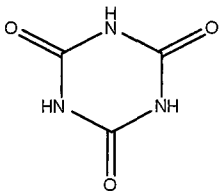
SIDS INITIAL ASSESSMENT PROFILE

CAS NO.	108-80-5
CHEMICAL NAME	Isocyanuric acid
Structural formula	

RECOMMENDATIONS OF THE SPONSOR COUNTRY

The chemical is currently of low priority for further work.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE RECOMMENDATIONS

Isocyanuric acid is not readily biodegradable (OECD 301C: 0% after 14-day) and stable in water. Bioconcentration factor to fish is low (<0.5, in Carp for 6 weeks).

Toxicity of this chemical to aquatic organisms seems to be low because all toxicity data are higher than 32 mg/l (NOEC for reproduction of *Daphnia magna*). 48-EC_{50} for immobilisation of *Daphnia magna* was 1000 mg/l. For testing in fish, Medaka (*Oryzias latipes*), both 96-h LC_{50} and 14-day LC_{50} were more than 100 mg/l. For algal test (*Selenastrum capricornutum*), 72-h EC_{50} and 72-h NOEC were 620.0 mg/l and 62.5 mg/l, respectively. No data are available for effects on terrestrial organisms.

Isocyanuric acid is lowly toxic in acute toxicity studies. This chemical is considered to be slightly irritating to eyes, but not to the skin. Several subchronic oral toxicity studies demonstrated renal damages, such as dilatation of the renal tubules, necrosis or hyperplasia of the tubular epithelium, increased basophilic tubules, neutrophilic infiltration, mineralization and fibrosis. These changes were probably caused by crystal of this chemical in renal tubules. The mechanism of this renal toxicity is supported by the toxicokinetics studies in animals and humans, showing that this chemical is quickly absorbed and excreted to urine within a few hours as an unchanged form. NOAEL is considered to be 150 mg/kg/day. In a developmental toxicity study, reduction of fetal body weights and crown/rump lengths was observed and NOAEL was 200 mg/kg/day, but this most likely reflects toxicty to the dams. No reproductive toxicity was observed (NOAEL: 600 mg/kg/day). A variety of *in vitro* and *in vivo* genotoxicity studies show this chemical is not genotoxic. Two years studies of rats and mice indicate this chemical has no carcinogenic potential.

The production volume is ca. 20,000 tons/year in Japan in 1995. This chemical is used as an intermediate of chemical products in a closed system at industries. A generic fugacity model (Mackey level III) shows that this chemical will be distributed mainly (99.9%) in water phase after it is discharged into water.

As for consumer exposure, this chemical is used in the form of chlorides for disinfection of water. In Japan, trichloroisocyanurate is mainly used in swimming pool, and the average concentration of isocyanuric acid is estimated as 50 to 100 μg/ml.

IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE

FULL SIDS SUMMARY

CAS NO: 108-80-5		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			330 °C
2.2	Boiling Point			Decomposed
2.3	Density			
2.4	Vapour Pressure		OECD TG 104	< 5.0 x 10^{-3} Pa at 25 °C
2.5	Partition Coefficient (Log Pow)		OECD TG 107	< 0.3
2.6 A.	Water Solubility		OECD TG 105	2.7 g/L at 25 °C
B.	pH			
	pKa			
2.12	Oxidation: Reduction Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation			
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4,7 and 9 pK_1 = 6.88, pK_2 = 11.40, pK_3 = 13.5
3.2	Monitoring Data			In surface water = not detected In soil/sediment = not detected
3.3	Transport and Distribution		Calculated (Fugacity Level III type)	Release: 100% to Water In Air 0.0 % In Water 99.6% In Sediment 0.0 % In Soil 0.4 %
			(local exposure)	0.19 mg/L (Japan)
3.5	Biodegradation		OECD 301C	Not readily biodegradable 0% in 28 days
3.7	Bioaccumulation		OECD 305C	BCF: < 0.5
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oryzias latipes*	OECD TG 203	LC_{50}(96hr) > 100 mg/l LC_{50}(14 d) > 100 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates *Daphnia*	*Daphnia magna*	OECD TG 202	EC_{50}(48hr): 1000 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	*Selenastrum capricornutum*	OECD TG 201	EC_{50}(72hr) = 620 mg/l NOEC= 62.5 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	*Daphnia magna*	OECD TG 202	EC_{50}(21d, Repro)= 65.9 mg/l NOEC= 32.0 mg/l
4.6.1	Toxicity to Soil Dwelling Organisms			None
4.6.2	Toxicity to Terrestrial Plants			None
4.6.3	Toxicity to Other Non-Mammalian Terrestrial Species (Including Birds)			None

