SCREENING-LEVEL HAZARD CHARACTERIZATION

SPONSORED CHEMICALS

Sodium dichloro-s-triazinetrione CASRN 2893-78-9
Sodium dichloro-s-triazinetrione, dihydrate CASRN 51580-86-0

SUPPORTING CHEMICAL

Sodium Cyanurate CASRN 2624-17-1

The High Production Volume (HPV) Challenge Program[1] was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

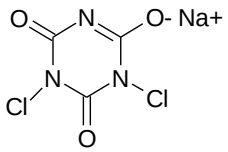
The evaluation is performed according to established EPA guidance[2,3] and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.), Science Direct and ECHA[4]. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

---

[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[4] European Chemicals Agency, http://echa.europa.eu.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	**Sponsored Chemicals** **2893-78-9** **51580-86-0** **Supporting Chemical** **2624-17-1**
Chemical Abstract Index Name	**Sponsored Chemicals** **1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3-dichloro-, sodium salt (1:1)** **1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3-dichloro-, sodium salt, dihydrate** **Supporting Chemicals** **Sodium Cyanurate**
Structural Formula[5]	**Sponsored Chemical(s)**  SMILES: N1=C(ONa)N(Cl)C(=O)N(Cl)C1(=O)

Summary

Sodium dichloro-s-triazinetrione is a white, crystalline powder with negligible vapor pressure that reacts immediately with water to form chlorine, hypochlorous acid, and cyanuric acid. It would be expected to have high mobility in soil, and volatilization would be low based on its Henry's Law constant; however, the rapid rate of hydrolysis suggests that these and other environmental fate pathways are not applicable for this substance. The rate of atmospheric photooxidation is slow. Sodium dichloro-s-triazinetrione is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Acute oral toxicity of sodium dichloro-s-triazinetrione dihydrate to rats is low. Acute inhalation toxicity of sodium dichloro-s-triazinetrione to rats is high. Acute dermal toxicity of sodium dichloro-s-triazinetrione and sodium dichloro-s-triazinetrione dihydrate to rats and rabbits, respectively, is low. In a 13-week drinking water study in rats with sodium dichloro-s-triazinetrione, dihydrate, clinical signs of toxicity (labored breathing, emaciation, accumulation of yellow material on the anogenital regions, decreased defecation, decreased activity) and

[5]The structure shown is the anhydrous form. It also exists as a dihydrate, 1,3,5-triazine-2,4,6(1H,3H,5H)-trione, 1,3-dichloro-, sodium salt, dihydrate (CASRN 51580-86-0) ($NaC_3N_3O_3Cl_2 \cdot 2H_2O$).

mortality were observed at 1000 mg/kg-day; the NOAEL is 300 mg/kg-day. In 13-week drinking water studies with the supporting chemical, sodium cyanurate, in rats and mice, no adverse effects were observed in females; the NOAEL is 2201 and 870 mg/kg-bw/day (highest dose tested) in rats and mice, respectively. In male mice, calculi in the urinary bladder, hyperplasia of the transitional epithelium and congestion or hemorrhage of the bladder lining were observed at 1994 mg/kg-bw/day; the NOAEL is 522 mg/kg-bw/day. In male rats, hyperplasia of the urinary epithelium was observed at 215 mg/kg-bw/day; the NOAEL is 101 mg/kg-bw/day. In a three-generation drinking water reproductive toxicity study in rats, the supporting chemical, sodium cyanurate, did not adversely affect reproduction; the NOAEL is 614/730 (male/female) mg/kg-bw/day (highest dose tested). In a prenatal developmental toxicity study in rats treated by oral gavage, the supporting chemical, sodium cyanurate, showed no maternal toxicity or developmental toxicity; the NOAEL for maternal and developmental toxicity is 5000 mg/kg-day (highest dose tested). In a similar study in rabbits, no adverse effects were seen in dams; the NOAEL for maternal toxicity is 500 mg/kg-day. Post-implantation losses and hydrocephaly were seen at 500 mg/kg-day; the NOAEL for developmental toxicity is 200 mg/kg-day. The supporting chemical, sodium cyanurate, did not induce mutations *in vitro* or chromosomal aberrations both *in vitro* and *in vivo*. Sodium dichloro-s-triazinetrione, dihydrate is irritating to the skin of rabbits. Sodium dichloro-s-triazinetrione and its dihydrate are irritating to the rabbit eye. Sodium dichloro-s-triazinetrione, dihydrate is not a skin sensitizer in guinea pigs. The supporting chemical, sodium cyanurate, did not increase the incidence of tumors in mice or rats.

For sodium dichloro-s-triazinetrione and sodium dichloro-s-triazinetrione, dehydrate, the 96-h LC_{50} for fish ranges from 0.14 – 0.18 mg/L, the 48-h EC_{50} for aquatic invertebrates is 0.11 mg/L, and the 96-h EC_{50} for aquatic plants is 0.60 mg/L for biomass.

No data gaps were identified under the HPV Challenge Program.

The sponsor, Isocyanurate Industry Ad Hoc Committee, submitted a test plan and robust summaries to EPA for sodium dichloro-s-triazinetrione and sodium dichloro-s-triazinetrione, dihydrate on August 11, 2003. EPA posted the submission on the ChemRTK HPV Challenge website on August 21, 2003 (http://www.epa.gov/HPV/pubs/summaries/sdditriz/c14660tc.htm). EPA comments on the original submission were posted to the website on January 12, 2004. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on May 20, 2004, which were posted to the ChemRTK website on August 27, 2004.

Justification for Supporting Chemical

Chlorinated isocyanurates are used as carriers of available chlorine. When trichloro-*s*-triazinetrione dissolves in water, it partially hydrolyzes to release free available chlorine in the form of hypochlorous acid. A series of rapid equilibria occur involving hypochlorous acid, hypochlorite ion, six chlorinated compounds and four non-chlorinated isocyanurate compounds. As the free available chlorine is reduced by reaction with various impurities in the water it is converted into chloride ion and additional free available chlorine is released from the chlorinated isocyanurates in solution. Once all of the available chlorine has been reduced, the stable reaction products are *s*-triazinetrione (isocyanuric acid) or its salts and chloride salts.

The free available chlorine that is released is a strong oxidizing agent and highly reactive. When free available chlorine is released into natural bodies of water, it reacts in seconds to minutes with the chlorine demand in the water. If less free available chlorine is added than the chlorine demand, then all of the free available chlorine will react. The stable reaction product of hypochlorous acid is chloride ion.

The chlorinated isocyanurates react with saliva and stomach fluid as fast as they hydrolyze. Thus, chlorinated isocyanurate compounds that are ingested in small amounts of pure materials, or that are ingested in pool or drinking water treated with these materials, are destroyed too quickly for the chlorinated compounds to be of toxicological consequence.

