinated compounds or with phenols and unsaturated lipids to form C-chlorinated compounds.

Use of chlorine (FAC) as a disinfectant in drinking water systems (and, e.g., process waters) containing naturally occurring organic compounds can result in formation of trihalomethanes (THM). THM, such as chloroform, are regarded as carcinogens. Thus, the potential exists for THM to form in water treated with chlorinated isocyanurates. Disinfectants that reduce the activity of FAC by binding to some of it and "stabilizing" it, can, under properly controlled conditions, minimize THM formation to levels well below those produced using elemental chlorine. Monochloroamine (NH_2Cl), in which chlorine exists as "combined" (stabilized) chlorine rather than FAC, is a common alternative to the use of FAC where THM are of concern. Other chlorine stabilizers should also be effective to varying degrees in limiting THM formation, depending on how strongly they stabilize the available chlorine. The chloroisocyanurates are not as effective as monochloroamine in limiting THM but, under controlled conditions of use, can be more effective than chlorine.

2. Description

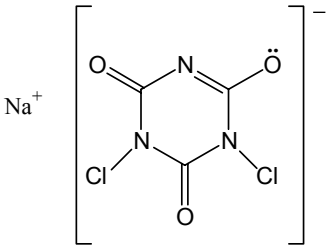
Chloroisocyanurates are best introduced by describing the parent compound, cyanuric acid, an odorless white crystalline solid with a melting point above 330°, which can exist in two tautomeric forms:



Cyanuric Acid (enol form)
2,4,6-trihydroxy-*s*-triazine

Isocyanuric Acid (keto form)
s-triazine-2,4,6(1H,3H,5H)-trione

NaDCC is the sodium salt of dichloroisocyanuric acid:



Both the anhydrous and hydrated forms are white crystalline powders or granules with a slight odor of chlorine. They have the following properties:

	Anhydrous	Dihydrate
CAS number	2893-78-9	51580-86-0
Chemical formula	$NaC_3N_3O_3Cl_2$	$NaC_3N_3O_3Cl_2 \cdot 2H_2O$
Formula weight	219.95	255.98
Assay (dry basis)	> 98%	> 98%
Solubility in water	24 g/100 g	28 g/100 g
pH (1% aqueous solution at 25°)	6.0-7.0	6.0-7.0
Melting range	240° (decomposes)	loses 1st H_2O at > 40 °; 2nd H_2O at > 80 °; 240° (decomposes)

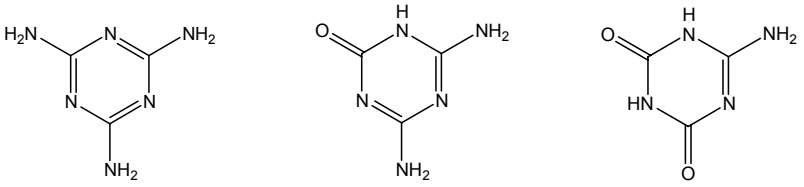
3. Manufacturing Process (Wojtowicz, J. 1993; FDA 1997)

3.1 Preparation of Cyanuric acid

Urea is first pyrolyzed (250°, ca. 1 hour) to produce crude cyanuric acid (see figure above), which is then purified (> 99%) by digestion with acid (e.g., hydrochloric, nitric, or sulfuric).

When heated, urea initially dissociates into isocyanic acid (HNCO) and ammonia. These recombine to form equilibrium amounts of ammonium cyanate, along with the intermediates biuret and triuret, through interactions of urea with the isocyanic acid. Isocyanic acid trimerizes to cyanuric acid; ammination of

biuret and triuret results in cyclic aminotriazine by-products, primarily ammelide, ammeline, and minor amounts of melamine:



melamine ammeline ammelide

AMINOTRIAZINES

The acid hydrolysis of this crude cyanuric acid converts acyclic impurities to carbon dioxide and ammonia; the cyclic aminotriazine by-products, which may constitute as much as 20% of the crude cyanuric acid, are converted to additional cyanuric acid and ammonia. And because ammination of urea and its intermediates results in the formation of water, any unreacted urea will also hydrolyze to produce ammonia and carbon dioxide. The purified cyanuric acid (> 99%) is recovered as the dihydrate and washed with water to remove residual acid and acid salts. Other means of purification of cyanuric acid are described by Wojtowicz (Wojtowicz, J. 1993); references are to the patent literature. However, the process described above is likely the most widely used.

