

A Review of Toxicology Studies on Cyanurate and its Chlorinated Derivatives

by Bruce G. Hammond,* Steve J. Barbee,** Takeshi Inoue,†
Norihsa Ishida,‡ George J. Levinskas,* Michel W.
Stevens,* Allen G. Wheeler,†† and Tito Cascieri§

Chlorinated cyanurates are added to swimming pools as disinfectants. In the presence of water, these materials hydrolyze to yield cyanurate and hypochlorous acid. To evaluate the safety of exposure to these materials, a comprehensive testing program was undertaken. This review summarizes the results of acute and subchronic tests on chlorinated isocyanurates. Findings from acute, subchronic, reproduction, metabolism, mutagenicity, and chronic/carcinogenicity tests on cyanurate are also summarized. Results from these tests indicate that chlorinated isocyanurates are safe for use in swimming pools.

Introduction

Chlorinated derivatives of cyanurate and its salts (chlorinated isocyanurates) are used as disinfectants and algicides for swimming pools and cooling towers and are regulated under provisions of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). These compounds are also used as cleansing, bleaching, and sanitizing agents in a variety of industrial applications. In the presence of water, chlorinated isocyanurates undergo hydrolysis to yield cyanurate and hypochlorous acid; the latter compound is an active bactericide and oxidizing agent. The cyanurate moiety stabilizes hypochlorite in the presence of sunlight, prolonging its disinfectant action in swimming pools.

The greatest potential for human exposure to cyanurate results from its use as a stabilizer of hypochlorite in swimming pools. Workers are also exposed to chlorinated isocyanurates during their manufacture and packaging. To assess the risks from such exposure, a variety of toxicology studies have been undertaken on both chlorinated isocyanurates and cyanurate. This review summarizes the results of published toxicity studies and unpublished information developed by member companies of The Industry *ad hoc* Committee on Isocyanurates. All of the latter studies have been submitted to the U.S. Environmental Protection Agency

(EPA) to support the registration of these materials under FIFRA.

Toxicology Studies on Chlorinated Isocyanurates

Acute Toxicity

Dichloro- and trichloroisocyanurates are considered no more than slightly toxic when administered as single oral doses in rats. The LD₅₀ values range from 600 to 1520 mg/kg. These materials are practically nontoxic when applied as a single dose to rabbit skin, since the dermal LD₅₀ is consistently greater than 5000 mg/kg (Monsanto, unpublished observations).

Chlorinated isocyanurates are generally corrosive when applied to the rabbit eye and are severely irritating or corrosive to rabbit skin when applied under occluded conditions for 24 hr according to procedures specified in the Federal Hazardous Substances Act (FHSA). However, when tested in the 4-hr Department of Transportation (DOT) test, these materials are not corrosive to rabbit skin (Monsanto, unpublished observations).

Subchronic Toxicity

Several inhalation studies have been conducted with rats exposed to chlorinated isocyanurate dust. In an early study that provided little information on experimental details, the LC₅₀ of trichloroisocyanurate dust was reported to be 25 mg/m³ (1). As part of this investigation, 1.88 mg/m³ of the trichloroisocyanurate dust,

*Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, MO 63167.

**Olin Corporation, 91 Shelton Ave., New Haven, CT 06511.

†Nissan Chemical Ind., Ltd., 200 Park Ave., New York, NY 10017.

‡Shikoku Chemicals Corp., 301 N. Rampart #C, Orange, CA 92668.

††ICI Americas, Inc., Wilmington, DE 19897.

§FMC Corporation, U.S. Highway 1, Box 8, Princeton, NJ 08540.

administered 4 hr/day for 10 weeks, was reported to have caused 30% mortality in rats.

Findings from more recent inhalation studies with dichloroisocyanurate (2) and trichloroisocyanurate (Monsanto, unpublished observations) did not agree with these results. In these studies, groups of 10 male and female CD rats were exposed separately to dichloroisocyanurate and trichloroisocyanurate dusts at analytical exposure levels of approximately 3, 10, and 30 mg/m³ for 6 hr/day, 5 days/week for a total of 4 weeks. The mass median diameter of chlorinated isocyanurate dusts ranged from 2.1 to 4.5 μm (the material was sieved to produce respirable dust particles). Contrary to the earlier report, no mortality occurred in test animals in either of these two studies. Adverse reactions were observed in both of the recent studies in mid- and particularly high-dose animals during the exposure period and included moist rales, nasal discharge, excess salivation, lacrimation, and labored breathing. Because of the deposition of dust on rat fur, the rats undoubtedly ingested the test materials during preening. Apparent treatment-related changes were observed in body weights, organ weights, and certain clinical parameters in mid- and, especially, high-dose animals. However, these changes were not consistently observed in both studies with the exception of increased lung weights, which were observed in high-dose rats in both studies. No remarkable gross pathologic changes were observed in test animals sacrificed at the end of the study.