In September 1992, EPA published a pesticide Reregistration Eligibility Document (RED; http://www.epa.gov/oppsrrd1/REDs/old_reds/chlorinated_isocyanurates.pdf) on chlorinated isocyanurates that included trichloro-*s*-triazinetrione. Data on both trichloro-*s*-triazinetrione (also known as trichloroisocyanuric acid) and *s*-triazinetrione, also known as isocyanuric acid, and its sodium salt, sodium cyanurate, were submitted to support reregistration. The RED stated:

> "Since the chronic effects of chlorine for humans are well known, EPA determined that isocyanuric acid can represent all of the chlorinated isocyanurates for the purpose of conducting metabolism, subchronic, chronic, developmental and mutagenicity studies. By using the non-chlorinated *s*-triazinetrione as the test substance, the effects of the triazinetrione moiety could be distinguished from those of the chlorine."

For the HPV Challenge Program, the sponsor used the same approach by proposing to use data on *s*-triazinetrione or its sodium salt, sodium cyanurate, to estimate certain health effects of sodium dichloro-s-triazinetrione and sodium dichloro-s-triazinetrione dihydrate on the basis that chlorinated isocyanurates hydrolyze in water to form *s*-triazinetrione and free available chlorine as hypochlorous acid. EPA agrees that the use of data on *s*-triazinetrione or sodium cyanurate is appropriate to address the health effects endpoints.

Several of the reaction products identified above have been evaluated in EPA's Integrated Risk Information System (IRIS). For chlorine (CASRN 7782-50-5), the oral reference dose (RfD) was set in 1994 and relies on a NOAEL of 14.4 mg/kg-day from a drinking water study administered for 104 weeks, based on no adverse effects at the highest dose tested (http://www.epa.gov/iris/subst/0405.htm).

The IRIS RfD for chlorine dioxide (CASRN 10049-04-4) and chlorite, sodium salt (CASRN 7758-19-2) was determined in the year 2000. The value relies on a on a two-generation drinking water study in rats using chlorite, sodium salt; the LOAEL from that study is 6 mg/kg-day using and is based on neurobehavioral effects (http://www.epa.gov/iris/subst/0496.htm). The inhalation reference concentration (RfC) for chlorine dioxide, also from 2000, relies on a 60-day inhalation study (using chlorine dioxide) in rats; the LOAEC is 0.0028 mg/L based on vascular congestion and peribronchial edema. In addition, chlorine (CASRN 7782-50-5) along with data for hypochlorous acid (CASRN 7790-92-3) and sodium hypochlorite (CASRN 7681-52-9) have been evaluated in a 2010 ATSDR *Toxicological Profile* (http://www.atsdr.cdc.gov/toxprofiles/tp172.pdf).

The sponsor included ecotoxicity data for a supporting chemical, trichloro-s-triazinetrione (CASRN 87-90-1), and argued that data for this chemical would provide a "worst-case for read-across" because it contains three chlorine ions per molecule instead of the two chlorine ions per molecule of the less reactive sponsored chemicals. EPA initially agreed with this approach, however adequate data were found for the sponsored chemicals, therefore data for the supporting chemical were not used to assess ecotoxicity.

1. Chemical Identity

1.1 Identification and Purity

Sodium dichloro-s-triazinetrione is a white, crystalline powder with negligible vapor pressure that reacts immediately with water yielding chlorine, hypochlorous acid, and cyanuric acid as degradation products.

1.2 Physical-Chemical Properties

The physical-chemical properties of sodium dichloro-s-triazinetrione are summarized in Table 1.

Table 1. Physical-Chemical Properties of Sodium dichloro-s-triazinetrione[1]	
Property	**Value**
CASRN	2893-78-9
Molecular Weight	219.95 (anhydrous form); 255.98 (dihydrate)
Physical State	White, crystalline powder
Melting Point	240–250°C (decomposes)
Boiling Point	Decomposes prior to boiling
Vapor Pressure	$<5\times10^{-5}$ mm Hg at 20°C (measured); $<1.0\times10^{-10}$ mm Hg at 25°C (estimated)[2]
Dissociation Constant (pK_a)	Not applicable
Henry's Law Constant	Not applicable[3]
Water Solubility	Not applicable[3]
Log K_{ow}	Not applicable[3]

[1]Isocyanurate Industry Ad Hoc Committee (IIAHC). 2003. Test Plan and Robust Summary for Sodium dichloro-s-triazinetrione or Sodium dichlor-s-triazinetrione dehydrate. Available online at http://www.epa.gov/hpv/pubs/summaries/sdditriz/c14660tc.htm as of March 26, 2012.

[2]U.S. EPA. 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of March 26, 2012.

[3] Sodium dichloro-s-triazinetrione is expected to hydrolyze in water to form chlorine, hypochlorous acid, and cyanuric acid.

2. General Information on Exposure

2.1 Production Volume and Use

The sodium dichloro-s-triazinetrione and sodium dichloro-s-triazinetrione, dihydrate category contains the following two chemicals. Neither was reported in the 2006 IUR.

- CASRN 2893-78-9
- CASRN 51580-86-0

2.2 Environmental Exposure and Fate

Sodium dichloro-s-triazinetrione is expected to have high mobility in soil, and volatilization is expected to be low; however, the rapid rate of hydrolysis indicates that volatilization, mobility in soil, and biodegradation will not be important environmental fate processes. The rate of atmospheric photooxidation is slow; however, this substance will likely react with moisture in the atmosphere. Sodium dichloro-s-triazinetrione is expected to have low persistence (P1) and low bioaccumulation potential (B1).

The environmental fate characteristics of sodium dichloro-s-triazinetrione are summarized in Table 2.

Conclusion: Sodium dichloro-s-triazinetrione is a white, crystalline powder with negligible vapor pressure that reacts immediately with water to form chlorine, hypochlorous acid, and cyanuric acid. It would be expected to have high mobility in soil, and volatilization would be low based on its Henry's Law constant; however, the rapid rate of hydrolysis suggests that these and other environmental fate pathways are not applicable for this substance. The rate of atmospheric photooxidation is slow. Sodium dichloro-s-triazinetrione is expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 2. Environmental Fate Characteristics of Sodium dichloro-s-triazinetrione [1]

Property	**Value**
CASRN	2893-78-9
Photodegradation Half-life	5.3 days (estimated)[2]
Hydrolysis Half-life	<1 second
Biodegradation	Not applicable due to hydrolysis
Bioaccumulation Factor	Not applicable due to hydrolysis
Log K_{oc}	Not applicable due to hydrolysis
Fugacity (Level III Model)[2,3] Air (%) Water (%) Soil (%) Sediment (%)	 100 <0.1 <0.1 <0.1
Persistence[4]	P1 (low)
Bioaccumulation[4]	B1 (low)

[1]Isocyanurate Industry Ad Hoc Committee (IIAHC). 2003. Test Plan and Robust Summary for Sodium dichloro-s-triazinetrione or Sodium dichlor-s-triazinetrione dehydrate. Available online at http://www.epa.gov/hpv/pubs/summaries/sdditriz/c14660tc.htm as of March 26, 2012.