3.2 Preparation of NaDCC

A slurry of purified cyanuric acid dihydrate is allowed to react with 50% sodium hydroxide at room temperature or slightly below to produce a solution of disodium cyanurate. In a continuous process, this solution is fed into a tank along with elemental chlorine. Dichloroisocyanuric acid (DCCA) monohydrate precipitates. Sodium chloride is a major by-product. Time, temperature, and pH of the reaction are carefully controlled. The precipitated DCCA monohydrate is filtered from the slurry and washed. Acyclic organics and ammonia are destroyed by the chlorine while any residual aminotriazines that may have been present in the cyanuric acid are either chlorinated or destroyed.

DCCA monohydrate is reslurried and allowed to react with 50% sodium hydroxide to form NaDCC dihydrate. The resulting slurry is dewatered until a wet cake with about 20% water is achieved. The wet cake is dried with mild heat using a forced-air dryer at temperatures ranging between 65^{o} and 105^{o} and residence times of less than one second. The resulting dry NaDCC dihydrate powder is then granulated and packaged. This material begins to lose its water of hydration at 40^{o}. Therefore, care must be taken to ensure proper storage conditions. Water liberated due to elevated temperatures will result in lumping of the product and other caking and heat effects in products formulated with the dihydrate.

To obtain anhydrous NaDCC, some manufacturers dry the NaDCC dihydrate wet cake directly, using a forced-air dryer at temperatures ranging between 300^{o} and 375^{o} and residence times of less than one second. The dried powder is then granulated and packaged. Other manufacturers first produce NaDCC dihydrate granules. Then, in a separate step, dry the dihydrate at temperatures between 80^{o} and 130^{o} to produce anhydrous NaDCC granules.

4. Chemical Characterization

4.1 Physicochemical properties

NaDCC (both the dihydrate and anhydrous material), as well as cyanuric acid, are well-characterized substances. Physical and chemical properties are described in the Kirk-Othmer Encyclopedia of Chemical Technology (Wojtowicz, J. 1993), in a web-based document on chloroisocyanurates by Occidental Chemical Corporation (OxyChem 2003), in a monograph developed by OxyChem on the chemistry of the

chloroisocyanurates (OxyChem 1997), and in a Food Additive Petition (FAP) submitted by Occidental to the U.S. Food and Drug Administration (FDA 1997).

Occidental Chemical Corporation literature (OxyChem 2003) declares purities for anhydrous NaDCC and NaDCC dihydrate of > 97% and > 99%, respectively, based on analyzed deliverable FAC. Sales specifications from July and August 2002 cite a range for moisture of 12.2-14.0% for the dihydrate and not more than 3.0% for the anhydrous material. Other manufacturers may produce product that differs slightly from these values. Thermal stabilities, pH of water solutions, and water solubilities are given in the Table above. The pH range is a critical parameter related to the purity of NaDCC as it permits an assessment of the presence of unacceptable levels of tri- or mono-chloroisocyanurates. NaDCC has a characteristic infrared spectrum (FDA 1997) and X-ray powder diffraction data are available (FDA 1997; OxyChem 1997) for distinguishing between anhydrous NaDCC and the dihydrate.

4.2 Impurities

The principal impurity in NaDCC is sodium chloride; minor amounts of unreacted cyanuric acid might also be present. The chlorinated aminotriazines, according to data in the FAP (FDA 1997), would likely each be present at levels no greater than 200 mg/kg or non-detectable at the reported detection limits.

Cyanuric acid (Wojtowicz, J., 1993) is unusually stable to hydrolysis. It is only slowly hydrolyzed by hot aqueous alkali and is virtually inert to acid hydrolysis. The triazine ring can be cleaved by alkaline hypochlorite to form elemental nitrogen and bicarbonate. Wojtowicz (Wojtowicz, J., 1993) notes that although numerous mono-, di-, and tri-substituted organic derivatives of cyanuric/isocyanuric acid are referenced in the literature, many are not accessible via cyanuric acid. The extensive review of the chemistry of cyanuric acid by Wojtowicz (Wojtowicz, J., 1993) allows a conclusion that cyanuric acid residues in drinking water would not be expected to show any additional reaction chemistry.

4.3 Rationale for proposed specifications for NaDCC (anhydrous and dihydrate)

Assay – Level of purity is based on measurable FAC, for which a standard analytical method is available.
Identification tests – Solubility properties, melting range, UV/VIS spectra, and infrared spectrum are characteristic physical properties for NaDCC. The sodium test distinguishes NaDCC from non-ionic chloroisocyanurates and confirms a sodium salt.
Water content – Determination of water content provides a means to distinguish the anhydrous material from the dihydrate and from mixtures of the two. This specification also serves as an indication of GMP.
pH – The pH range can be related to the purity of NaDCC, as it permits a qualitative assessment of the presence of unacceptable levels of tri- or mono-chloroisocyanurates.
Sodium chloride - Residual sodium chloride may be present in the final product. It is an important indicator of purity. An analytical method is available.
Lead – JECFA specifications for food additives include lead limits as a matter of course. For inorganic salts such as NaDCC, the presence of residual lead must always be considered. Moreover, as reagents such as mineral acids and sodium hydroxide are employed in the manufacture of NaDCC, a lead limit is clearly appropriate. The selected limit is based on industry information. Atomic absorption spectrophotometry is satisfactory for the analysis. No demonstrable need exists for specifying limits for arsenic or for other heavy metals.