Microscopic examination of tissues from high-dose animals did not reveal any changes that were attributed to treatment. (Animals administered trichloroisocyanurate dust were sacrificed 4 days after exposure had terminated). The lower exposure concentration of 3 mg/m³ was considered a no-effect level in both studies. The approximate daily dose of chlorinated isocyanurate dust administered to rats in these 2 studies was 0.64 mg/kg for the lowest exposure level. This dose was calculated by assuming that total volume of air inspired by a rat over a 6 hr exposure period is 0.086 m³. The comparable dose administered to a man (total volume of air inspired over 8 hr is 10.4 m³) exposed to 0.5 mg/m³ of chlorinated isocyanurate dust (a nonirritating level based on Monsanto workplace experience) can be estimated to be about 0.074 mg/kg. This exposure level is lower by a factor of 8 than the no-effect exposure level in the rat.

Chlorinated isocyanurates have also been administered in the feed and drinking water of rats to evaluate their potential subchronic toxicity. In one study, dichloro- and trichloroisocyanurate were administered separately in drinking water to rats at concentrations of 0, 400, 1200, 4000, and 8000 ppm for 59 days (Industry *ad hoc* Committee, unpublished observations). Each treatment group consisted of five animals/sex/group except controls (ten/sex). Mortality and adverse signs (labored breathing, decreased activity) were observed in the 4000- and, especially, the 8000-ppm treatment groups administered dichloro- or trichloroisocyanurate. Animals in these groups also exhibited moderate to marked reductions in body weight, and in food and water con-

sumption. (Water consumption was reduced in all treatment groups presumably because of unpalatability.) Hematology, clinical chemistry, and urinalysis parameters were evaluated for all treatment groups at the end of the study. Most values were within historical limits although urine volume and urinary creatinine were reduced relative to control values for males administered 8000 ppm chlorinated isocyanurates. At necropsy, animals administered 8000 ppm chlorinated isocyanurates exhibited an increased incidence of bleeding in the gastrointestinal tract. (No histopathology was performed on these animals.) With the exception of reduced drinking water consumption, administration of 400 ppm (males) and 1200 ppm (females) of chlorinated isocyanurates did not cause observable adverse effects in test animals. This finding translates to no-effect doses ranging from approximately 50 to 130 mg/kg, depending on the sex of the animals.

In another subchronic study, dichloroisocyanurate was incorporated in the diet of albino rats at concentrations of 0, 2000, 6000, and 12,000 ppm (Monsanto, unpublished observations). Groups of 10 animals/sex were administered these test diets for 13 weeks. Body weights and food consumption were reduced in the two highest treatment groups; mortality was limited to one high-dose female rat. Urinary and hematological parameters were unaffected by any of the treatments. Relative kidney and liver weights were increased for mid- and high-dose animals of both sexes. No dose-related, gross or microscopic pathologic changes were observed in any of the test animals. The no-effect level was considered to be 2000 ppm dichloroisocyanurate, which is equivalent to a daily consumption of 100 mg/kg.

Teratology

Dichloroisocyanurate was administered by gavage to pregnant dd strain mice at daily doses of 0, 25, 100, and 400 mg/kg during the major period of organogenesis (days 6–15 gestation) (3). Each treatment group consisted of approximately 30 mice. Mortality occurred in approximately 50% of high-dose animals, because of irritation of the gastrointestinal tract. Body weights were reduced significantly for high-dose animals, and less so for other groups.

There was no evidence that dichloroisocyanurate was fetotoxic as the mean number of live/dead fetuses and resorptions were comparable for control and treated groups. The sex ratio and neonatal body weights were also similar for all groups. There were no apparent differences in the incidence of external malformations or internal anomalies between the various groups. A delay in skeletal ossification was apparent in the fetuses from high-dose animals. Ossification delays occur frequently at doses that cause maternal toxicity and were not considered compound related. The incidence of other skeletal anomalies was comparable for all groups. There was no evidence that dichloroisocyanurate was fetotoxic or teratogenic in mice.