[2]U.S. EPA. 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.10. U.S. Environmental Protection Agency, Washington, DC, USA. Available online at http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm as of March 26, 2012.

[3]Half-lives of 0.0001 hours were used for the water, soil, and sediment compartments while a half-life of 127 hours was used for the atmosphere compartment.

[4]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3. Human Health Hazard

A summary of human health data submitted for SIDs endpoints is provided in Table 3. The table also indicates where data for one sponsored chemical is read-across (RA) to the other.

Acute Oral Toxicity

Sodium dichloro-s-triazinetrione, dihydrate (CASRN 51580-86-0)
Sprague-Dawley rats (5/sex/dose) were administered single doses of sodium dichloro-s-triazinetrione, dihydrate by gavage in corn oil at 0, 1500, 2000, 2500, 3000 or 4000 mg/kg and observed for up to 14 days following dosing. Mortalities were observed at all doses: 1500 mg/kg (one female), 2000 mg/kg (4 males and all females), 2500 mg/kg (4 males and all females), 3000 mg/kg (3 males and all females) and 4000 mg/kg (all males and 3 females).
LD_{50} (male rats) = 2094 mg/kg
LD_{50} (female rats) = 1671 mg/kg
LD_{50} (combined) = 1823 mg/kg

Acute Inhalation Toxicity

Sodium dichloro-s-triazinetrione (CASRN 2893-78-9)
Sprague-Dawley rats (5/sex/dose) were exposed whole-body to dusts of sodium dichloro-s-triazinetrione for 4 hours at concentrations of 0.27 or 1.17 mg/L and observed for up to 14 days following exposure. The robust summary did not provide information on the use of a control group. Mortalities were observed at 1.17 mg/L (4 males and 2 females).
0.27 mg/L < LC_{50} < 1.17 mg/L

Acute Dermal Toxicity

Sodium dichloro-s-triazinetrione (CASRN 2893-78-9)
Rabbits (strain not specified; 5/sex) were administered 0.5 g sodium dichloro-s-triazinetrione via the dermal route at 2000 mg/kg for 24 hours and were observed for 14 days. The robust summary did not provide information regarding whether the area was occluded. Control rabbits were administered 0.5 mL positive control test substance (substance not stated). No mortalities were observed.
LD_{50} > 2000 mg/kg

Sodium dichloro-s-triazinetrione, dihydrate (CASRN 51580-86-0)
Sprague-Dawley rats (5/sex/dose) were administered a single dose of sodium dichloro-s-triazinetrione, dihydrate in acetone via the dermal route (occluded) at 5000 mg/kg for an unspecified period of time and observed for 14 days. The robust summary did not provide information on the use of a control group. No mortalities were observed.
LD_{50} > 5000 mg/kg

Repeated-Dose Toxicity

Sodium dichloro-s-triazinetrione, dihydrate (CASRN 51580-86-0)

(1) CD rats (10/sex controls, 5/sex treated groups) were administered sodium dichloro-s-triazinetrione, dihydrate in the drinking water for 59 days at concentrations providing estimated doses of 0, 100, 300, 1000 or 2000 mg/kg-day. Endpoints evaluated included body weight, food and water consumption, hematology, clinical chemistry and urinalysis, organ weights and gross pathology. The robust summary did not provide information on whether histopathologic examinations were conducted. Only two males and one female in the high-dose group survived until the end of the study; at 1000 mg/kg-day, four males and females each survived to the end of the study. Decreased body weights were seen at 1000 and 2000 mg/kg-day (statistically significant in males at 4 and 8 weeks). After 8 weeks of study, animals in the two highest dose groups showed compound-related signs, including labored breathing, emaciation, accummulation of yellow material on the anogenital regions, decreased defecation, and decreased activity. For some of the animals in the high-dose group, these signs were evident by week 1 of the study and were followed by death of the animals. No alterations in hematology and clinical chemistry tests were noted. The urinalysis showed decreased urine volume and urine creatinine in high-dose males. The robust summary did not provide the results of the gross examinations.
LOAEL ~ 1000 mg/kg-day (based on mortality and clinical signs)
NOAEL ~ 300 mg/kg-day

(2) In a 28-day inhalation toxicity study, CD rats (10/sex/concentration) were exposed (whole-body) to trichloroisocyanurate dust (sieved to include only respirable particles; MMD 2.1 to 4.5 µm) at approximately 0.003, 0.010, and 0.030 mg/L for 6 hrs/day, 5 days/week for 4 weeks. No mortalities were observed. Clinical signs of toxicity in the mid and high concentration groups included rales, nasal discharge, excessive salivation, lacrimation and labored breathing. Deposition of the dust was observed on rat fur. At the mid and high concentrations, treatment-related changes were observed in body weights, organ weights (unspecified) and some clinical parameters (unspecified). There were no remarkable gross pathologies. Microscopic examination of tissues from the highest concentration did not reveal changes related to treatment (tissues not specified). The lowest concentration (0.003 mg/L) was considered a no effect level; however limited details preclude setting a LOAEL or NOAEL (Hammond *et al*., 1986).

Sodium cyanurate (CASRN 2624-17-1, supporting chemical)

(1) In a 13-week drinking water study, B6C3F1 mice (25/sex/dose) where administered sodium cyanurate (99.5% pure) at 0 (control), 896, 1792 or 5375 ppm (approximately 0, 252, 522 and 1994 mg/kg-bw/day for males and approximately 0, 298, 610 and 2201 mg/kg-bw/day for females) for 13 weeks, with the exception of 5 mice/sex/dose sacrificed at 6 weeks. An additional control group received sodium hippurate at a nominal concentration of 7769 ppm (approximately 1210 mg/kg-bw/day for males and approximately 1320 mg/kg-bw/day for females). No clinical biochemistry was conducted and limited microscopic examination (kidneys, urinary bladders, ureters and gross lesions) was performed on controls and high-dose animals. The death of a single high-dose male at 11 weeks was considered to be accidental. At the high-dose level, increased water consumption was noted during all weeks with the exception of weeks 1, 2 and 8 in males and weeks 1-5, 10 and 12 in females. There were no treatment-related clinical observations or effects on bodyweight, food consumption or hematology.

