

## (2) 形態 (Tables 20, 21, Appendices 28, 29)

外表異常について、痕跡尾が対照群および150mg/kg群の各1匹に認められたが、被験物質の投与に起因すると考えられる異常は認められなかった。内臓異常はいずれの児動物にも認められなかった。内臓変異についても、胸腺の頸部遺残、左臍動脈遺残あるいは腎盂の拡張が総対照群で5匹(3.1%)に対し被験物質投与各群で2~6匹(1.7~4.2%)の範囲で、有意な変化は認められなかった。

### 考察および結論

#### 1. 反復投与毒性

雌雄の親動物とも、腎臓および膀胱に対する毒性影響ならびにそれとの関連性が考えられる変化が600mg/kg群に認められた。150mg/kg以下の群では、被験物質の投与による毒性影響と考えられる変化は、認められなかった。析出した被験物質と思われる尿中の結晶物質は40および150mg/kg群にも認められたが、これらの用量では生体に有害と思われる変化を伴っていなかった。

すなわち、600mg/kg群で、腎臓においては、剖検で腫大、退色および重量の増加が認められた。組織学的には、尿細管上皮の壊死、脱落およびそれによる尿の停滞を示唆する尿細管の拡張を特徴とする変化であった。

腎臓および膀胱の組織標本では結晶物質の存在は確認できなかったが、尿中には析出した被験物質と思われる結晶物質が認められた。Cascieriら<sup>9)</sup>はシアヌル酸ナトリウムのラットおよびマウスへの投与により発現する腎障害は、腎臓で析出したイソシアヌル酸の結晶による物理的な影響によることを報告している。本試験において認められた腎臓および膀胱の変化も、尿細管内で水分の再吸収に伴って析出した被験物質の結晶が起炎物質として作用して発現したものと推察される。類似した変化はサルファ剤、メチシリンなどでも報告されている<sup>9)</sup>。

また、膀胱においても、刺激に対する反応性増殖と考えられる粘膜上皮の過形成が認められたが、変化は腎臓に比べて軽度なものであった。

雌雄の親動物で認められた赤色尿の排泄、雄親の検査で認められた尿沈渣中赤血球および白血球の増加、血液尿素窒素およびクレアチニンの増加、ナトリウムの減少は、いずれも主に腎臓の変化と関連する所見と考えられる。また、雄親の貧血所見も、骨髓および脾臓に造血能に対する影響や赤血球破壊亢進を示唆する変化が認められなかったことから、障害されたおそらく腎臓からの出血によるものと推察される。

雌雄の親動物とも、副腎の退色および相対重量の増加が認められ、皮質束状帯細胞に脂質の増加を示唆する空胞化が組織学的に観察された。また、雌親では胸腺皮質の萎縮する例が増加する傾向にあった。副腎および胸腺の変化は、イソシアヌル酸の毒性影響に対するストレスと

関連した二次的な変化と判断される。

これらの変化に加えて、雄親では体重増加の抑制が、雌親においても体重の平均値では有意な変化は認められなかったものの消瘦する例が認められた。

なお、最終体重が対照群と比べて小さかった600mg/kg群で、雄は下垂体および脾臓、雌は脳のいずれも相対重量が増加し、下垂体重量の変化は150mg/kg群の雄にも認められたが、これらの器官に病理組織学的変化は認められなかった。したがって、下垂体、脾臓および脳の重量変化は主に体重の変化に伴う所見で、毒性影響を示唆する変化ではないと判断された。

以上の結果から、イソシアヌル酸のラットへの反復投与による主な毒性影響は腎臓および膀胱に認められ、副腎および胸腺に対する影響も認められた。無影響量は雌雄とも150mg/kg/dayと推定された。

## 2. 生殖発生毒性

雄親および雌親の生殖能に対する被験物質の投与による影響について、観察した各指標とも対照群と比べ有意な変化は認められなかった。また、児動物の発生に関する指標に対しても、影響は認められなかった。

交配および妊娠の不成立の対、分娩後全児が死亡した雌親が投与量とは無関係に散発したが、いずれにも生殖能の異常を示唆する病理学的な異常は認められず、偶発的な変化と考えられた。

以上の結果から、雌雄親動物の生殖能および児動物の発生に対する影響は600mg/kg/day投与によっても認められず、無影響量はいずれも600mg/kg/dayと推定された。

## 参考文献

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Table I  
 Mortality rate of male rats treated orally with isocyanuric acid in the  
 combined repeat dose and reproductive/developmental toxicity screening test

Dose (mg/kg)	No. of animals	No. of animals that died	Mortality (%)
0	10	0	0
10	10	0	0
40	10	0	0
150	10	0	0
600	10	0	0

Table 2 Mortality rate of female rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Dose (mg/kg)	0	10	40	150	600
No. of animals	10	10	10	10	10
No. of animals that died	0	0	0	0	0
Mortality (%)	0	0	0	0	0

Table 3 Incidence of clinical signs of male rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Clinical sign	Dose(mg/kg)	0		10		40		150		600			
		Fate		TK	FP	TK	UC	TK	UC	TK	TK		
		No. of animals		(Total)	(Total)	(Total)	(Total)	(Total)	(Total)	(Total)	(Total)		
		10	(10)	8	2	(10)	9	1	(10)	10	(10)	10	(10)
Reddish urine		0	(0)	0	0	(0)	0	0	(0)	0	(0)	9	(9)**
Chromodacryorrhea		0	(0)	0	0	(0)	1	0	(1)	1	(1)	0	(0)
Ptosis		0	(0)	0	0	(0)	0	0	(0)	1	(1)	0	(0)
Alopecia		0	(0)	0	0	(0)	0	0	(0)	1	(1)	0	(0)
Loss of upper incisors		0	(0)	0	0	(0)	1	0	(1)	0	(0)	0	(0)