Toxicology Studies on Cyanurate

Acute Toxicity

Cyanuric acid is practically nontoxic when administered as a single oral or dermal dose. The oral LD₅₀ in rats is greater than 10,000 mg/kg; the dermal LD₅₀ in rabbits is greater than 7940 mg/kg. According to FHSA tests in rabbits, cyanuric acid is a slight eye irritant (1.5/110) and nonirritating to rabbit skin (Monsanto, unpublished observations).

Metabolism Studies

In a series of metabolism studies, cyanurate has been shown to be readily eliminated from the body unchanged. In one study, [¹⁴C] sodium cyanurate was administered to rats at single doses of 5 mg/kg (oral, intravenous routes) and 500 mg/kg (oral route) (4). The elimination half-life was 30 to 60 min at 5 mg/kg and 2.5 hr at 500 mg/kg. At the lower dose, the material was completely absorbed and largely eliminated in urine. At the higher dose, cyanurate was incompletely absorbed, and a larger percentage of the dose was eliminated in feces. Radioactivity remaining in tissues 7 days following treatment was below the level of detection (0.1–1.0 µg/g) for most tissues. Rats were also given 5 mg/kg/day of unlabeled sodium cyanurate orally for 14 days followed by a single dose of 5 mg/kg radiolabeled sodium cyanurate on day 15. Results from the repeat treatment study showed no bioaccumulation and no significant changes in disposition or metabolism compared to the single exposure. There was no evidence that sodium cyanurate was metabolized, as only unchanged cyanurate was found in excreta. These findings are supported by previous studies in the rat that also demonstrated that cyanurate was poorly absorbed when applied dermally (5).

The metabolic fate of sodium cyanurate was also investigated in the dog using the same experimental design (6). As in the rat, a lower dose of 5 mg/kg was completely absorbed, whereas a bolus dose of 500 mg/kg was only partially absorbed. Sodium cyanurate distributed into an apparent volume of distribution of 0.7 L/kg, which is somewhat greater than total body water volume. The elimination half-life ranged from 1.5 to 2 hr; cyanurate was readily eliminated into urine unchanged. Radioactivity remaining in tissues was below the detection level (0.1–3.3 µg/g) for all sampling times for both single and repeated dose administration. The latter finding indicates that cyanurate does not bioaccumulate in tissues. There was no evidence that cyanurate was biodegraded in the dog, as no metabolites were detected in excreta.

These findings appear to be applicable to humans, since cyanurate was found to be rapidly and quantitatively eliminated unchanged in urine following oral ingestion by volunteers (7).

Teratology Studies

Sodium cyanurate was administered to pregnant rats and rabbits to evaluate its potential developmental tox-

icity. Pregnant Dutch belted rabbits were given sodium cyanurate by oral gavage during the major period of organogenesis, days 6–18 of gestation. (FMC Corporation, unpublished observations.) Each group consisted of 9 to 10 pregnant rabbits with the exception of the control and high-dose groups, which contained 20 to 21 pregnant rabbits. Sodium cyanurate was administered at daily dosages of 50, 200, and 500 mg/kg (controls were administered 20 mL/kg water). No compound-related mortality or adverse reactions were observed during the study. Slight body weight decreases were observed in mid- and high-dose animals during the treatment period. After termination of treatment on day 18, compensatory weight gains occurred in these groups. No evidence of dose-related fetotoxicity was apparent in test animals examined on day 28 of gestation. The mean number of live fetuses/dam and sex ratio were essentially comparable for all groups. Fetal body weights and crown/rump lengths were reduced slightly in high-dose animals when compared to controls, although these values were within historical limits for the laboratory. The mild reductions in body weight gain and crown/rump lengths may have resulted from the slight manifestations of maternal toxicity that occurred during treatment. No evidence of a dose-related increase was observed in the incidence of external or internal malformations or skeletal anomalies in the fetuses that were examined. It was concluded that sodium cyanurate was not fetotoxic or teratogenic in rabbits.