Consideration was given to the need for specifying upper limits for residual chlorinated cyclic aminotriazines, which, as noted above, have been observed at levels no greater than 200 mg/kg or non-detectable at the reported detection limits. The analytical approach calls for dechlorinating a sample of NaDCC with thiosulfate and determining the three cyclotriazines (above figure) using High Performance Liquid Chromatography with a proprietary column. As no suitable generally available analytical method has been developed and, at this time, no demonstrable need exists to specify limits, none have been proposed.

5. Functional Use

NaDCC is being evaluated by JECFA for its use as a disinfectant in drinking water. Registrations for its use in drinking water and waste water systems have been approved by the U.S. Environmental Protection Agency. The United Kingdom (United Kingdom 2000) lists NaDCC as suitable in "emergency" situations for drinking water disinfection as do a number of other countries. NaDCC is used for routine disinfection of drinking water in some Latin American countries and by military personnel of several countries for disinfection of drinking water in the field.

"Chlorine" has been in use for the treatment of water, especially drinking water, for over a century. The term "chlorine" is often used generically in reference to various materials known to provide, when dissolved in water, "free available chlorine" (FAC), i.e., chlorine available as hypochlorous acid (HOCl) and hypochlorite ion (ClO^-). Commonly used sources of FAC are elemental chlorine, sodium hypochlorite, calcium hypochlorite, and the chloroisocyanurates, including NaDCC. Solutions of hypochlorous acid/hypochlorite have both excellent oxidizing and disinfecting properties. Hypochlorite is a strong oxidizing agent and is highly effective for eliminating organic contaminants, whereas undissociated HOCl is the principal microbiocidal agent, effective against bacteria, fungi, algae, viruses, and other microorganisms (OxyChem 2003; Pinto, G. and Rohrig, B. 2003).

A typical value of available chlorine for effectiveness in drinking water is about 1 mg/L, according to OxyChem (OxyChem 2000). OxyChem's report also notes that above about 25 mg/L of available chlorine water becomes unpalatable and consumption of heavily chlorinated (> 90 mg/L) water produces throat constriction and irritation of the throat and mouth. A US-EPA-registered label for NaDCC (Occidental Chemical Corp., EPA label no. 935-41) provides detailed directions for use in a variety of water-treatment applications. For example, for disinfection of public water systems, a quantity of NaDCC necessary to achieve at least 0.2 ppm FAC is recommended. For emergency disinfection of raw or pre-treated (settled, coagulated, and/or filtered) drinking water supplies (lakes, rivers, wells, etc.), NaDCC should be introduced to achieve 10 ppm FAC initially, followed by maintenance of 1 ppm.

The United Kingdom water supply regulations (United Kingdom 2000) specify that NaDCC may be used only where the water is not grossly contaminated and only for as long as it takes to restore "conventional" treatment or "for no more than 90 days in any period of a year, whichever is applicable." It must be used in a controlled contact time of not less than 15 minutes between dosings whereby not more than 10 mg/L of NaDCC should be applied and not more than 1 mg/L of free residual chlorine should be present at the end of the relevant contact time. Provision is also made for use in grossly contaminated water sources.

6. Reactions and Fate upon Consumption (O'Brien, J.E. et al. 1974; OxyChem 1997; OxyChem 2000)

When added to water, NaDCC (anhydrous or dihydrate) rapidly hydrolyzes to release FAC and establish a complex series of equilibria (see attached Figure) involving six chlorinated and four non-chlorinated isocyanurates. These equilibria are established on the order of seconds (Matte, D. et al. 1989). The concentration of each species depends on the concentrations of total available chlorine (TAC = FAC and "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 (see Figure). The latter function as reservoirs of rapidly-released FAC, as FAC is depleted. Thus, if HOCl is consumed by reaction with organic material (oxidation), chloroisocyanurates will rapidly dissociate to release more HOCl.