Urinalysis revealed that at 2201 mg/kg-bw/day, females in two groups had significantly increased BUN levels. The effect was not considered treatment-related as the concentrations were within normal range in all groups of both sexes at 53 weeks. Increased absolute and relative ovarian weights noted in high-dose and sodium control groups at 13 weeks were attributed to high daily sodium consumption levels of 282 and 303 mg/kg-bw/day[6], respectively. Microscopic examination following the13-week sacrifice revealed histological alterations in the bladder lining of two high-dose males including hyperplasia of the transitional epithelium and congestion or hemorrhage associated with the presence of calculi in the bladder. Although the robust summary notes that lesions other than those in the bladder were not different between controls and treatment groups, five mice at the highest dose had focal hepatic necrosis versus one control male.
LOAEL (male) = 1994 mg/kg-bw/day (based on calculi in the urinary bladder, hyperplasia of the transitional epithelium and congestion or hemorrhage of the bladder lining)
NOAEL (male) = 522 mg/kg-bw/day
NOAEL (female) = 2201 mg/kg-bw/day (based on no adverse effects at the highest dose tested)

(2) In a 13-week drinking water study, CD® rats (24 – 40/sex/dose) were administered sodium cyanurate (purity not specified) at 0 (control; 40/sex), 896, 1792 (24/sex/dose) or 5375 ppm (40/sex) (approximately 0, 101, 214 or 710 mg/kg-bw/day for males and approximately 0, 130, 265 or 870 mg/kg-bw/day for females). An additional control group (40/sex) received 7812 ppm sodium hippurate (approximately 916 and 1210 mg/kg-bw/day for males and females, respectively). Interim sacrifices of animals from the high-dose and both control groups (4/sex/group) were conducted at 2, 4, 6, 8 and 10 weeks. Limited histopathology was conducted; kidneys, ureters and urinary bladders were examined in controls, sodium controls and high-dose rats. No mortality or clinical signs of toxicity were observed. There were no treatment-related effects on bodyweight or food consumption, or gross pathology. Relative testes and heart weights were decreased at the highest dose in males ($p < 0.05$). Increased in water consumption was seen at the two highest doses (males); females had decreases in water consumption at 896 and 1792 ppm (but not at the highest dose). Treatment-related histopathological findings included very slight to slight hyperplasia of the urinary bladder epithelium in 4/20 high-dose and 1/24 mid-dose males sacrificed at 13 weeks and in 1/4, 1/4 and 2/4 high-dose males sacrificed at 6, 8 and 10 weeks, respectively.
LOAEL (male) = 214 mg/kg-bw/day (based on hyperplasia of the urinary bladder epithelium)
NOAEL (male) = 101 mg/kg-bw/day
NOAEL (female) = 870 mg/kg-bw/day (based on no adverse effects at the highest dose tested)

(3) In a 104-week drinking water study, B6C3F1 mice (80 – 100/sex) were administered sodium cyanurate (77.5% pure) at 0 (vehicle control; 100/sex), 100 (80/sex), 400, 1200 or 5375 ppm (100/sex) (actual compound consumption of 24, 97, 307 and 1523 mg/kg-bw/day for males and 26, 100, 315 and 1582 mg/kg-bw/day for females). An additional control group (80/sex) received 8005 – 10,281 ppm sodium hippurate (actual compound consumption 2093 and 2219 mg/kg-bw/day for males and females, respectively). Interim sacrifices (10/sex/dose) were conducted at 26, 52 and 78 weeks and all remaining animals were sacrificed at 104 weeks. No mortality occurred. High-dose females exhibited lower mean absolute body weight values at 13 and 26

[6] Estimated mean daily sodium consumption for the 13-week period. Consumption at the high-dose level is based on the amount of sodium present in sodium cyanurate (12.8%, as proved by sponsor).

weeks; at terminal sacrifice, female body weights at the high dose were lower than sodium controls. Mean growth rates for the 13-week interval were lower in females from the 400, 1200 and 5375 ppm sodium cyanurate and sodium control groups and in high-dose females for the 26-week interval. Mean total food consumption values were decreased at 1200 ppm at weeks 13 and 26 in both males and females and at week 52 in males only. When compared with sodium controls, food consumption at 5375 ppm was higher in males throughout the study and lower in females through week 13. Water consumption was increased in males at 5375 and 1200 ppm compared with vehicle controls; both sexes at 5375 ppm had higher water consumption than sodium controls. Clinical observations included increased incidences of swollen/enlarged abdomens in males of the 1200, 5373 ppm and sodium control groups at week 15 and continuing throughout the study. Swollen abdomens were also seen in females after week 27 (although less frequently than males) at the same concentrations. Rough hair-coat in mid- and high-dose and sodium control females and sporadic findings of tissue masses (including wart-like lesions) were observed in all groups of females except the 1200 ppm group. There were no treatment-related hematological effects noted. Mean urine sodium concentrations and excretion values were increased in high-dose and sodium control females at all collection intervals and in high-dose and sodium control males at week 79. There were no treatment-related gross pathological findings. Most statistically significant differences in organ weights could not be attributed to treatment due to outliers, lack of dose response or lack of effect at later time points. However, at the highest dose, females had lower absolute kidney and kidney to brain weight ratios compared with sodium controls. A variety of spontaneous disease lesions and incidental findings were observed at interim and terminal sacrifices but were not considered treatment-related.
LOAEL ~ 307/315 (male/female) mg/kg-bw/day (based increased incidence of swollen/enlarged abdomens)
NOAEL ~ 97/100 (male/female) mg/kg-bw/day

(4) In a 104-week drinking water study, CD® rats (80/sex/dose) were administered sodium cyanurate (99.7% pure) at 0 (vehicle control), 400, 1200, 2400 or 5375 ppm (average compound consumption of 0, 25, 76, 154 and 371 mg/kg-bw/day for males and 0, 42, 129, 266 and 634 mg/kg-bw/day for females). A positive control group (80/sex) received 7768 ppm sodium hippurate (average compound consumption of 60 and 99 mg/kg-bw/day for males and females, respectively). An additional group (20/sex/dose) received sodium cyanurate at 0 (vehicle control), 1200, 2400 or 5375 ppm for 62 weeks and were observed without exposure during a recovery period from weeks 63 – 104. In the rats dosed for 104 weeks, a slight reduction in survival was observed in male rats at the highest dose. Death occurred in 5/20, 13/20, 11/20 and 9/20 recovery females at 0, 1200, 2400 and 5375 ppm, respectively. During the no-exposure period, group mean body weights in recovery females that received 2400 or 5375 ppm were slightly increased compared to the respective control (14 – 18%) or non-recovery group (12 – 14%). There were treatment-related increases in water consumption in males and females receiving 2400 and 5375 ppm when compared to negative controls; however, the mean values were comparable to the sodium controls. Thus, the increased water consumption in these groups was attributed to a high intake of sodium and a consequent increase in urinary excretion of sodium. There were no treatment-related trends in water consumption in the recovery groups; however, mean water consumption of high-dose males and females in the recovery group was lower between weeks 63 and 104 than non-recovery high-dose animals. There was an increase in