TK : Terminal kill

UC : Animal with unsuccessful copulation

FP : Failed to cause pregnancy, killed at the termination

\*\* : Significantly different from control at 1 % level of probability

Table 4 Incidence of clinical signs of female rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Clinical sign	Dose (mg/kg)	0		10			40			150			600		
		TK (Total)		TK	NP	(Total)		TK	UC	KL	(Total)		TK	(Total)	
		No.	(Total)												
Emaciation		0	(0)	0	0	(0)	0	0	0	(0)	0	0	(0)	4	(4)*
Reddish urine		0	(0)	0	0	(0)	0	0	0	(0)	0	0	(0)	3	(3)
Decrease in locomotor activity/ piloerection/hypothermia		0	(0)	0	0	(0)	0	0	0	(0)	0	0	(0)	1	(1)
Soiled fur		0	(0)	0	0	(0)	0	0	0	(0)	0	0	(0)	2	(2)
Alopecia/scabbing		0	(0)	0	0	(0)	0	0	0	(0)	1	0	(1)	1	(1)

TK : Terminal kill

NP : Non-pregnant, killed on 26 days after copulation

UC : Animal with unsuccessful copulation

KL : Killed because all pups died after delivery

\* : Significantly different from control at 5 % level of probability

Table 5

Body weights of male rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

(g)

Dose (mg/kg)	Days of treatment								Gain 1~44
	1	8	15	22	29	36	43	44	
0	343 ± 13 (10)	376 ± 21 (10)	408 ± 28 (10)	435 ± 30 (10)	463 ± 35 (10)	490 ± 40 (10)	503 ± 45 (10)	505 ± 44 (10)	163 ± 33 (10)
10	343 ± 13 (10)	390 ± 15 (10)	431 ± 14 (10)	458 ± 15 (10)	490 ± 16 (10)	511 ± 15 (10)	525 ± 22 (10)	528 ± 22 (10)	185 ± 20 (10)
40	343 ± 12 (10)	383 ± 21 (10)	420 ± 26 (10)	449 ± 26 (10)	478 ± 27 (10)	502 ± 29 (10)	511 ± 36 (10)	514 ± 36 (10)	171 ± 27 (10)
150	343 ± 11 (10)	385 ± 11 (10)	422 ± 19 (10)	443 ± 26 (10)	475 ± 27 (10)	499 ± 36 (10)	514 ± 40 (10)	518 ± 42 (10)	174 ± 34 (10)
600	344 ± 12 (10)	358 ± 30 (10)	391 ± 25 (10)	402* ± 20 (10)	425** ± 18 (10)	453* ± 25 (10)	461* ± 30 (10)	464* ± 33 (10)	120** ± 27 (10)

Each value is expressed as mean±S.D. and (number of animals examined).

\* : Significantly different from control at 5% level of probability

\*\* : Significantly different from control at 1% level of probability

Table 6

Body weights of female rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

( g )

Dose (mg/kg)	Days of pre mating				Days of pregnancy				Days of lactation			
	1	8	15	Gain 1~15	0	7	14	20	Gain 0~20	0	4	Gain 0~4
0	223 ± 5 (10)	246 ± 10 (10)	265 ± 13 (10)	43 ± 11 (10)	271 ± 11 (10)	311 ± 11 (10)	353 ± 12 (10)	451 ± 16 (10)	180 ± 10 (10)	330 ± 22 (10)	345 ± 16 (10)	15 ± 16 (10)
10	223 ± 5 (10)	240 ± 10 (10)	258 ± 11 (10)	36 ± 10 (10)	265 ± 16 ( 8)	302 ± 13 ( 8)	344 ± 15 ( 8)	436 ± 18 ( 8)	171 ± 12 ( 8)	316 ± 24 ( 8)	336 ± 17 ( 8)	21 ± 17 ( 8)
40	222 ± 5 (10)	247 ± 9 (10)	263 ± 11 (10)	41 ± 9 (10)	273 ± 7 ( 9)	314 ± 6 ( 9)	359 ± 8 ( 9)	456 ± 13 ( 9)	182 ± 16 ( 9)	338 ± 28 ( 9)	359 ± 14 ( 8)	16 ± 20 ( 8)
150	223 ± 4 (10)	245 ± 7 (10)	262 ± 9 (10)	39 ± 6 (10)	274 ± 13 (10)	308 ± 10 (10)	346 ± 15 (10)	432 ± 34 (10)	157 ± 31 (10)	343 ± 18 (10)	350 ± 16 ( 9)	4 ± 10 ( 9)
600	222 ± 5 (10)	227 ± 28 (10)	252 ± 19 (10)	30 ± 17 (10)	261 ± 17 (10)	291 ± 23 (10)	337 ± 19 (10)	429 ± 26 (10)	168 ± 18 (10)	309 ± 27 (10)	307 ± 38 (10)	-2 ± 25 (10)

Each value is expressed as mean±S.D. and (number of animals available ).



Table 7

Food consumption of male rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Dose (mg/kg)	Days of treatment					
	1	8	22	29	36	43
0	24 ± 2 (10)	27 ± 4 (10)	28 ± 3 (10)	28 ± 3 (10)	29 ± 3 (10)	27 ± 2 (10)
10	25 ± 2 (10)	30 ± 2 (10)	27 ± 1 (10)	28 ± 3 (10)	27 ± 3 (10)	26 ± 2 (10)
40	25 ± 3 (10)	28 ± 3 (10)	27 ± 2 (9)	27 ± 2 (10)	24 ± 8 (10)	26 ± 4 (10)
150	24 ± 2 (10)	28 ± 4 (10)	28 ± 2 (10)	28 ± 4 (10)	27 ± 3 (10)	28 ± 4 (10)
600	18 ± 10 (10)	24 ± 6 (10)	24 ± 7 (10)	24 ± 5 (10)	28 ± 3 (10)	27 ± 5 (10)

Each value is expressed as mean ± S.D. and (number of animals examined).

Table 8

Food consumption of female rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

(g/rat/day)

Dose (mg/kg)	Days of pre mating		Days of pregnancy				Days of lactation	
	1	8	0	7	14	20	0	3
0	19 ± 3 (10)	20 ± 3 (10)	20 ± 3 (10)	25 ± 3 (10)	28 ± 3 (10)	23 ± 3 (10)	14 ±10 (10)	52 ± 8 (10)
10	17 ± 3 (10)	20 ± 3 (10)	19 ± 2 ( 8)	25 ± 3 ( 8)	25 ± 3 ( 8)	23 ± 4 ( 8)	17 ±11 ( 8)	49 ± 3 ( 8)
40	17 ± 3 (10)	21 ± 3 (10)	20 ± 4 ( 9)	26 ± 3 ( 9)	27 ± 3 ( 9)	25 ± 4 ( 9)	15 ±10 ( 9)	49 ± 6 ( 8)
150	18 ± 3 (10)	20 ± 4 (10)	20 ± 2 (10)	24 ± 3 (10)	26 ± 2 (10)	25 ± 3 (10)	11 ± 7 ( 9)	42 ±12 ( 9)
600	16 ± 5 (10)	19 ± 6 (10)	15 ± 4 (10)	23 ± 7 (10)	27 ± 4 (10)	22 ± 7 (10)	12 ±11 (10)	37 ±22 (10)

Each value is expressed as mean±S.D. and (number of animals available).