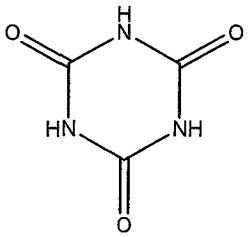
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Other (unknown)	LD_{50} = 7700 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	Other (unknown)	Minimum toxic concentration = 612 mg/m^3
5.1.3	Acute Dermal Toxicity	Rabbit	Other (unknown)	LD_{50} = > 7940 mg/kg
5.2.1	Skin Irritation/Corrosion	Rabbit	FHSA test	Not irritating
5.2.2	Eye Irritation/Corrosion	Rabbit	FHSA test	Slightly irritating
5.4	Repeated Dose Toxicity	Rat	OECD Combined	NOAEL = 150 mg/kg/day
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	*S. typhimurium*	Other (unknown)	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial In Vitro Test (Chromosomal aberrations)	Chinese hamster CHL cells	Japanese TG and OECD TG 473	- (With metabolic activation) - (Without metabolic activation)
5.6	Genetic Toxicity In Vivo (Chromosomal aberrations)	Rat	Other	-
5.7	Carcinogenicity	Rat	Other	Not carcinogenic
5.8	Toxicity to Reproduction	Rat	OECD combined	NOAEL = 600 mg/kg/day
5.9	Developmental Toxicity/ Teratogenicity	Rabbit	Other	NOAEL = 200 mg/kg/day
5.11	Experience with Human Exposure		Other (Toxicokinetics)	

[Note] Data beyond SIDS requirements can be added if the items are relevant to the assessment of the chemical, e.g. corrosiveness/irritation, carcinogenicity.

SIDS INITIAL ASSESSMENT REPORT

1. IDENTITY

- OECD Name: Isocyanuric acid
- Synonym: sym-Triazine-2,4,6-triol; sym-Triazinetriol; normal Cyanuric acid; 2,4,6-Trihydroxy-1,3,5-triazine; Trihydroxycyanidine; Tricyanic acid; Isocyanuric acid; Pseudocyanuric acid; 1,3,5-Triazine-2,4,6(1H,3H,5H)-trione; 1,3,5-Triazine-2,4,6-triol; 1,3,5-Triazinetriol; 1,3,5-Triazinetrione; Tricarbimide; Trihydroxy-1,3,5-triazine
- CAS Number: 108-80-5
- Empirical Formula: $C_3H_3N_3O_3$
- Structural Formula:



- Degree of Purity: 99.7 %
- Major Impurity: None
- Essential Additives: None
- Physical-chemical properties
  - Melting Point: 330 °C
  - Vapour pressure: < 5.0 x 10^{-3} Pa at 25 °C
  - Water solubility: 2.7 g/L
  - Log Pow: < 0.3

2. GENERAL INFORMATION ON EXPOSURE

2.1 Production and import

The production volume of isocyanuric acid in Japan is 20,000 tonnes/year in 1995.

2.2 Use pattern

All of isocyanuric acid produced in Japan is used as intermediate of chemical products, and no consumer use is reported.

2.3 Other information

None

3. ENVIRONMENT

3.1 Environmental Exposure

3.1.1 General Discussion

Isocyanuric acid is not readily biodegradable (OECD 301C: 0 % after 14d) and stable in water. Direct photodegradation is not expected because isocyanuric acid has not absorption band in UV and VIS region.

Isocyanuric acid is low bioaccumulative (BCF < 0.5, Carp).

The potential environmental distributions of isocyanuric acid obtain from a generic Mackay level III fugacity model is shown in Table 1. Parameters used for this model are shown as Annex to this report. The results show that, if isocyanuric acid is released into water, it is unlikely to be distributed into other compartments. If isocyanuric acid is released into air and soil, it is likely to be distributed in other compartments.

Table 1
Environmental distribution of isocyanuric acid
Using a generic level III fugacity model.