the incidence of reddish urine in high-dose males during the first year of the study as well as an increased incidence of palpable masses in high-dose and sodium control males during weeks 1 – 13 when compared to vehicle controls. In the recovery groups, clinical findings were similar when compared to the corresponding group that continued treatment. There were no treatment-related effects on hematology or clinical chemistry parameters. At the high-dose, gross lesions of the urinary tract were observed primarily in males that died in the first year of the study and included hydronephrosis of the kidneys in 9/22 males, calculi in the kidneys of 10/32 males as well as hydroureter in 6/13 males. No treatment-related organ weight changes were observed except for significantly lower ($p < 0.05$ or 0.01) absolute and relative thyroid and parathyroid weights in males at 154 and 371 mg/kg-bw/day at the 12-month sacrifice that were not seen at later time points. There was a treatment-related increase in the incidence of urinary tract and heart lesions in high-dose males, most of which occurred during the first 12 months of the study and were more frequent in high-dose males that died or were sacrificed moribund. Urolithiasis was noted more frequently in high-dose males than high-dose females and was attributed to obstruction of the urethra. Heart lesions were considered secondary to uremia caused by the urinary tract obstructions and included acute myocarditis, necrosis and vascular mineralization. Nine of 11 high-dose males that died and/or were sacrificed in extremis during the first year of the study having heart lesions also had calculi in and distension of the bladder. The incidence of splenic hemosiderosis was also increased in high-dose males during the first year of the study.
LOAEL ~ 371/634 (male/female) mg/kg-bw/day (based on reddish urine, palpable masses, hydronephrosis of the kidneys calculi in the kidneys, hydroureter, urolithiasis, obstruction of the urethra, calculi in the bladder, distension of the bladder and acute myocarditis, necrosis and vascular mineralization of the heart)
NOAEL ~ 154/266 (male/female) mg/kg-bw/day

(5) In a 59-day drinking water range-finding study, CD® rats (5/sex/dose) were administered sodium cyanurate (purity not specified) in drinking water at 0 (vehicle control; 10/sex), 400, 1200, 2000 or 4000 ppm (approximately 0, 62, 187, 311 or 622 mg/kg-bw/day for males and 68, 203, 339 or 677 mg/kg-bw/day for females). No mortality or clinical signs of toxicity were observed. There were no treatment-related effects on body weight, food and water consumption, hematological or clinical chemistry parameters. The urine values were within the normal range except for the urea nitrogen, which was decreased (~ 50%) in females at 1200 ppm and in both males and females at 2000 and 4000 ppm. However, macroscopic examination revealed no evidence of liver or kidney disease to suggest a relationship to treatment. Mild and focal inflammatory changes were observed in the kidneys of a few animals from each experimental group but were considered to be spontaneous and of comparable incidence to controls. There were no treatment-related gross pathological findings, organ weight changes or histopathological findings.

Reproductive Toxicity

Sodium cyanurate (CASRN 2624-17-1, supporting chemical)

In a three-generation drinking-water reproductive toxicity study, CD® rats (12 males and 24 females/dose) were administered sodium cyanurate (77.05% pure) at 0 (vehicle control), 400, 1200 or 5375 ppm (approximately 0, 47, 130 or 614 mg/kg-bw/day for males and 0, 62, 196 or

730 mg/kg-bw/day for females) for ≥ 100 days premating. An additional group of animals (12 males and 24 females/dose) received 8056 ppm sodium hippurate (approximately 945 mg/kg-bw/day for males and approximately 1366 mg/kg-bw/day for females). A minimum of 14 days after weaning of the F1a litters, F0 females were mated again (to different males) to produce the Flb offspring. Pups from the Flb litters were selected at random to become parents for the next generation. After a minimum of 120 days of sodium cyanurate administration the Flb parents were mated twice, as described above, to produce "a" and "b" litters and the F2b parents were mated once to produce the F3a offspring. Offspring from the Fla and F2a generations were sacrificed on lactation day 21, necropsied and discarded. At weaning, 12 male and 12 female F3 pups per group were randomly selected for continued treatment for another 4 weeks. They were then sacrificed and necropsied, and designated tissues were collected. The remaining F3 weanlings were sacrificed and necropsied. All of the litters were reduced to 10 pups on lactation day 4. A total of seven F0 males did not survive to scheduled sacrifice (two controls, two high-dose animals and one sodium control). In addition, one male each in the control and high-dose groups were sacrificed prior to termination. The deaths and sacrifices occurred between study weeks 11 and 34. Six F1 parents died (one male each in the high-dose and sodium control groups and one female each in the control, low- and mid-dose and sodium control groups). Additionally, one control group F1 female was sacrificed in extremis. Mortality and unscheduled sacrifices occurred between weeks 38 and 63. Five F2 parents did not survive to scheduled sacrifice (two each in the low- and high-dose groups and one in the sodium control group). Deaths occurred between weeks 69 and 100. During the first generation, slight (non-significant) increases in body weight were seen in the high-dose and sodium control males. In contrast, during the second generation, body weight inhibition was noted for the high-dose and sodium control males and females and mid-dose females. Throughout the third generation, low-dose male and female body weights were generally higher than the control values. Since no cross-generation trends were apparent, it was concluded that parental body weights were not affected by sodium cyanurate administration. Maternal weights during gestation and lactation were similarly unaffected. There was no treatment-related effect on food consumption. Increased water consumption was noted for high-dose females in all generations and for sodium control females in the F1 and F2 generations. No treatment-related gross pathological, histopathological or organ weight effects were noted for F0 or Fl parents. In the F2 generation, an increased incidence of calculi in the urinary bladder was noted in 5/12 high-dose males. The urinary bladders of three of these males had epithelial hyperplasia or chronic cystitis, which was considered secondary to chronic irritation from the calculi. There were no treatment-related effects on reproductive parameters (fertility indices, gestation length, litter size, pup survival and pup weights). Dystocia or behavioral abnormalities during nesting and nursing were not observed. Female fertility indices and corresponding mating indices revealed 2 – 11 sterile matings/treatment group/breeding; these were increased in the second generation but not in other generations. The number of viable pups at birth decreased at the mid-dose for the F2a and F2b litters and in high-dose F2b litters. In the third generation, pup body weights for the dose groups and values for the sodium control group were lower than the controls throughout lactation. No treatment-related macroscopic changes, organ weight variations or microscopic changes were evident in the F0, F1b, F1, F2b or F3 animals. Gross necropsy of pups that died or weanlings at scheduled sacrifice revealed no treatment-related findings with respect to malformations, variations or pathological findings.