Table 9 - 1 Urinary findings of male rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Dose No. of animals (mg/kg)	Color			pH	Specific Gravity	Protein					
	C	PY	PB								
0	4	3	3	1.050 <sup>a)</sup> ± 0.021	1	2	5	2	6	2	
10	3	5	5	1.068 ± 0.031	1	4	5	5	4	1	
40	4	5	3	1.051 ± 0.019	2	2	4	2	10		
150	1	5	2	1.056 ± 0.018	2	3	2	3	5	5	
600	1	1	1	1.033 ± 0.012	1	1	4	1	3	1	9

Dose No. of animals (mg/kg)	Glucose			Ketone body			Occult blood			Urobilinogen			Bilirubin		
	-	±	+	-	±	+	-	±	+	-	±	+	-	±	+
0	10	4	1	10	4	1	10	7	3	10	10	10	10	10	10
10	10	1	6	10	3	9	1	9	1	10	10	10	10	10	10
40	10	5	5	10	5	8	2	8	2	10	10	10	10	10	10
150	10	2	7	10	1	9	1	9	1	10	10	10	10	10	10
600	10	6	4	10	4	7	1	7	1	10	10	10	10	10	10

a) : Mean ± S.D.  
 Color : C(colorless), PY(pale yellow), Y(yellow), PB(pale brown)  
 Cloudy : -(negligible), +(cloudy)  
 Protein : -(negligible), ±(15~30mg/dl), +(30mg/dl), ++(100mg/dl), +++(300mg/dl), ++++(1000mg/dl)  
 Glucose : -(negligible), ±(0.1g/dl), +(0.25g/dl), ++(0.5g/dl), +++(1g/dl)  
 Ketone body : -(negligible), ±(trace), +(trace), +(slight), ++(moderate), +++(marked)  
 Occult blood : -(negligible), ±(trace), +(trace), +(slight), ++(moderate), +++(marked)  
 Urobilinogen : Ehrlich unit/dl  
 Bilirubin : -(negligible), +(slight), ++(moderate), +++(marked)  
 \* : Significantly different from control at 5% level of probability  
 \*\* : Significantly different from control at 1% level of probability



Table 10

Hematological findings of male rats treated orally with isocyanuric acid  
in the combined repeat dose and reproductive/developmental toxicity screening test

Dose (mg/kg)	No. of animals	RBC (10 <sup>4</sup> /μl)	Hb (g/dl)	Ht (%)	MCV (fl)	MCH (pg)	MCHC (%)	Ret. (%)	WBC (10 <sup>2</sup> /μl)	Plat. (10 <sup>4</sup> /μl)	PT (sec)	APTT (sec)
0	10	805 ± 47	14.9 ± 0.4	43.7 ± 0.9	55 ± 3	18.5 ± 0.8	34.0 ± 0.4	26 ± 10	69 ± 14	133 ± 18	13.0 ± 0.3	19.4 ± 1.5
10	10	806 ± 29	14.9 ± 0.6	43.9 ± 1.3	54 ± 2	18.5 ± 0.9	33.9 ± 0.5	26 ± 7	71 ± 16	131 ± 15	13.3 ± 0.4	18.5 ± 0.6
40	10	821 ± 29	15.0 ± 0.5	44.2 ± 1.4	54 ± 2	18.3 ± 0.7	33.9 ± 0.5	23 ± 7	79 ± 34	137 ± 9	13.3 ± 0.3	19.6 ± 0.6
150	10	804 ± 28	15.0 ± 0.4	44.0 ± 1.0	55 ± 1	18.6 ± 0.3	34.0 ± 0.4	21 ± 5	59 ± 12	136 ± 9	13.2 ± 0.9	19.4 ± 1.0
600	10	752** ± 32	13.6** ± 0.5	40.5** ± 1.4	54 ± 1	18.1 ± 0.4	33.7 ± 0.5	32 ± 18	72 ± 20	147 ± 10	13.3 ± 0.2	18.9 ± 0.8

Each value is expressed as mean±S.D.

\*\* : Significantly different from control at 1% level of probability

Table 11

Blood biochemical findings of male rats treated orally with isocyanuric acid  
in the combined repeat dose and reproductive/developmental toxicity screening test

Dose (mg/kg)	No. of animals	GOT (IU/l)	GPT (IU/l)	ALP (IU/l)	$\gamma$ -GTP (IU/l)	T.P. (g/dl)	Alb. (g/dl)	A/G	T-Cho. (mg/dl)	T.G. (mg/dl)
0	10	57 ± 5	33 ± 5	257 ± 68	0.34 ± 0.14	6.21 ± 0.15	3.14 ± 0.12	1.03 ± 0.10	70 ± 16	73 ± 31
10	10	52 ± 4	27** ± 3	261 ± 47	0.25 ± 0.20	6.27 ± 0.24	3.20 ± 0.21	1.04 ± 0.12	83 ± 17	83 ± 40
40	10	50 ± 4	27** ± 3	240 ± 50	0.70 ± 0.78	6.33 ± 0.17	3.26 ± 0.16	1.07 ± 0.08	71 ± 10	83 ± 34
150	10	53 ± 10	28* ± 5	262 ± 57	0.50 ± 0.43	6.35 ± 0.23	3.25 ± 0.10	1.06 ± 0.07	76 ± 14	88 ± 37
600	10	55 ± 7	27** ± 5	254 ± 38	0.68* ± 0.21	6.21 ± 0.26	3.18 ± 0.14	1.05 ± 0.10	85 ± 11	69 ± 30
Dose (mg/kg)	No. of animals	Glu. (mg/dl)	T-Bil. (mg/dl)	BUN (mg/dl)	Crea. (mg/dl)	Ca (mg/dl)	P (mg/dl)	Na (mEq/l)	K (mEq/l)	Cl (mEq/l)
0	10	141 ± 14	0.30 ± 0.02	14.2 ± 2.8	0.57 ± 0.05	10.1 ± 0.3	7.3 ± 0.4	142.9 ± 0.9	4.20 ± 0.25	101 ± 1
10	10	156* ± 11	0.28 ± 0.03	13.8 ± 1.4	0.57 ± 0.05	10.2 ± 0.3	7.2 ± 0.6	142.4 ± 0.8	4.36 ± 0.22	101 ± 1
40	10	151 ± 9	0.28 ± 0.02	12.0 ± 1.0	0.57 ± 0.05	10.3 ± 0.2	7.5 ± 0.6	143.0 ± 1.1	4.13 ± 0.19	101 ± 1
150	10	155 ± 17	0.31 ± 0.03	13.3 ± 1.1	0.58 ± 0.05	10.3 ± 0.3	7.3 ± 0.7	143.2 ± 0.9	4.22 ± 0.31	101 ± 1
600	10	140 ± 6	0.29 ± 0.04	38.2** ± 12.8	1.08** ± 0.37	10.4 ± 0.2	8.5 ± 1.4	141.6* ± 1.6	4.46 ± 0.44	100 ± 1