Compartment	Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.1 %	0.0 %	0.0 %
Water	46.5 %	99.6 %	40.5 %
Soil	53.3 %	0.0 %	59.3 %
Sediment	0.2 %	0.4 %	0.2 %

As this chemical is used in closed system as an intermediate of chemical products and is not included in consumer products, its release to the environment may occur only from the production cite.

3.1.2 Predicted Environmental Concentration

As isocyanuric acid is produced under the well-controlled closed system, amount of release to air phase is negligibly small. The waste of isocyanuric acid from the production system is released to water phase after treated its own wastewater treatment plant. Therefore, Predicted Environmental Concentration (PEC) will be calculated only for the water environment.

a. Regional exposure

According to report from a Japanese manufacturer, 407.7 tonnes/year (measured) of isocyanuric acid are released with 2.19 x 10^{10} L/year of effluent into river. Local Predicted Environmental Concentration (PEC_{local}) is calculated to be 0.186 mg/L as a worst case scenario, employing the following calculation model and dilution factor of 100.

$$\frac{\text{Amount of release } (4.08 \times 10^{11} \text{ mg/y})}{\text{Volume of effluent } (2.19 \times 10^{10} \text{ L/y}) \times \text{Dilution Factor } (100)}$$

3.2 Effects on the Environments

3.2.1 Effects on aquatic organisms

Acute and chronic toxicity data of isocyanuric acid to aquatic organisms are summarized below (Table 2). Toxicity of this chemical to aquatic organisms seems low because all toxicity data are higher than 32 mg/l (NOEC of reproduction of *Daphnia magna*). Predicted No Effect Concentration (PNEC) of this chemical was determined based mainly on the toxicity data obtained by the Environment Agency of Japan through a GLP-laboratory. Toxicity data by different organizations were few. As the lowest acute and chronic toxicity data, 96 h LC_{50} of *Oryzias latipes* and 21 d NOEC (reproduction) of *D. magna* were used, respectively (Table 2). All toxicity in Table 2 were calculated based on the nominal concentration as the measured concentrations were kept within 95 to 102 % of the nominal concentrations.

The assessment factors of 100 were used to both acute and chronic toxicity data to determine PNEC, according to the OECD Provisional Guidance for Initial Assessment of Aquatic Effects (EXCH/MANUAL/96-4-5.DOC/May 1996), because chronic toxicity data for fish was absent.

From chronic toxicity data (21 d NOEC of *Daphnia*):

PNEC = 32/100 = 0.32 mg/l

Thus, PNEC of isocyanuric acid is 0.32 mg/l.

Table 2

Acute and chronic toxicity data of isocyanuric acid to aquatic organisms at different trophic levels. The data were obtained by the Environmental Agency of Japan based on the OECD Test Guide Lines.

Species	Endpoint	Conc. (mg/l)	Remarks
Selenastrum capricornutum (algae)	Bms 72 h EC50 Bms. 72 h NOEC	620.0 62.5	a, 1) c, 1),
Daphnia magna (Water flea)	Imm 48 h EC50 Rep 21 d EC50 Rep 21 d NOEC	1000 65.9 32.0	a, 1), c, 1) c, 1), C
Oryzias latipes (fish, Medaka)	Mor 96 h LC50 Mor 14 d LC50	> 100 > 100	a, 1), A a, 1)

Notes: Bms; biomass, Mor; mortality, Rep; reproduction, NR; not recorded.
A), C); the lowest values among the acute or chronic toxicity data of algae, Cladocera (water flea) and fishes to determine PNEC of isocyanuric acid.

1) Toxicity data were obtained by the Environment Agency of Japan based on OECD Test Guidelines and GLP.

3.2.2 Terrestrial effects

No data available

3.2.3 Other effects

No data available

3.3 Initial Assessment for the Environment

Predicted No Effect Concentration (PNEC) of this chemical has been calculated as 0.32 mg/l.

PEC from Japanese local exposure scenario is 0.186 mg/l.

PEC_{local} / PNEC = 0.186/0. 32 = 0.58 < 1

Therefore, it is currently considered of low potential risk for environments and low priority for further work.