Sodium cyanurate was also administered by oral gavage to pregnant CD rats during the major period of organogenesis, days 6–15 of gestation (8). The test material was administered at doses of 200, 1000, and 5000 mg/kg/day to groups of approximately 25 pregnant rats. Two sodium control groups of 25 rats each received sodium hippurate at a concentration sufficient to provide a level of sodium cations equal to the sodium levels in the 1000 and 5000 mg/kg cyanurate groups. Another control group received the dosing vehicle, 4% aqueous carboxymethyl cellulose, and an untreated control group received only water by gavage.

No mortality, body weight changes or adverse reactions were observed in vehicle and untreated control groups, the cyanurate groups, and the low-dose sodium control groups. In the high-dose sodium control group, 11 animals died. Fetotoxic effects and an increased incidence of bent ribs occurred in the fetuses from females administered the higher dose of sodium hippurate. These effects were attributed to the maternal toxicity observed in treated animals from this group.

The cesarean section observations and fetal examination data found no evidence that sodium cyanurate was fetotoxic or teratogenic in the rat.

Reproductive Studies

To assess the long-term effects of sodium cyanurate on reproductive performance, the test material was administered to rats throughout three consecutive gen-

erations (9). Sodium cyanurate was administered in the drinking water at concentrations of 400, 1200, and 5375 ppm (maximum water solubility) to groups of 12 male and 24 female CD rats. Two control groups received either tap water or sodium hippurate, which provided an equivalent amount of sodium administered to high-dose sodium cyanurate animals. Treatment was initiated at 36 days of age for parents and continued for a minimum of 100 days before mating. Parents were mated to produce two litters (F_{1a} , F_{1b}). Weanlings from the F_{1b} litter were randomly selected as parents for the next generation and continued on treatment for an additional 120 days. These animals were subsequently mated to produce 2 litters (F_{2a} , F_{2b}). Weanlings from the F_{2b} litter were randomly selected as parents for the last generation. These animals were also administered sodium cyanurate for 120 days and mated to produce one litter (F_{3a}). Randomly selected F_{3a} progeny continued on cyanurate treatment for an additional 4 weeks and were then sacrificed. Where possible, all progeny from various matings were given a post mortem examination. Organ weight measurements and microscopic examination of tissues (including gonads and gross lesions) were carried out for all parental animals i.e., selected F_{1b} and F_{2b} progeny and F_{3a} offspring that were sacrificed 4 weeks after weaning. No compound-related mortality or adverse reactions were observed during the study. Body weights and food consumption were similar among all groups. There was no evidence of dose-related or cross-generational changes in gestation length, litter size, pup survival to weaning, sex ratio, or pup weight. No compound-related macroscopic or microscopic pathologic changes or organ weight variations were apparent in cyanurate treated animals with one exception: a few high-dose cyanurate males did exhibit calculi in the urinary bladder accompanied by microscopic evidence of epithelial hyperplasia or chronic cystitis. These histologic changes were attributed to chronic irritation by the calculi. It was concluded that sodium cyanurate did not interfere with reproductive performance in the rat when administered throughout three consecutive generations.

Mutagenicity Studies

The mutagenic potential of sodium cyanurate was evaluated using *in vitro* and *in vivo* tests (10). All *in vitro* tests were carried out in the presence and absence of metabolic activation. In each assay, the highest concentration tested generally exceeded the solubility of monosodium cyanurate in the incubation medium. In the Salmonella microbial assay, sodium cyanurate was not mutagenic in test strains TA 98, TA 100, TA 1535, and TA 1537 up to a concentration of 10,000 $\mu\text{g}/\text{plate}$. Sodium cyanurate did not induce forward mutations at the TK locus of L5178Y mouse lymphoma cells up to a concentration of 2000 $\mu\text{g}/\text{mL}$. No significant increases in sister-chromatid exchanges were observed when sodium cyanurate was incubated with Chinese hamster ovary cells at concentrations up to 1500 $\mu\text{g}/\text{mL}$. In an

in vivo test, rats were administered sodium cyanurate by gavage at single doses up to 5000 mg/kg and sacrificed 24 and 48 hr after dosing. Bone marrow cells were collected and examined for chromosomal aberrations. At the time points examined, there was no evidence of cyanurate-induced chromosomal aberrations in rat bone marrow cells.