Each value is expressed as mean±S.D.

\* : Significantly different from control at 5% level of probability

\*\* : Significantly different from control at 1% level of probability

Table 12 Incidence of necropsy findings of male rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Organ	Findings	Degree	Fate	Dose(mg/kg)				
				0	10	40	150	600
Liver	Diaphragmatic nodule	-	TK (10)	7 2 (9)	9 1 (10)	10 (10)	10 (10)	10 (10)
Kidney	Enlargement	-	TK (10)	8 2 (10)	9 1 (10)	10 (10)	10 (10)	3 (3)
		++	0 0 (0)	0 0 (0)	0 0 (0)	3 (1)**	4 (4)	
Decoloration	Decoloration	-	TK (10)	8 2 (10)	9 1 (10)	10 (10)	10 (10)	3 (3)
		++	0 0 (0)	0 0 (0)	0 0 (0)	5 (1)**	2 (1)**	
Adrenal	Decoloration	-	TK (10)	8 2 (10)	9 1 (10)	10 (10)	10 (10)	4 (4)
		+	0 (0)	0 (0)	0 (0)	6 (6)**	6 (6)**	
Skin	Alopecia	-	TK (10)	8 2 (10)	9 1 (10)	9 (9)	10 (10)	10 (10)
		+	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	

- : Negative; + : Slight; ++ : Moderate; TK : Terminal kill; FP : Failed to cause pregnancy, killed at the termination; UC : Animal with unsuccessful copulation, killed at the termination; T : Total  
 \*\* : Significantly different from control at 1% level of probability

Table 13 Incidence of necropsy findings of female rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Organ : Findings	Degree	Dose(mg/kg)											
		0		10		40		150		600			
		Fate No. of animals	TK (T) 10 (10)	TK NP (T) 8 2 (10)	TK UC KL (T) 8 1 1 (10)	TK UC KL (T) 9 1 1 (10)	TK UC KL (T) 9 1 1 (10)	TK UC KL (T) 9 1 1 (10)	TK UC KL (T) 9 1 1 (10)	TK UC KL (T) 9 1 1 (10)	TK UC KL (T) 9 1 1 (10)	TK UC KL (T) 9 1 1 (10)	
Stomach : Distention	-		10 (10)	8 2 (10)	8 1 0 (9)	9 1 (10)	10 (10)						
	++		0 (0)	0 0 (0)	0 0 1 (1)	0 0 (0)	0 (0)						
Kidney : Enlargement	-		10 (10)	8 2 (10)	8 1 1 (10)	9 1 (10)	0 (0)						
	+		0	0 0	0 0 0	0 0	4						
	++		0 } (0)	0 0 } (0)	0 0 0 } (0)	0 0 } (0)	6 } (10)**						
Decoloration	-		10 (10)	8 2 (10)	8 1 1 (10)	9 1 (10)	1 (1)						
	+		0	0 0	0 0 0	0 0	6						
	++		0 } (0)	0 0 } (0)	0 0 0 } (0)	0 0 } (0)	2 } (9)**						
	+++		0	0 0	0 0 0	0 0	1						
Adrenal : Decoloration	-		10 (10)	8 2 (10)	8 1 0 (9)	9 0 (9)	5 (5)						
	+		0	0 0	0 0 1	0 1	2						
	++		0 } (0)	0 0 } (0)	0 0 0 } (1)	0 0 } (1)	3 } (5)**						
Thymus : Atrophy	-		9 (9)	7 2 (9)	8 1 0 (9)	9 1 (10)	6 (6)						
	+		1 (1)	1 0 (1)	0 0 1 (1)	0 0 (0)	4 (4)						
Skin : Alopecia	-		10 (10)	8 2 (10)	8 1 1 (10)	9 1 (10)	9 (9)						
	+		0 (0)	0 0 (0)	0 0 0 (0)	0 0 (0)	1 (1)						

- : Negative; + : Slight; ++ : Moderate; +++ : Marked; TK : Terminal kill; NP : Non-pregnant; UC : Animal with unsuccessful copulation; KL : Killed because all pups died after delivery; T : Total  
 \* : Significantly different from control at 5% level of probability  
 \*\* : Significantly different from control at 1% level of probability

-239-

Study No. 95-047



Table 14

Absolute and relative organ weights of male rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