4. HUMAN HEALTH

4.1 Human Exposure

4.1.1 Occupational exposure

Isocyanuric acid is produced in a closed system and used as an intermediate for organic chemicals. The occupational exposure is expected through inhalation and the dermal route is assumed negligible because this chemical is solid. As the atmospheric concentration in plant was not measured, the maximum exposure level is estimated according to working schedules as follows. If a single worker (body weight; 70 kg, respiratory volume; 1.25 m^3/hr) is assigned to implement this operation without protection, the highest daily intake (EHE) is calculated as 0.23 mg/kg/day as the worst case. Practically, workers always wear protective gloves and respiratory protective equipment (mask) during the operation.

	Frequency Times/day	Duration hr	Working hr/day	Maximum Concentration mg/m^3	Maximum EHE mg/kg/day
Bag Filling	80	0.08	6.5	2	0.23

EHE: Estimated Human Exposure

4.1.2 Consumer exposure

Chloroisocyanurates such as sodium dichloroisocyanurate, potassium dichloroisocyanurate, sodium dichloroisocyanurate hydrate, potassium dichloroisocyanurate hydrate and trichloroisocyanuric acid have been used in sterilizing water tank, swimming pool, bathing water, and kitchen. In water, chloroisocyanurates are hydrolized to isocyanuric acid and hypochloric acid, that is the active agent (Golaszewski & Seux: 1994). The antimicrobial activity of sodium dichloroisocyanurate was evaluated against Gram negative bacteria such as *E. coli* or *Salmonella typhimurium* and against some fungi (D'Auria, *et al.*: 1989).

It is considered that the potential for exposure to pool chemicals through swallowing water and/or dermal absorption is quite high. Allen et al. (1982) reported cumulative recovery of isocyanuric acid in the urine of swimmers, 20 hr after swimming, averaging 9.8 mg. As the worst case, high performance athletes in training are known to spend up to 4 hr/day in the pool for 300 day/year and are estimated to swallow up to 60 ml/hr of pool water (Datta: 1979). In Japan, trichloroisocyanurate is mainly used in swimming pool and the average concentration of isocyanuric acid is estimated as 50 to 100 μg/ml. Based on this information, oral daily intake of isocyanuric acid for 60 kg b.w.

person is calculated as 0.17 to 0.33 mg/kg/day. Continuous-dose automated *in vitro* dermal absorption studies conducted with isocyanuric acid demonstrated minimal absorption through rat, hairless guinea pig, human, and Test skin (Moody: 1993). Total cumulative absorption of isocyanuric acid by 24 h in Test skin and human skin was 0.02 μg/cm^2 in both cases. As 1.5 m^2 of body surface is estimated for 60 kg b.w. person, the daily intake through skin is calculated as 5 μg/kg/day as the maximum value.

4.1.3 Indirect exposure via the environment

As isocyanuric acid is persistent in water and low bioaccumulative, the exposure to the general population via the environment would be possible through drinking water processed from surface water and through fish which may accumulate this chemical.

The concentration in drinking water should be estimated to be equal to PEC calculated in Section 3.1, i.e. 0.186 mg/l. The daily intake through drinking water is calculated as 6.20 x 10^{-3} mg/kg/day (2 l/day, 60 kg b.w.).

Using the maximum bioconcentration factor of 0.5 obtained by tests, the concentration of this chemical in fish can be calculated as follows:

$$PEC_{fish} = 0.186 \text{ mg/l} \times 0.5 = 9.03 \times 10^{-5} \text{ mg/g-wet}$$

As a daily intake of fish in Japan is estimated to be 90 g for 60 kg body weight person, a daily intake of this chemical will be 1.40 x 10^{-4} mg/kg/day.

4.2 Effects on Human Health

a) Acute toxicity

[SIDS data] Oral LD_{50} for isocyanuric acid was 7,700 mg/kg b.w. for rats. In inhalation study, the minimum toxic concentration was reported to be 612 mg/m^3 in rats. (Babayan and Aleksandryan: 1985) Dermal LD_{50} for isocyanuric acid was higher than 7940 mg/kg b.w. for rabbits (Toxikologische Bewertung: 1993).

Other acute toxicity information including sodium isocyanurate are given in Table. In addition, it is also reported that a single oral dosage of isocyanuric acid up to 10 g/kg was tolerated by rats and daily dosage of 20 g/kg was tolerated by rabbits for periods up to 4 days (Hodge et al.: 1965). Based on these data, isocyanuric acid is considered to be low toxic when administered as a single dose.