Subchronic Toxicity Studies

The subchronic toxicity of sodium cyanurate has been evaluated in both CD rats and B6C3F1 mice (Industry *ad hoc* Committee, unpublished observations). In these studies, sodium cyanurate was administered at concentrations up to 5375 ppm (maximum solubility limit for cyanurate). At this concentration, the daily compound consumption was 500 to 700 mg/kg for rats and 2000 to 2200 mg/kg for mice. The only adverse effect observed in test animals was the finding of bladder calculi with accompanying bladder epithelial hyperplasia in a few high-dose male rats and mice. This finding was not unexpected, since sodium cyanurate is not appreciably water soluble and precipitates to form calculi in urine at high concentrations. In a related study, sodium cyanurate was administered by gavage to F334 rats and B6C3F1 mice at doses ranging from 500 to 6000 mg/kg/day for 14 weeks (National Toxicology Program, private communication). At the higher treatment levels, it was unclear whether the test animals received the targeted dose levels. At these levels, the test material precipitated out of solution during dosing, making it difficult to deliver the desired dose quantitatively. There was no evidence of compound-related clinical changes and gross or microscopic lesions in the tissues of high dosage rats and mice.

Chronic Toxicity/Carcinogenicity Studies

Sodium cyanurate was administered in the drinking water of CD rats and B6C3F1 mice for most of their lifetime; e.g., 2 years (Industry *ad hoc* Committee, unpublished observations) (11). CD rats were randomly assigned to treatments of 80 to 100/sex/group administered either 400, 1200, 2400, or 5375 ppm sodium cyanurate (maximum solubility level). An equal number of control animals received either tap water or sodium hippurate to provide an equivalent amount of sodium administered to high-dose cyanurate animals. Animals were observed regularly for adverse reactions and mortality. Body weights and food and water consumption were measured at regular intervals. Clinical parameters (hematology, clinical chemistry, urinalysis) were evaluated for each group at 6, 12, 18, and 24 months. Animals used for measuring clinical parameters were sacrificed and examined for possible dose-related gross or microscopic pathologic changes.

All animals in the study were given a *post mortem* examination. Organ weights were recorded for animals sacrificed at interim times and all animals surviving to

terminal sacrifice. A comprehensive set of tissues was examined microscopically for all high-dose and control animals. Tissues identified as target organs for cyanurate-induced toxicity were examined from animals administered lower doses of sodium cyanurate.

Treatment-related mortality was observed in some (13/100) high-dose male animals that died on test during the first 12 months of the study. Mortality was attributed to the development of calculi in the urinary tract of test animals. The urethra of the male rat is anatomically more susceptible to blockage from calculi than that of the female. The high concentrations of cyanurate administered in drinking water favored the development of calculi in the urinary tract. Susceptible males that could not pass calculi were thought to have succumbed to secondary effects such as uremia from urinary tract obstruction. Pathologic changes secondary to urinary tract blockage were observed in some males that died on test and in some that were sacrificed at 12 months. These changes included hyperplasia, bleeding, and inflammation of the bladder epithelium, dilated and inflamed ureters, and renal tubular nephrosis. Slight tubular nephrosis was also observed in a few high-dose females during the first 12 months. These animals did not exhibit bladder calculi. Inflammatory lesions in the heart were also apparent in some of the high-dose males that died early.

During the last 12 months of the study, no treatment-related mortality occurred. No evidence of dose-related gross or microscopic pathologic changes was apparent in the tissues of test animals that died on test or that were sacrificed during the last 12 months.

Body weights, food consumption, and clinical parameters were generally comparable for both control and treated groups. Water consumption was increased for the high-dose cyanurate and sodium control groups.

Survival and tumor incidence data were statistically analyzed. Time-to-tumor data were analyzed for all benign or malignant tumors, all tumors combined, and for each individual tumor type that appeared in two or more animals in the high-dose group. A few statistically significant variations were found in unadjusted trend or homogeneity of life table data. None of these variations were considered to be biologically significant since they resulted from several factors including an early death among high dose males and an earlier discovery of clinically silent tumors. Based on the analysis performed, it was concluded that sodium cyanurate was not carcinogenic to male and female rats. During the first 12 months of the study, no adverse effects were observed at 2400 ppm (average daily compound consumption was 154 mg/kg [males], 266 mg/kg [females]). During the last 12 months, no adverse effects were observed at the highest treatment level—5375 ppm (371 mg/kg [males], 634 mg/kg [females]).