	Dose (mg/kg)	No. of animals	B.W. (g)	Brain (g)	Liver (g)	Kidney (g)	Spleen (g)	Heart (g)	Thymus (g)	Thyr. (mg)	Pitui. (mg)	Adrenal (mg)	Testis (g)	Epidid. (g)
Absolute	0	10	483 ± 41	2.14 ± 0.08	13.68 ± 2.09	3.01 ± 0.34	0.74 ± 0.09	1.49 ± 0.08	0.35 ± 0.06	30.3 ± 7.9	15.6 ± 2.2	63.8 ± 8.9	3.60 ± 0.26	1.45 ± 0.17
	10	10	508 ± 19	2.10 ± 0.07	15.71* ± 1.33	3.36 ± 0.37	0.79 ± 0.08	1.48 ± 0.06	0.33 ± 0.07	34.2 ± 5.0	16.6 ± 2.0	63.2 ± 6.2	3.47 ± 0.24	1.37 ± 0.11
	40	10	492 ± 32	2.07 ± 0.06	14.35 ± 1.47	3.06 ± 0.29	0.81 ± 0.11	1.58 ± 0.15	0.34 ± 0.08	36.3 ± 4.9	16.3 ± 0.8	63.2 ± 7.5	3.40 ± 0.14	1.36 ± 0.09
	150	10	495 ± 38	2.06 ± 0.07	14.76 ± 1.48	3.12 ± 0.15	0.78 ± 0.06	1.48 ± 0.12	0.31 ± 0.08	38.2 ± 6.3	19.8*** ± 2.8	66.4 ± 14.5	3.41 ± 0.27	1.41 ± 0.13
	600	10	444* ± 31	2.08 ± 0.08	12.08 ± 1.62	4.62** ± 0.96	0.83 ± 0.10	1.38 ± 0.11	0.28 ± 0.07	33.6 ± 6.4	17.4 ± 2.7	72.1 ± 10.8	3.32 ± 0.24	1.32 ± 0.10
Relative@	0	10	483 ± 41	0.45 ± 0.03	2.82 ± 0.26	0.62 ± 0.03	0.16 ± 0.01	0.31 ± 0.02	0.07 ± 0.02	6.32 ± 1.71	3.23 ± 0.42	13.18 ± 1.19	0.75 ± 0.06	0.30 ± 0.04
	10	10	508 ± 19	0.41 ± 0.02	3.09* ± 0.22	0.66 ± 0.08	0.16 ± 0.02	0.29 ± 0.02	0.07 ± 0.01	6.75 ± 1.01	3.29 ± 0.49	12.46 ± 1.27	0.68 ± 0.04	0.27 ± 0.02
	40	10	492 ± 32	0.42 ± 0.03	2.92 ± 0.19	0.62 ± 0.05	0.16 ± 0.01	0.32 ± 0.02	0.07 ± 0.02	7.38 ± 0.98	3.33 ± 0.22	12.88 ± 1.55	0.69 ± 0.03	0.28 ± 0.02
	150	10	495 ± 38	0.42 ± 0.04	2.98 ± 0.17	0.63 ± 0.05	0.16 ± 0.02	0.30 ± 0.02	0.06 ± 0.01	7.80 ± 1.71	4.02* ± 0.61	13.39 ± 2.64	0.69 ± 0.07	0.28 ± 0.03
	600	10	444* ± 31	0.47 ± 0.03	2.71 ± 0.21	1.04** ± 0.21	0.19** ± 0.02	0.31 ± 0.02	0.07 ± 0.02	7.61 ± 1.62	3.95* ± 0.68	16.23** ± 2.14	0.75 ± 0.07	0.30 ± 0.03

Each value is expressed as mean ± S.D.

@ : Relative organ weight per 100g body weight

\* : Significantly different from control at 5% level of probability

\*\* : Significantly different from control at 1% level of probability

Table 15

Absolute and relative organ weights of female rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

	Dose (mg/kg)	No. of animals	B.W. (g)	Brain (g)	Liver (g)	Kidney (g)	Spleen (g)	Heart (g)	Thymus (g)	Thyr. (mg)	Pitui. (mg)	Adrenal (mg)
Absolute	0	10	345 ± 16	1.88 ± 0.06	13.93 ± 1.19	1.89 ± 0.13	0.64 ± 0.06	1.04 ± 0.06	0.20 ± 0.06	25.4 ± 3.5	18.6 ± 2.0	73.8 ± 10.1
	10	8	336 ± 17	1.90 ± 0.06	14.20 ± 1.22	1.89 ± 0.13	0.64 ± 0.09	1.01 ± 0.06	0.22 ± 0.09	28.1 ± 3.8	21.6 ± 3.5	77.2 ± 13.3
	40	8	359 ± 14	1.94 ± 0.05	14.55 ± 1.10	1.83 ± 0.11	0.71 ± 0.10	1.07 ± 0.09	0.26 ± 0.06	30.7* ± 3.2	19.5 ± 1.7	76.5 ± 6.6
	150	9	350 ± 16	1.91 ± 0.08	13.87 ± 1.46	1.93 ± 0.10	0.66 ± 0.07	1.07 ± 0.10	0.25 ± 0.09	26.2 ± 3.7	22.0* ± 2.0	74.0 ± 10.0
	600	10	307 ± 38	1.88 ± 0.09	12.33 ± 2.00	2.97* ± 0.41	0.63 ± 0.13	0.98 ± 0.17	0.15 ± 0.08	24.4 ± 3.9	17.7 ± 3.0	80.9 ± 10.3
Relative@	0	10	345 ± 16	0.55 ± 0.02	4.04 ± 0.32	0.55 ± 0.04	0.19 ± 0.02	0.30 ± 0.02	0.06 ± 0.02	7.36 ± 0.90	5.42 ± 0.64	21.47 ± 3.29
	10	8	336 ± 17	0.57 ± 0.03	4.22 ± 0.28	0.56 ± 0.04	0.19 ± 0.02	0.30 ± 0.01	0.06 ± 0.02	8.37 ± 1.09	6.39* ± 0.78	23.02 ± 4.17
	40	8	359 ± 14	0.54 ± 0.03	4.06 ± 0.35	0.51 ± 0.03	0.20 ± 0.03	0.30 ± 0.03	0.07 ± 0.02	8.58 ± 0.96	5.46 ± 0.61	21.36 ± 2.17
	150	9	350 ± 16	0.55 ± 0.03	3.96 ± 0.44	0.55 ± 0.03	0.19 ± 0.03	0.31 ± 0.03	0.07 ± 0.02	7.50 ± 1.28	6.31* ± 0.69	21.23 ± 3.45
	600	10	307 ± 38	0.62* ± 0.06	4.02 ± 0.44	0.99** ± 0.22	0.20 ± 0.03	0.32 ± 0.02	0.05 ± 0.02	7.94 ± 0.81	5.76 ± 0.53	26.69* ± 4.65

Each value is expressed as mean ± S. D.