Routes	Strain	Type	Values	
Isocyanic acid				
Oral	Rats	LD_{50}	7,700 mg/kg	SIDS data, Ref.1
	Mice	LD_{50}	3,400 mg/kg	Ref.1
	Rabbits	LDL_0	> 10 g/kg	Ref.2
Inhalation	Rats	Other*	612 mg/m^3	SIDS data, Ref.1
Dermal	Rabbits	LD_{50}	> 7,940 mg/kg	SIDS data, Ref.3

Intravenous	Rats	LD_{50}	> 100 mg/kg	Ref.4
	Mice	LD_{50}	> 500 mg/kg	Ref.4
Sodium isocyanurate				
Oral	Rats	LD_{50}	> 7,500 mg/kg	Ref.4
Intravenous	Cats	LD_{50}	2,144 mg/kg	Ref.5

Ref.1: Babayan & Aleksandryan: 1985, Ref.2: Toxicity Information: 1972, Ref.3: Toxikologische Bewertung: 1993, Ref.4: *Gigiena i Sanitariya*: 1962, Ref.5: *J Pharmacol Exp Ther*: 1951, *: Minimum toxic concentration

b) Irritation

Federal Hazardous Substances Act (FHSA) tests of isocyanuric acid were performed in rabbits. As a result, isocyanuric acid slightly irritated to eyes but not to the skin (Hammond *et al.*: 1986). As for eye irritation, there are two other data. Moderate eye irritation followed administration into the rabbit eyes for 24 hr at 20 or 500 mg (Toxicity Information: 1972, Marhold: 1972). This chemical is not listed in IUCLID labelling and classification.

Based on these data, this chemical is considered as a slightly irritant to eyes, but not to the skin.

c) Sensitisation

There is no available data.

d) Repeated toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeat dose and reproductive/developmental toxicity screening test. Isocyanuric acid was administered by gavage at doses of 10, 40, 150 and 600 mg/kg/day for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

Isocyanuric acid induced toxic effects at 600 mg/kg in both sexes. Excretion of reddish urine was evident. In addition, depression of body weight gain was observed in males. Urinalyses of males revealed appearance of crystals, which is considered this chemical precipitated from urine, and increases of erythrocytes and leukocytes. In hematological examination of males, significant decreases in erythrocyte counts, hemoglobin concentrations and hematocrit values were observed. In blood chemical examination of males, increases in urea nitrogen and creatinine, and a decrease of sodium were revealed. In histopathological examination, dilatation of the renal tubules, necrosis or hyperplasia of the tubular epithelium, increased basophilic tubules, neutrophilic infiltration, mineralization and fibrosis in the kidney, hyperplasia of the mucosal epithelium in the urinary bladder and vacuolization of the zona fasciculata in the adrenals were observed in both sexes. In addition, the incidence of atrophic thymus also showed a tendency for increase in females. Absolute and relative kidney weights and relative adrenal weights were increased in both sexes. As no toxic sign was observed at doses of 150 mg/kg and the less, NOAEL was considered to be 150 mg/kg/day in both sexes.

Oral toxicity study of sodium isocyanurate for 90 days was performed in B6C3F1 mice at doses of 896, 1,792 and 5,375 ppm in drinking water. Sodium hippurate was used as a second control in order

to have the sodium burden as the top concentration. Although an increase in water consumption in both sexes and absolute and relative weights of ovaries in females were observed, these changes were considered due to the high sodium intake. Therefore, NOAEL was considered to be 5,375 ppm (male: 1,994 mg/kg/day, female: 2,200mg/kg/day). (Hazleton: 1982)

Hodge *et al.* (1965) conducted oral toxicity study in rats and beagle dogs, and skin and eye application study in rabbits.

In first study, rats of the Rochester strain were maintained for 20 weeks on diets containing 0.8 %, and 8 % sodium isocyanurate. As a result, 14/20 males and 4/20 females died at 8 %, but no died at 0.8 %. Considerable decrease in body weight gain was observed at 8 %. Urine samples taken prior to the start of feeding and again near termination of the study showed normal concentrations of protein and sugar. In hematological examination no change was observed. There were no changes in organ weights (thyroid, liver, brain, lungs, heart, etc.), except kidney weight, which increased at 8 % in females. In histologic study, dilatation of distal collecting tubules and ducts of Bellini, with focal areas of epithelial proliferation were observed at 8 % in both sexes. Therefore, NOAEL was considered to be 0.8 % (56 mg/kg/day).