LOAEL (systemic toxicity) ~ 614/730 (male/female) mg/kg-bw/day (based on increased incidence of calculi in the urinary bladders)
NOAEL (systemic toxicity) ~ 130/196 (male/female) mg/kg-bw/day
NOAEL (reproductive toxicity) ~ 614/730 (male/female) mg/kg-bw/day (based on no consistent adverse effects on reproductive parameters at the highest dose tested)

Developmental Toxicity

Sodium cyanurate (CASRN 2624-17-1, supporting chemical)
(1) In a prenatal developmental toxicity study, pregnant COBS® CD® rats (25/dose) were administered sodium cyanurate (99.7% pure) in 4% aqueous carboxymethyl cellulose via oral gavage at 0 (untreated control), 0 (vehicle control), 200, 1000 or 5000 mg/kg-day on gestation days 6 – 15 and dams were sacrificed on gestation day 20. An additional low and high sodium control group received 1118 and 5590 mg/kg-day of sodium hippurate, respectively. Eleven females in the high sodium control group died between days 8 and 16 of gestation. No deaths occurred in any of the other control or treated groups. No treatment-related clinical signs or effects on body weight were noted in any dams treated with sodium cyanurate. The mean maternal body weight gain in the high sodium control group was slightly decreased over the entire gestation period. No treatment-related clinical signs were observed in any dams from the sodium cyanurate groups. Clinical signs and gross pathological changes were observed in the high sodium control group. There were no treatment-related effects on uterine weights but there was a decrease in mean gravid uterus weight in dams the high sodium controls. There were no significant effects on reproductive parameters including the number of pregnant animals, early or late resorptions, implantations, corpora lutea, postimplantation losses or the duration of pregnancy. In both sodium control groups there was a dose-related increase in mean postimplantation loss when compared to vehicle and untreated control groups. There were no treatment-related effects on mean fetal body weights, number of viable fetuses, litter size or fetal sex ratio, or fetal crown rump length in the sodium cyanurate groups. However, decreases in mean fetal body weight, mean number of viable fetuses, and mean fetal crown rump length were seen in the high sodium control group. There were no treatment-related effects on the total number of litters with malformed fetuses in the sodium cyanurate group. However, bent ribs and limb bones were observed in seven fetuses from one litter at the high-dose and ; bent ribs were observed in seven and three fetuses from the low- and mid-dose groups, respectively; these effects were not considered to be treatment-related. In the high sodium control group, a markedly increased occurrence of bent ribs was observed. An increased incidence of fetal variations were noted in one litter from the high-dose group and included unossified sternebrae (numbers 1, 2, 3 and/or 4) or reduced vertebral ossification. However, this effect was not considered to be treatment-related. Several additional fetal effects (skeletal and tissue effects) were observed in the high sodium control group compared to vehicle and untreated controls. Such developmental variations were not observed in the low sodium control group.
NOAEL (maternal/developmental toxicity) = 5000 mg/kg-day (based on no treatment-related effects at the highest dose tested)

(2) In a prenatal developmental toxicity study, pregnant New Zealand White rabbits (20/dose) were administered sodium cyanurate (> 99% pure) in 1% aqueous carboxymethyl cellulose via

oral gavage at 0 (vehicle control), 50, 200 or 500 mg/kg-day on gestation days 6 – 18. Females that aborted during the study were sacrificed and necropsied. On day 29 of gestation, the surviving dams were necropsied and their fetuses removed by cesarean section. One high-dose female and two low-dose females aborted on gestation days 22, 24 and 26, respectively, and were sacrificed and necropsied. All other females survived to scheduled sacrifice on gestation day 29. The pregnancy rates at 0, 50, 200 and 500 mg/kg-day were 90, 100, 90 and 80%, respectively. Despite some differences in body weight and body weight gains in the treatment groups compared with controls, no statistically significant differences were noted. No treatment-related clinical signs of toxicity or gross abnormalities were observed in dams. There were no treatment-related effects on gravid uterus weight, duration of pregnancy or the mean number of corpora lutea. An increase in post implantation loss was noted at the high-dose level as a result of seven late resorptions in one dam. The mean post-implantation loss at the high-dose (1.5) was within the range of historical control data (0.2 – 1.9). There were 3, 9, 2 and 16 late resorptions in the control, low-, mid- and high-dose groups, respectively. Mean fetal body weight was comparable between the control and treatment groups. The number of litters at 0, 50, 200 and 500 mg/kg-day were 18, 20, 18 and 16, respectively. There were no treatment-related effects on fetal body weight. A slight decrease in the mean number of viable fetuses was noted at the mid-dose level. A difference was noted in the fetal sex ratio at the low-dose. However, since a similar difference was not noted at the 200 and 500 mg/kg-day levels, this change was considered incidental and not related to treatment. No statistically significant differences were noted in fetal malformation data. Malformations observed were generally dissimilar in nature and included filamentous tail, microphthalmia, flexed paw, spinal bifida, iris bombe, unascended kidneys, lung cysts, hydrocephaly and vertebral, skull and rib anomalies. With the exception of 1fetus in the mid-dose group, all fetuses with hydrocephaly were also observed to have domed heads. The developmental malformations, with the exception of hydrocephaly, occurred at a very low incidence (one to two fetuses/malformation). Hydrocephaly occurred at 0, 200 and 500 mg/kg-day in three fetuses (one litter), three fetuses (two litters) and nine fetuses (two litters), respectively. Hydrocephaly is not uncommon for this species and strain.
NOAEL (maternal toxicity) = 500 mg/kg-day (based on no significant adverse effects at the highest dose tested)
LOAEL (developmental toxicity) = 500 mg/kg-day (based on increased incidences of hydrocephaly and post-implantation loss)
NOAEL (developmental toxicity) = 200 mg/kg-day

Genetic Toxicity – Gene Mutation

In vitro

Sodium dichloro-s-triazinetrione (CASRN 2893-78-9)
In a National Toxicology Program (NTP) study, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to sodium dichloro-s-triazinetrione in water at concentrations ranging from 0.33 to 100 μg/plate with and without metabolic activation. No cytotoxicity was observed. Data are limited because concentrations tested are lower than recommended. Negative and positive controls were included and yielded appropriate responses

(http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?searchterm=2893-78-9&fuseaction=ntpsearch.searchresults).
Sodium dichloro-s-triazinetrione was not mutagenic in this assay.

Sodium cyanurate (CASRN 2624-17-1, supporting chemical)
(1) L5178Y mouse lymphoma cells were exposed to sodium cyanurate (purity not specified) in deionized water for 4 hours at concentrations of 250, 500, 750, 1000, 1250, 1500, 1750 or 2000 µg/mL (with activation) and 50, 100, 250, 500, 750, 1000, 1250, 1500, 1750 or 2000 µg/mL (without activation). Positive controls responded appropriately. At 200 µg/mL (limit of solubility in water), no cytotoxicity was observed with or without activation. At 2000 µg/mL (suspension), a 7 and 10% reduction in growth was noted with or without metabolic activation, respectively.
Sodium cyanurate was not mutagenic in this assay.

(2) *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to sodium cyanurate (77.34% pure) in dimethylsulfoxide (DMSO) and water at concentrations of 0.01, 0.04, 0.2, 1, 3 and 10 mg/plate in the presence and absence of metabolic activation. Positive controls responded appropriately. No cytotoxicity was observed at concentrations ≤ 10 mg/plate with or without metabolic activation.
Sodium cyanurate was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo

Sodium cyanurate (CASRN 2624-17-1, supporting chemical)
Sprague-Dawley rats (10 males/dose) were administered sodium cyanurate (99.6% pure) in 4% carboxymethyl cellulose via gavage at doses of 0 (vehicle control), 1.25, 2.5 or 5 g/kg-bw. Additional animals were treated with a positive control. Bone marrow samples (5 rats/dose) were taken at 24 and 48 hours each. Positive controls responded appropriately. No mortality or treatment-related effects were observed at any of the doses tested.
Sodium cyanurate did not induce chromosomal aberrations in this assay.