@ : Relative organ weight per 100g body weight

\* : Significantly different from control at 5% level of probability

\*\* : Significantly different from control at 1% level of probability

Table 16 - 1 Incidence of histopathological findings of male rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Organ	Findings	Degree	Dose (mg/kg)			Fate No. of animals	No. of animals	No. of animals	No. of animals	No. of animals	No. of animals	No. of animals
			0	10	40							
Kidney	Necrosis, tubular epithelium	-	10 (10)	8 (2 (10))	9 (1 (10))	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)
		+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mineralization, cortex/cortico-medullary junction		-	10 (10)	8 (2 (10))	9 (1 (10))	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)
		+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cellular infiltration, lymphocyte, cortex		-	9 (9)	8 (2 (10))	9 (1 (10))	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)
		++	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cellular infiltration, neutrophils, medulla		-	10 (10)	8 (2 (10))	9 (1 (10))	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)
		++	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eosinophilic body, proximal tubular epithelium		-	8 (8)	4 (1 (5))	7 (1 (8))	8 (8)	8 (8)	8 (8)	8 (8)	8 (8)	8 (8)	8 (8)
		++	1 (1)	2 (2)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)	1 (1)
Dilatation, distal/collecting tubules, focal		-	10 (10)	6 (2 (8))	9 (1 (10))	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)
		+	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dilatation, renal tubule, diffuse		-	10 (10)	8 (2 (10))	9 (1 (10))	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)
		+++	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Basophilic tubules		-	5 (5)	2 (1 (3))	6 (1 (7))	5 (5)	5 (5)	5 (5)	5 (5)	5 (5)	5 (5)	5 (5)
		+++	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperplasia, tubular epithelium		-	10 (10)	8 (2 (10))	9 (1 (10))	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)
		+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fibrosis		-	9 (9)	7 (2 (9))	9 (1 (10))	9 (9)	9 (9)	9 (9)	9 (9)	9 (9)	9 (9)	9 (9)
		++	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gyst		-	8 (8)	2 (2 (10))	9 (1 (10))	8 (8)	8 (8)	8 (8)	8 (8)	8 (8)	8 (8)	8 (8)
		++	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Heart	Myocardial degeneration/fibrosis, focal	-	9 (9)	2 (2 (10))	1 (1)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)	10 (10)
		+	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

— : Not examined; - : Negative; + : Slight; ++ : Moderate; +++ : Marked; TK : Terminal Kill; FP : Failed to cause pregnancy; Killed at the termination; UC : Animal with unsuccessful copulation; \* : Significantly different from control at 5% level of probability; \*\* : Significantly different from control at 1% level of probability

Table 15 - 2 Incidence of histopathological findings of male rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Organ	Findings	Degree	Dose(mg/kg)											
			0		10		40		150		600			
			Fate No. of animals	TK (T)	TK (T)	FP (T)	TK (T)	UC (T)	TK (T)	TK (T)	TK (T)	TK (T)	TK (T)	
Lung	Mineralization, artery	-	8	(8)	-	1	(1)	-	1	(1)	-	-	10	(10)
		+	2	(2)	-	1	(1)	-	0	(0)	-	-	0	(0)
	Metaplasia, osseous	-	8	(8)	-	2	(2)	-	1	(1)	-	-	7	(7)
		+	2	(2)	-	0	(0)	-	0	(0)	-	-	3	(3)
	Accumulation, foam cell	-	9	(9)	-	2	(2)	-	1	(1)	-	-	8	(8)
		+	1	(1)	-	0	(0)	-	0	(0)	-	-	0	(0)
Liver	Microgranuloma	-	6	(6)	1*	2	(3)	-	1	(1)	-	-	6	(6)
		+	4	(4)	0	0	(0)	-	0	(0)	-	-	4	(4)
	Fibrosis, capsule	-	10	(10)	0	2	(2)	-	1	(1)	-	-	10	(10)
		+	0	(0)	1*	0	(1)	-	0	(0)	-	-	0	(0)
	Hyperplasia, bile duct	-	10	(10)	0	2	(2)	-	1	(1)	-	-	10	(10)
		+	0	(0)	1*	0	(1)	-	0	(0)	-	-	0	(0)
	Hemorrhage	-	10	(10)	0	2	(2)	-	1	(1)	-	-	10	(10)
		+	0	(0)	1*	0	(1)	-	0	(0)	-	-	0	(0)
Pancreas:	Proliferation, ductule	-	8	(8)	-	1	(1)	-	1	(1)	-	-	9	(9)
		+	2	(2)	-	1	(1)	-	0	(0)	-	-	1	(1)
Stomach:	Hyperplasia, squamous, limiting ridge	-	9	(9)	-	2	(2)	-	1	(1)	-	-	10	(10)
		+	1	(1)	-	0	(0)	-	0	(0)	-	-	0	(0)
Urinary bladder:	Hyperplasia, mucosal epithelium	-	10	(10)	8	2	(10)	9	1	(10)	10	(10)	8	(8)
		+	0	(0)	0	0	(0)	0	0	(0)	0	(0)	2	(2)
	Cellular infiltration, neutrophile, submucosa	-	10	(10)	8	2	(10)	9	1	(10)	10	(10)	9	(9)
		+	0	(0)	0	0	(0)	0	0	(0)	0	(0)	1	(1)
Testis:	Atrophy, seminiferous tubule, focal	-	9	(9)	-	2	(2)	-	1	(1)	-	-	10	(10)
		+	1	(1)	-	0	(0)	-	0	(0)	-	-	0	(0)
Prostate:	Cellular infiltration, lymphocyte, interstitium	-	9	(9)	-	2	(2)	-	1	(1)	-	-	9	(9)
		+	1	(1)	-	0	(0)	-	0	(0)	-	-	1	(1)
Pituitary:	Cyst, Rathke's pouch, anterior lobe	-	10	(10)	-	2	(2)	-	1	(1)	-	-	9	(9)
		+	0	(0)	-	0	(0)	-	0	(0)	-	-	1	(1)
Adrenal:	Vacuolization, zona fasciculata	-	9	(9)	8	2	(10)	8	1	(9)	9	(9)	4	(4)
		+	1	(1)	0	0	(0)	1	0	(1)	1	(1)	5	(5)
		++	0	(1)	0	0	(0)	0	0	(1)	0	(1)	1	(6)

- : Not examined; - : Negative; + : Slight; ++ : Moderate; TK : Terminal kill; FP : Failed to cause pregnancy, killed at the termination; UC : Animal with unsuccessful copulation, killed at the termination; T : Total  
 \* : Significantly different from control at 5% level of probability  
 The organs of the heart, lung, liver, pancreas, stomach, intestine, kidney, urinary bladder, testis, epididymis, seminal vesicle, prostate, pituitary, thyroid, parathyroid, adrenal, thymus, spleen, bone marrow, lymph node and brain were examined from animals of the control and 600 mg/kg groups, and UC and FP animals. The skin from an animal of the 150 mg/kg group, which had a macroscopic skin lesion, was also examined.  
 : The liver with diaphragmatic nodule from one animal was examined.