In second study, groups of 3 dogs were maintained in diets of 0.8 % sodium isocyanurate for 6 months and 8 % for 2 years. In 0.8 % dogs, there were no changes in body weight gain, organ weight, and sugar and protein in urine. In addition, hematological and histological changes were not observed. In 8 % group, 2 dogs died after 16 and 21 months on the regimen. No change or slight increase in body weights was observed. Periodic urinalyses gave normal trace values for sugar and protein. In hematologic study, only a survival dog showed changes, which are low red blood cell counts, hemoglobin values, and hematocrits. There was no change in organ weights (thyroid, liver, brain, lungs, heart, etc.), except decrease in kidney weight of 2 dogs surviving more than 20 months. In these dogs, there was gross evidence of kidney fibrosis. Sections revealed numerous linear streaks of gray fibrous tissue extending from the papillary tip to the cortical surface. Microscopically, similar changes were observed in the kidneys of all three dogs. The collecting tubules were more uniformly and severely involved, but all portions of the nephron were compressed by fibrosis. There were slight focal dilatation and epithelial proliferation in the ducts of Bellini. In survival dog, focal areas of thyroid atrophy were found with lymphocytic infiltration, but without evidence of hyperplasia. Therefore, NOAEL for 6 months study was considered to be 0.8 % (291 mg/kg/day) and LOAEL for 2 years study to be 8 % (2,912 mg/kg/day).

In skin application study, 5 ml of 0.8 % or 8 % aqueous suspension were administered to the skin of albino rabbits 5 days/week for about 3 months, respectively. Urinalyses (sugar and protein) and hematological study showed no changes. There were no irritation or other adverse effects on the skin. In histological findings of liver and skin from treated and untreated area, no change was observed at the termination of the study. In the kidneys of the rabbits treated with the 8 % sodium isocyanurate suspension, slight dilation of the ducts of Bellini and mild tubular changes were found. Therefore, NOAEL was considered to be 0.8 %.

In eye application studies, 0.1 ml of 0.8 % or 8 % aqueous suspension were administered to eye of albino rabbits 5 days/week for about 3 months, respectively. Increase in body weight was observed during the period of the study in all treated groups. No eye injury and irritation was caused. Therefore, NOAEL was considered to be 8 %.

e) Reproductive/developmental toxicity

Reproductive toxicity

[SIDS data] Oral toxicity study was performed in SD (Crj: CD) rats by an OECD combined repeated dose and reproductive/developmental toxicity screening test. Isocyanuric acid was administered by gavage at doses of 10, 40, 150 and 600 mg/kg/day for 45 days in males and from 14 days before mating to day 3 of lactation in females. (MHW, Japan: 1997)

The parental animals exhibited no alteration in reproductive parameters including the copulation index, fertility index, gestation length, numbers of corpora lutea or implantation, implantation index, gestation index, delivery index, and behavior at delivery and lactation. There were no significant differences in offspring parameters including number of offspring or live offspring, the sex ratio, live birth index, viability index and body weight. No external or visceral abnormalities related to the test substance were detected in any of the offspring. Therefore, NOAEL for parents and offsprings was considered to be 600 mg/kg/day.

Three-generation study was conducted. Sodium isocyanurate was given by drinking water at concentrations of 400, 1,200 and 5,375 ppm to CD rats. Treatment was initiated at 36 days of age and continued for a minimum of 100 days before mating. Weanlings from the F1 and F2 litters were randomly selected as the next parents and continued on treatment for the additional 120 days. Selected litters and F3 offsprings were sacrificed 4 weeks after weaning, and organ weight measurements and microscopic examination of tissues were carried out. (Wheeler *et al.*: 1985)

No compound-related changes were observed in mortality, body weights, food consumption, gestation length, litter size, pup survival to weaning, sex ratio, and pup weight. In pathological and histological findings, epithelial hyperplasia with chronic cystitis was observed only in a few of high-dose treated males in F2 offsprings, which were attributed to chronic irritation by the calculi in the urinary bladder. However, this change is considered not to be due to reproductive toxicity of this chemical. In other treated groups, there were no changes. Therefore, NOAEL for reproductive toxicity was considered to be 5,375 ppm (approx. 370 mg/kg/day for male and 630 mg/kg/day for female).