In the chronic mouse study, sodium cyanurate has been administered in drinking water at levels of 100, 400, 1200, and 5375 ppm to groups of 80 to 100 mice/sex/treatment. The experimental design is similar to the aforementioned chronic rat study. Final results for this

study are not yet available. However, during the first 18 months, no evidence of dose-related mortality was found in any of the treatment groups. Slight reductions in body weight were apparent at some study intervals for high-dose female mice. No treatment-related changes in clinical parameters have been apparent to date with the possible exception of increased urinary sodium levels in high-dose and sodium control animals. No evidence of compound-related, gross or microscopic pathologic changes has been apparent in the tissues of animals examined up to 18 months.

Conclusions

Chlorinated isocyanurates are registered under FIFRA for use in swimming pools. To assess the potential human health effects from this use, an extensive testing program was developed with the concurrence of EPA scientists. The decision was made to undertake the majority of the testing with sodium cyanurate (12). The rationale for this decision is as follows. In pool water, chlorinated isocyanurates hydrolyze to yield cyanurate and sodium hypochlorite as shown in equation (1) (13,14):



In pool water, the chlorine level is maintained at concentrations from 1 to 3 ppm, which is comparable to the levels used to disinfect drinking water (15). The available chlorine is eventually consumed, whereas the sodium cyanurate remains in the pool water. Over a pool season, the concentration of sodium cyanurate in water will exceed that of available chlorine. In public pools, the level of sodium cyanurate is normally controlled to levels ranging from 30 to 100 ppm; in private pools, the levels of cyanurate can attain higher concentrations (16).

Exposure to high levels of chlorinated isocyanurates may cause tissue irritation because of their ability to release hypochlorite. Although hypochlorite can oxidize and damage tissues at high concentrations, it was not found to be carcinogenic when administered in drinking water to F334 rats and B6C3F1 mice (17). Mice were administered 500 to 1000 ppm sodium hypochlorite for 78 weeks and rats, 500 to 2000 ppm for 104 weeks.

The hydrolysis product of chlorinated isocyanurates exhibited very little toxicity in the tests that have been conducted. Cyanurate was not mutagenic in a battery of short-term tests and was not teratogenic or fetotoxic in the rabbit and rat. Moreover, cyanurate did not interfere with reproductive performance in rats when administered throughout three consecutive generations. No significant toxicity was apparent in subchronic and chronic toxicity studies in rats and mice. The only finding of significance resulted from physical effects of calculi that obstructed the urinary tract of susceptible male rats causing mortality and secondary pathologic effects.

The low toxicity of cyanurate is not unexpected, considering its chemical structure. Cyanuric acid is a mem-

ber of the symmetrical triazine family. It is produced by the polymerization of urea to yield 2,4,6-trihydroxy-s-triazine. Compounds structurally related to cyanuric acid are quite stable *in vivo* as they are resistant to ring hydrolysis. For example, hydrolysis of the oxopyrimidine ring of barbiturates occurs to only a minor extent in man and animals. Cyanurate is also resistant to ring hydrolysis or further degradation, as it is readily eliminated unchanged in excreta (primarily urine) following its administration to rats, dogs, and man.

The absence of significant cyanurate-induced effects in a variety of studies designed to measure different toxic endpoints indicates that there is a substantial margin of safety for human exposure to cyanurate in swimming pools. A 70-kg adult who swims in a pool containing 100 ppm cyanurate might ingest 1 to 2 cups of water, resulting in an exposure of up to 0.7 mg/kg. This level of exposure is far below the no-effect level that lies between 154 and 371 mg/kg for male rats, which are more susceptible than females to developing calculi. If a swimmer were exposed to higher levels of cyanurate, there would still be a substantial margin of safety. Swimmers are intermittently exposed to cyanurate (unlike the laboratory animals in chronic studies, which were continuously exposed). Since cyanurate is rapidly eliminated from the body, there would not be an opportunity for it to build up in urinary tract tissues at high enough levels to form calculi. The evidence to date indicates that cyanurate is safe for its intended use in swimming pools and other applications.

NOTE ADDED IN PROOF: Final results of the chronic mouse study were recently received. Sodium cyanurate was not carcinogenic to mice and did not produce definitive treatment-related effects at any of the levels tested.

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