-22-  
243-

Study No. 95-047

Table 17 - 1 Incidence of histopathological findings of female rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Organ : Findings	Dose(mg/kg) 0		10		40		150		600	
	TK (1)	TK NP (1)	TK (1)	TK NP (1)	TK UC KL (1)	TK UC KL (1)	TK KL (1)	TK KL (1)	TK (1)	TK (1)
Kidney : Degeneration, fatty, proximal tubular epithelium	10 (10)	2 (10)	8 (8)	0 (0)	8 (10)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Degeneration, vacuolar, proximal tubular epithelium	10 (10)	2 (10)	8 (8)	0 (0)	8 (10)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Necrosis, tubular epithelium	10 (10)	2 (10)	8 (8)	0 (0)	8 (10)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Mineralization, cortex	10 (10)	2 (10)	8 (8)	0 (0)	8 (10)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Cellular infiltration, neutrophils, medulla	10 (10)	2 (10)	8 (8)	0 (0)	8 (10)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Dilatation, distal tubule, focal/multifocal	9 (9)	2 (10)	8 (8)	0 (0)	8 (8)	1 (10)	8 (8)	1 (10)	10 (10)	10 (10)
Dilatation renal tubule, diffuse	10 (10)	2 (10)	8 (8)	0 (0)	8 (8)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Basophilic tubules	9 (9)	2 (10)	7 (7)	1 (10)	8 (8)	1 (10)	6 (6)	1 (7)	0 (0)	0 (0)
Hyperplasia, tubular epithelium	10 (10)	2 (10)	8 (8)	0 (0)	8 (8)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Fibrosis	10 (10)	2 (10)	8 (8)	0 (0)	8 (8)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Cast hyaline/proteinous/granular	10 (10)	2 (10)	7 (7)	1 (10)	8 (8)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Heart : Myocardial degeneration/fibrosis, focal	9 (9)	2 (10)	8 (8)	0 (0)	8 (8)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Lung : Inflammatory cell infiltration, focal	10 (10)	2 (10)	8 (8)	0 (0)	8 (8)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)
Edema, alveolar	10 (10)	1 (10)	1 (10)	0 (0)	1 (10)	0 (0)	1 (10)	0 (0)	10 (10)	10 (10)
Hemorrhage	10 (10)	2 (10)	8 (8)	0 (0)	8 (8)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)

Organ : Findings Degree No. of animals  
 TK (1) TK NP (1) TK UC KL (1) TK UC KL (1) TK KL (1) TK KL (1) TK (1) TK (1)  
 TK : Terminal Kill; NP : Non-pregnant; UC : Animal with  
 ++ : Not examined; - : Negative; + : Slight; ++ : Moderate; +++ : Marked; TK : Total  
 KL : Killed because all pups died after delivery; I : Total  
 \* : Significant difference from control at 5% level of probability  
 \*\* : Significantly different from control at 1% level of probability

Table 17 - 2 Incidence of histopathological findings of female rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Organ	Findings	Degree	Dose (mg/kg) 0		10		40			150			600	
			Fate No. of animals	TK (T)	TK NP (T)	TK UC KL (T)	TK KL (T)	TK KL (T)	TK (T)					
Lung	Mineralization, artery	-	9 (9)	-	2 (2)	-	1 (1)	1 (2)	-	1 (1)	10 (10)	10 (10)		
		+	1 (1)	-	0 (0)	-	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)		
	Metaplasia, osseous	-	10 (10)	-	2 (2)	-	1 (1)	1 (2)	-	1 (1)	8 (8)	8 (8)		
Liver	Degeneration, fatty, hepatocyte, periporlal	-	10 (10)	8 (8)	2 (10)	7 (7)	1 (1)	0 (0)	0 (8)	9 (9)	1 (10)	8 (8)	8 (8)	
		+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	
	Necrosis, focal	-	10 (10)	7 (7)	2 (9)	7 (7)	1 (1)	0 (0)	1 (9)	9 (9)	1 (10)	9 (9)	9 (9)	
Pancreas	Proliferation, ductule	-	8 (8)	-	2 (2)	-	1 (1)	1 (2)	-	1 (1)	9 (9)	9 (9)		
		+	2 (2)	-	0 (0)	-	0 (0)	0 (0)	-	0 (0)	1 (1)	1 (1)		
	Hypertrophic foci, acinar cell	-	10 (10)	-	2 (2)	-	1 (1)	1 (2)	-	1 (1)	9 (9)	9 (9)		
Stomach	Hyperplasia, squamous, forestomach	-	10 (10)	-	2 (2)	-	1 (1)	1 (2)	-	0 (0)	10 (10)	10 (10)		
		+	0 (0)	-	0 (0)	-	0 (0)	0 (0)	-	1 (1)	0 (0)	0 (0)		
	Erosion, glandular stomach	-	10 (10)	-	2 (2)	-	1 (1)	0 (1)	-	1 (1)	10 (10)	10 (10)		
Urinary bladder	Hyperplasia, mucosal epithelium	-	10 (10)	8 (8)	2 (10)	8 (8)	1 (1)	1 (10)	9 (9)	1 (10)	6 (6)	6 (6)		
		+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (4)	4 (4)		
	Cyst, Rathke's pouch, anterior lobe	-	9 (9)	-	2 (2)	-	1 (1)	1 (2)	-	1 (1)	10 (10)	10 (10)		
Adrenal	Vacuolization, zona fasciculata	-	10 (10)	8 (8)	2 (10)	8 (8)	1 (1)	0 (9)	9 (9)	1 (10)	6 (6)	6 (6)		
		+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	3 (3)	3 (3)	
	Hyperplasia, nodular, cortical cell	-	10 (10)	8 (8)	2 (10)	8 (8)	1 (1)	0 (9)	9 (9)	1 (10)	10 (10)	10 (10)		
Thymus	Atrophy, cortical	-	8 (8)	6 (6)	2 (8)	8 (8)	1 (1)	0 (9)	9 (9)	1 (10)	5 (5)	5 (5)		
		+	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	3 (3)	3 (3)	
	Hemorrhage	-	10 (10)	7 (7)	2 (9)	8 (8)	1 (1)	1 (10)	9 (9)	1 (10)	10 (10)	10 (10)		
Skin	Cellular infiltration, neutrophile, focal	-	-	-	-	-	-	-	-	-	-	-	0 (0)	
		+	-	-	-	-	-	-	-	-	-	-	-	1 (1)