Male CD-1 mice were treated intraperitoneally at doses of sodium isocyanurate (125 and 250 mg/kg/day). As positive control, methyl methane sulfonate was used at dose of 50 mg/kg/day. Males were mated with non-treated females. Although early resorptions were observed in females mated with males treated with methyl methane sulfonate, any chemical-related effects were not observed in females, mated with sodium isocyanurate treated males. Therefore, NOAEL was considered to be 250 mg/kg/day. (FMC Corporation: 1972)

Developmental toxicity

[SIDS data] Pregnant Dutch belted rabbits were given sodium isocyanurate at doses of 50, 200 and 500 mg/kg/day by gavage during days 6-18 of gestation. (FMC Corporation, unpublished observations)

Although slight decrease in body weight was observed in mid- and high-dose dams during the treatment period, compensatory weight gains occurred after termination of treatment on day 18. There were no compound related mortality or other adverse reactions in all treated dams. The mean number of live fetus/dam and sex ratio was essentially comparable for all groups. Fetal body weights and crown/rump lengths were reduced slightly in high-dose groups, compared to control. These changes may have resulted from the slight manifestations of maternal toxicity that occurred during treatment. There was no evidence of external or internal malformations or skeletal anomalies. Therefore, NOAEL for developmental toxicity was considered to be 200 mg/kg/day.

Sodium isocyanurate was administered at doses of 200, 1,000, and 5,000 mg/kg/day by oral gavage to pregnant CD rats during days 6-15 of gestation. Sodium control groups received sodium hippurate at dose of 1,118 and 5,590 mg/kg/day. (Industry ad hoc Committee for Isocyanurates: 1982)

There was no mortality in all treated groups. Although decrease in body weight and crown/rum length, increase in post-implantation loss, incidence incomplete ossification were observed in sodium control group, no treatment related effect on maternal appearance, behaviour and body weight gain, and no teratogenic effect were observed in all groups treated with sodium isocyanurate. Therefore, NOAEL for developmental toxicity was considered to be 5,000 mg/kg/day.

f) Genetic toxicity

Bacterial test
[SIDS data] Isocyanuric acid was not mutagenic to *S. typhimurium* TA1535, TA1537, TA98, TA100 with or without metabolic activation (Hayworth *et al.*: 1983).

Isocyanuric acid did not induce the bacteriophage Lambda in *Escherichia coli* K12 en VA UVRB (NORSOLOR/APC: 1977).

Non-bacterial test *in vitro*
[SIDS data] In chromosomal aberration test *in vitro*, clastogenicity or polyploidy in CHL/IU cells was not induced in the absence or presence of an exogenous metabolic activation system (MHW, Japan: 1997).

In lymphoma assay, this chemical also showed negative result at up to a concentration of 2000 μg/ml in the TK locus of L5178Y mouse lymphoma cells (Industry ad hoc Committee for Isocyanurates: 1981a). This chemical did not induce sister chromatid exchange in CHO cells (Industry ad hoc committee for Isocyanurates: 1981b), and this negative result was confirmed on human lymphoid cell line (LAZ-007) by Sobti *et al.* (1981), although the concentration was very low (2μg/ml).

in vivo Test
[SIDS data] In chromosomal aberration test *in vivo*, rats were killed 24 and 48 hr after administration of sodium isocyanurate by gavage at single dosages up to 5000 mg/kg, and bone marrow cells were collected and examined. As a result, this chemical did not induce chromosomal aberrations in rat bone marrow cells (Hammond *et al*: 1985).

g) Carcinogenicity

CD rats were administered sodium isocyanurate in drinking water at concentrations of 400, 1,200, 2,400 or 5,375 ppm for 2 years. Estimated daily doses were indicated only for 2,400 and 5,375 ppm (male: 154 and 371 mg/kg/day, female: 266 and 634 mg/kg/day, respectively). For a second control, sodium hippurate was administered as the same amount of sodium as the highest dose. Treatment-related mortality was observed in some males of the highest dose group, which died during the first 12 months of the study. This mortality was due to the development of calculi in the urinary tract. In some males that died on test and in some that were sacrificed at 12 months, there were pathologic changes, including hyperplasia, bleeding, and inflamed ureters, and renal tubular nephrosis. Although slight tubular nephrosis was also observed in a few females of the highest dose group during the first 12 months, these animals did not exhibit bladder calculi. Inflammatory