Additional Information

Skin Irritation

Sodium dichloro-s-triazinetrione, dihydrate (CASRN 51580-86-0)
Undiluted sodium dichloro-s-triazinetrione, dihydrate was applied once on an unspecified area of skin of New Zealand White rabbits (3/sex/dose) at 0.5 g for 24 hours. The robust summary did not provide information on whether the area was covered. The rabbits were observed for 21 days. No mortalities were observed. Very slight to moderate erythema and very slight to slight edema was noted at 30 – 60 minutes after dosing. All sites had cleared at 96 hours. Other dermal effects included thickening, blanching, necrosis, epidermal scaling, raw areas and sodium dichloro-s-triazinetrione, dihydrate adhering to the skin. All irritation cleared by 21 days.
Sodium dichloro-s-triazinetrione, dihydrate was irritating to rabbits in this assay.

Eye Irritation

Sodium dichloro-s-triazinetrione (CASRN 2893-78-9)
Sodium dichloro-s-triazinetrione was applied at 0.1 g into the conjunctival sac of the right eye of New Zealand White rabbits (3/sex/dose) followed by irrigation with physiological saline for 20 – 30 seconds. Ocular irritation was evaluated at 1, 24, 48 and 72 hours and 4, 7, 10, 14, 17 and 21days after administration. Severe irritation, including corneal opacity, iritis and conjunctivitis, was noted in all treated eyes throughout the study. Ocular irritation persisted in all animals through the study termination. There were no other adverse clinical signs.
Sodium dichloro-s-triazinetrione was severely irritating to rabbits in this assay

Sodium dichloro-s-triazinetrione, dihydrate (CASRN 51580-86-0)
Sodium dichloro-s-triazinetrione, dihydrate was applied at 0.5 g into the conjunctival sac of eyes of New Zealand White rabbits (3/sex/dose level) for 24 hours and observed for 21 days. There were no deaths. Severe eye irritation involving the cornea, iris and conjunctivae was noted in all rabbits. On day 7, the corneas of all rabbits were not observable due to the nictitating membrane that was adhered to the cornea; in some rabbits, the cornea appeared to be ruptured.
Sodium dichloro-s-triazinetrione, dihydrate was severely irritating to rabbits in this assay.

Dermal Sensitization

Sodium dichloro-s-triazinetrione, dihydrate (CASRN 51580-86-0)
In a guideline skin sensitization assay, an intradermal injection ((1)0.1% formulation in distilled water or (2) 0.1% in distilled water and Freund's Complete Adjuvant) followed by a second induction of a topical application (1% w/w in distilled water) of sodium dichloro-s-triazinetrione, dihydrate to the skin of 10 Albino Dunkin Hartley guinea pigs was then followed by a topical challenge (0.5% and 0.1% in distilled water). No mortalities were observed. The test substance produced a 0% (0/10) sensitization rate and was not considered a skin sensitizer.
Sodium dichloro-s-triazinetrione, dihydrate was not a dermal sensitizer to guinea pigs in this assay.

Carcinogenicity

Sodium cyanurate (CASRN 2624-17-1, supporting chemical)
(1) In the 104-week repeated-dose toxicity study on sodium cyanurate in mice described above, histopathological examination revealed a variety of neoplastic hepatocellular lesions in the liver without relationship to treatment. Neoplasms were noted in the tissues examined from the weeks 52 and 78 sacrifices and consisted of a hepatocellular adenoma in the liver of a male in the sodium control group (week 52) and hepatocellular neoplasms in three mice each in the vehicle control and high dose (week 78) group; and an alveolar bronchiolar adenoma in the lungs of a female in the sodium control group (week 52) and one vehicle control male (week 78). In the epididymis of two control, one high dose and two sodium control male mice, there was an increased incidence of a connective tissue tumor designated "Sarcoma -Not Otherwise Specified." All of these tumors were generally similar morphologically and were composed of

both spindle and oval cells with a foamy pale cytoplasm. Multinucleated giant cells were often present. These tumors appeared similar to histiocytic sarcomas described in the uterus and cervix of female mice.
Sodium cyanurate did not increase the incidence of tumors in mice in this study.

(2) In the 104-week repeated-dose toxicity study on sodium cyanurate in rats describe above, histopathological examination revealed no evidence of oncogenic effects. There were no increases in the incidence of tumors at any site when high-dose groups were compared to controls.
Sodium cyanurate did not increase the incidence of tumors in rats in this study.

Conclusion: Acute oral toxicity of sodium dichloro-s-triazinetrione dihydrate to rats is low. Acute inhalation toxicity of sodium dichloro-s-triazinetrione to rats is high. Acute dermal toxicity of sodium dichloro-s-triazinetrione and sodium dichloro-s-triazinetrione dihydrate to rats and rabbits, respectively, is low. In a 13-week drinking water study in rats with sodium dichloro-s-triazinetrione, dihydrate, clinical signs of toxicity (labored breathing, emaciation, accumulation of yellow material on the anogenital regions, decreased defecation, decreased activity) and mortality were observed at 1000 mg/kg-day; the NOAEL is 300 mg/kg-day. In 13-week drinking water studies with the supporting chemical, sodium cyanurate, in rats and mice, no adverse effects were observed in females; the NOAEL is 2201 and 870 mg/kg-bw/day (highest dose tested) in rats and mice, respectively. In male mice, calculi in the urinary bladder, hyperplasia of the transitional epithelium and congestion or hemorrhage of the bladder lining were observed at 1994 mg/kg-bw/day; the NOAEL is 522 mg/kg-bw/day. In male rats, hyperplasia of the urinary epithelium was observed at 215 mg/kg-bw/day; the NOAEL is 101 mg/kg-bw/day. In a three-generation drinking water reproductive toxicity study in rats, the supporting chemical, sodium cyanurate, did not adversely affect reproduction; the NOAEL is 614/730 (male/female) mg/kg-bw/day (highest dose tested). In a prenatal developmental toxicity study in rats treated by oral gavage, the supporting chemical, sodium cyanurate, showed no maternal toxicity or developmental toxicity; the NOAEL for maternal and developmental toxicity is 5000 mg/kg-day (highest dose tested). In a similar study in rabbits, no adverse effects were seen in dams; the NOAEL for maternal toxicity is 500 mg/kg-day. Post-implantation losses and hydrocephaly were seen at 500 mg/kg-day; the NOAEL for developmental toxicity is 200 mg/kg-day. The supporting chemical, sodium cyanurate, did not induce mutations *in vitro* or chromosomal aberrations both *in vitro* and *in vivo*. Sodium dichloro-s-triazinetrione, dihydrate is irritating to the skin of rabbits. Sodium dichloro-s-triazinetrione and its dihydrate are irritating to the rabbit eye. Sodium dichloro-s-triazinetrione, dihydrate is not a skin sensitizer in guinea pigs. The supporting chemical, sodium cyanurate, did not increase the incidence of tumors in mice or rats.