The FAC for anhydrous NaDCC is ca. 63% and the dihydrate contains ca. 56% FAC; by definition, FAC for elemental chlorine is 100% (Pinto, B. and Rohrig, B. 2003). Therefore, development of 1 mg/L FAC, typical for drinking water treatment, requires ca. 1.6 mg /L of anhydrous NaDCC and ca. 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/L total available chlorine, at pH 7.0, gives the following: 48.1% from HOCl, 26.8% from

monochlorocyanurate, 11.8% from dichlorocyanurate, 12.8% 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. But, as long as NaDCC is added to water to maintain a certain level of total available chlorine or FAC, the various cyanurates will be present at levels dependent on the properties of the water (i.e., pH, temperature, etc.)

FAC readily reacts with components of saliva and stomach fluid: proteins and amino acids form N-chlorinated compounds; phenols and unsaturated lipids form C-chlorinated compounds; and sulfur-containing amino acids, thiocyanate ion, and carbohydrates form chloride ion and unchlorinated oxidation products (Tan, H. et al. 1987; Ghanbari, H.A. et al. 1982; Fukayama, M.Y. et al. 1986; Wei, C.I. et al. 1987). In contact with saliva (ca. pH 7), chlorinated isocyanurates react nearly instantaneously and chlorine demand (presence of oxidizable organics) is sufficiently high to reduce nearly all FAC to chloride ion in treated drinking water, as it is swallowed (e.g., $t_{1/2}$ =0.01s for thiocyanate at pH 7). In the stomach, pH 2-3, remaining chlorinated isocyanurates rapidly dissociate into FAC; oxidizable organics will rapidly reduce FAC to chloride. The neutral dichloroisocyanuric acid (HCl_2CY, see Figure) quickly becomes the only chloroisocyanurate of significance and dissociates as FAC continues to react. Because nearly all FAC is reduced to chloride, the quantities of chlorinated organics will be extremely low. For comparison, monochloroamine or MCA (NH_2Cl), a widely used disinfectant for drinking water, has a very short lifetime in the stomach, releasing its combined (bound) chlorine in less than one 1 minute when present initially at concentrations below 15 mg/L. Because monochloroisocyanurate has been shown to release its reservoir (bound) chlorine almost 9000 times as fast as MCA and the dissociation constants of the chloroisocyanurates are much higher than MCA, all the chloroisocyanurates may be expected to react much more rapidly than MCA in both saliva and stomach fluids. Cyanuric acid and chloride ion are the stable end-products.

THM formation (OxyChem 1997; OxyChem 2003a): The use of elemental chlorine (FAC) as a disinfectant in drinking water systems (and e.g., process waters) where naturally occurring organic compounds are present is well-known to result in the formation of trihalomethanes (THM), such as chloroform, which are regarded as carcinogens. Thus, the potential exists for THM to form in water treated with chloroisocyanurates. Disinfectants that can reduce the activity of FAC by binding to some of it and "stabilizing" it, can, under properly controlled conditions, reduce the formation of THM to levels well below those produced using elemental chlorine as the disinfectant. Thus, MCA, in which all the chlorine is combined (stabilized) chlorine rather than FAC, is a common alternative to the use of FAC where THM are of concern. Other chlorine stabilizers should also be effective to varying degrees in limiting THM formation, depending on how strongly they stabilize the available chlorine. The chloroisocyanurates are not as effective as MCA in limiting THM, but under controlled conditions of use can be more effective than elemental chlorine.

7. Intake of Chloroisocyanurates

A typical concentration of FAC for drinking water treatment is 1.0 mg/L (OxyChem 2000). As anhydrous NaDCC contains ca. 63% FAC, achievement of 1 mg/L FAC requires 1.6 mg/L NaDCC. Currently, the U.S. EPA (EPA 1999) uses the quantity of 2 L per day for adults and 1 L per day for infants (individuals of 10 kg body mass or less) as default upper-percentile drinking water intake rates. These rates include water consumed in the form of juices and other beverages containing tap water (e.g., coffee). Thus, the daily intake of "NaDCC" resulting from consumption of 2 liters of water would be 3.2 mg/person/day. Given that 1 mole of NaDCC corresponds to 1 mole of cyanuric acid and the latter is the ultimate end-product of application of NaDCC, ingestion of 3.2 mg "NaDCC" per day leads to an exposure estimate for cyanuric acid of 1.9 mg/person/day.

The quantities of chlorinated organics will be extremely low (noted above), as nearly all FAC is reduced to chloride by the high chlorine demand in the saliva and the stomach. Therefore, exposures to such substances should be negligible and in any case be regarded in the same light as exposures to them from use of sources of FAC other than NaDCC to disinfect drinking water.

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Equilibrium Reactions for Isocyanurate and Chlorinated Isocyanurate Compounds

(Figure from "Chemistry of the Chlorinated Isocyanurates," OxyChem, 1997)