Table 3. Summary Table of the Screening Information Data Set under the U.S. HPV Challenge Program – Human Health Data

Endpoint	SPONSORED CHEMICAL Sodium dichloro-s-triazinetrione (2893-78-9)	SPONSORED CHEMICAL Sodium dichloro-s-triazinetrione, dihydrate (51580-86-0)	SUPPORTING CHEMICAL Sodium cyanurate (2624-17-1)
Acute Oral Toxicity LD_{50} (mg/kg)	No Data 1671 (RA)	**1823**	–
Acute Inhalation Toxicity LC_{50} (mg/L)	**0.27 to < 1.17**	No Data 0.27 to < 1.17 (RA)	–
Acute Dermal Toxicity LD_{50} (mg/kg)	**> 2000**	**> 5000**	–
Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-day)	No Data (rat) NOAEL ~ 101 (m) ~266 (f) LOAEL ~ 214 (m) ~315 (f) (mouse) NOAEL ~ 2201 (f; highest dose tested) ~522 (m) LOAEL ~ 1994 (m) (RA)	**NOAEL = 300** **LOAEL = 1000**	**(rat; 13-week)** **NOAEL ~ 101 (m)** **~266 (f)** **LOAEL ~ 214 (m)** **~315 (f)** **(mouse; 13-week)** **NOAEL ~ 2201 (f; highest dose tested)** **~522 (m)** **LOAEL ~ 1994 (m)**
Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-day) **Reproductive Toxicity**	No Data NOAEL ~ 614 –730 (RA)	No Data NOAEL ~ 614 –730 (RA)	**NOAEL ~ 614 (m) – 730 (f)** **(highest dose tested)**

Table 3. Summary Table of the Screening Information Data Set under the U.S. HPV Challenge Program – Human Health Data

Endpoint	SPONSORED CHEMICAL Sodium dichloro-s-triazinetrione (2893-78-9)	SPONSORED CHEMICAL Sodium dichloro-s-triazinetrione, dihydrate (51580-86-0)	SUPPORTING CHEMICAL Sodium cyanurate (2624-17-1)
Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-day)			
Maternal Toxicity	No Data (rabbit) NOAEL = 500	No Data (rabbit) NOAEL = 500	**(rabbit) NOAEL = 500 (highest dose tested)**
Developmental Toxicity	NOAEL = 50 LOAEL = 200	NOAEL = 50 LOAEL = 200	**NOAEL = 200 LOAEL = 500**
Maternal/ Developmental Toxicity	(rat) NOAEL = 5000 (RA)	(rat) NOAEL = 5000 (RA)	**(rat) NOAEL = 5000 (highest dose tested)**
Genetic Toxicity – Gene Mutation *In vitro*	**Negative**	No Data Negative (RA)	**Negative**
Genetic Toxicity – Chromosomal Aberrations *In vivo*	**Negative**	No Data Negative (RA)	**Negative**
Additional Information			
Skin Irritation	**–**	**Slightly irritating**	–
Eye Irritation	**Severely irritating**	**Severely irritating**	–
Skin Sensitization	**–**	**Not sensitizing**	–
Carcinogenicity	**–**	**–**	**Negative**

Measured data in BOLD; (RA) = Read Across; – indicates that data for this endpoint are not required for this chemical.

4. Hazard to the Environment

A summary of aquatic toxicity data submitted for SIDs endpoints is provided in Table 4. The table also indicates where data for one sponsored chemical is read-across (RA) to the other.

Acute Toxicity to Fish

Sodium dichloro-s-triazinetrione (CASRN 2893-78-9)
In several tests, bluegill sunfish (*Lepomis macrochirus*) and rainbow trout (*Oncorhynchus mykiss*) were exposed to sodium dichloro-s-triazinetrione (63% purity) at unreported measured concentrations for 96 hours under flow-through conditions. http://cfpub.epa.gov/ecotox/ and http://www.ipmcenters.org/Ecotox/index.cfm.
96-h LC_{50} = 0.14 – 0.18 mg/L

Acute Toxicity to Aquatic Invertebrates

Sodium dichloro-s-triazinetrione (CASRN 2893-78-9)
Water fleas (*Daphnia magna*) were exposed to sodium dichloro-s-triazinetrione (98% purity) at unspecified nominal concentrations for 48 hours under static conditions. Analytical measurements were not conducted. http://cfpub.epa.gov/ecotox/ and http://www.ipmcenters.org/Ecotox/index.cfm
48-h EC_{50} = 0.11 mg/L

Sodium dichloro-s-triazinetrione, dihydrate (CASRN 51580-86-0)
Water fleas (*Daphnia magna*) were exposed to sodium dichloro-s-triazinetrione, dihydrate at nominal concentrations of 0, 0.15, 0.17, 0.19, 0.22, 0.24, 0.28 or 0.32 mg/L under static conditions for 48 hours (available chlorine concentrations were provided as 0, 0.08, 0.09, 0.11, 0.12, 0.13, 0.16 and 0.18 mg/L, respectively). Analytical measurements were not conducted. Test water pH, temperature and dissolved oxygen content were monitored. Mortalities were observed at all concentrations ≥ 0.17 mg/L.
48-h EC_{50} = 0.20 mg/L

Toxicity to Aquatic Plants

Sodium dichloro-s-triazinetrione (CASRN 2893-78-9)
Green algae (*Pseudokirchneriella subcapitata*) were exposed to sodium dichlor-s-triazinetrione (purity unknown) at nominal concentrations of 0 (control), 0.06, 0.13, 0.25, 0.50 or 1.0 mg/L for 96 hours. Analytical measurements were not conducted. (OTS0570796).
96-h EC_{50} (biomass) = 0.60 mg/L

Conclusion: For sodium dichloro-s-triazinetrione and sodium dichloro-s-triazinetrione, dehydrate, the 96-h LC_{50} for fish ranges from 0.14 – 0.18 mg/L, the 48-h EC_{50} for aquatic invertebrates is 0.11 mg/L, and the 96-h EC_{50} for aquatic plants is 0.60 mg/L for biomass.

Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program – Aquatic Toxicity Data		
Endpoint	**SPONSORED CHEMICAL Sodium dichloro-s-triazinetrione (2893-78-9)**	**SPONSORED CHEMICAL Sodium dichloro-s-triazinetrione, dihydrate (51580-86-0)**
Fish 96-h LC_{50} (mg/L)	**0.14 – 0.18**	No Data 0.14 – 0.18 (RA)
Aquatic Invertebrates 48-h EC_{50} (mg/L)	**0.11**	**0.20**
Aquatic Plants 96-h EC_{50} (mg/L) (biomass)	**0.60**	No Data 0.60 (RA)

Bold = experimental data (i.e. derived from testing); (RA) = Read Across