- : Not examined; - : Negative; + : Slight; ++ : Moderate; TK : Terminal kill; NP : Non-pregnant; UC : Animal with unsuccessful copulation; KL : Killed because all pups died after delivery; T : Total  
 The organs of the heart, lung, liver, pancreas, stomach, intestine, kidney, urinary bladder, ovary, uterus, vagina, mammary gland, pituitary, thyroid, parathyroid, adrenal, thymus, spleen, bone marrow, lymph node and brain were examined from animals of the control and 600 mg/kg groups, and NP, UC and KL animals.  
 \* : Animal with macroscopic skin lesions

-245-

Study No. 95-047

Table 1 8                      Reproduction results of rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

	Dose (mg/kg)	0	10	40	150	600
No. of pairs mated		10	10	10	10	10
No. of pairs with successful copulation		10	10	9	10	10
Copulation index (%)		100	100	90	100	100
Pairing days until copulation(days, Mean±S.D.)		2.0±0.9	2.2±1.2	2.7±0.9	3.0±1.9	2.3±0.9
No. of pregnant females		10	8	9	10	10
Fertility index (%)		100	80	100	100	100
No. of corpora lutea (Mean±S.D.)		18.4±1.4	18.5±2.7	18.4±1.8	17.7±1.8	18.5±1.9
No. of implantation sites (Mean±S.D.)		17.8±1.8	17.4±1.3	17.1±1.2	16.2±3.6	16.8±1.2
Implantation index (%. Mean±S.D.)		96.7±4.8	94.8±8.5	93.2±7.4	90.6±17.3	91.6±10.1
No. of pregnant females with parturition		10	8	9	10	10
Gestation length (days, Mean±S.D.)		22.5±0.5	22.9±0.4	22.9±0.6	22.4±0.5	22.7±0.5
No. of pregnant females with live pups		10	8	9	10	10
Gestation index (%)		100	100	100	100	100
No. of pregnant killed <sup>a)</sup>		0	0	1	1	0
No. of pregnant females with live pups on day 4		10	8	8	9	10

Copulation index = (No. of pairs with successful copulation/No. of pairs mated) ×100

Fertility index = (No. of pregnant animals/No. of pairs with successful copulation) ×100

Gestation index = (No. of females with live pups/No. of living pregnant females) ×100

a) : All pups died after delivery, killed during the study for pathological examination

Table 19

Litter results of female rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Dose (mg/kg)	0	10	40	150	600
No. of pups born	16.8± 2.3	15.4± 1.2	16.1± 1.3	14.1± 5.2	15.4± 2.2
Delivery index (%)	94.1± 6.8	89.0±10.2	94.3± 6.2	88.1±25.4	91.6±10.2
No. of pups alive on day 0 of lactation					
Total	16.6± 2.2	14.8± 1.9	15.0± 2.3	11.9± 6.4	15.1± 2.0
Male	8.6± 2.8	6.6± 2.4	9.0± 2.8	5.8± 3.9	7.2± 2.4
Female	8.0± 2.8	8.1± 2.6	6.0± 1.7	6.1± 4.3	7.9± 2.6
Live birth index (%)	98.9± 2.4	95.7± 7.5	92.9±10.7	86.9±30.9	98.2± 4.1
Sex ratio (Male/Female)	1.10	0.81	1.46	1.04	0.95
No. of pups alive on day 4 of lactation					
Total	16.5± 2.2	14.8± 1.9	12.8± 5.2	13.1± 5.1	14.0± 1.7
Male	8.5± 2.9	6.6± 2.4	7.8± 3.7	6.4± 3.5	7.0± 2.2
Female	8.0± 2.8	8.1± 2.6	5.0± 2.7	6.7± 3.9	7.0± 1.8
Viability index (%)	99.4± 1.9	100 ± 0	86.2±32.8	99.4± 1.9	93.3± 9.4
Body weight of live pups (g)					
on day 0					
Male	7.0± 0.4	7.6± 0.7	7.1± 0.6	7.3± 0.9	6.9± 0.8
Female	6.8± 0.6	7.0± 0.7	6.7± 0.4	6.8± 0.8	6.6± 0.7
on day 4					
Male	11.1± 1.8	11.9± 2.3	11.5± 1.7	12.0± 2.5	10.0± 2.3
Female	10.7± 1.8	11.3± 2.2	11.2± 1.6	11.3± 2.4	9.8± 2.1

Delivery index = (No. of pups born / No. of implantation sites) x 100

Live birth index = (No. of live pups on day 0 / No. of pups born) x 100

Viability index = (No. of live pups on day 4 / No. of live pups on day 0) x 100

Sex ratio = Total No. of male pups / Total No. of female pups

Each value is expressed as Mean ± SD., except sex ratio



Table 20 Incidence of external findings of rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Findings	Dose (mg/kg)	10	40	124	150	600
External	No. of pups examined	123	145	124	154	
No. of pups with external anomalies <sup>a</sup>		0	0	1	0	
(Mean $\pm$ S.D. of individual litter percentages)		(0)	(0)	(0.7 $\pm$ 2.1)	(0)	
External anomalies <sup>a</sup>						
Vestigial tail		1	0	1	0	
(Mean $\pm$ S.D. of individual litter percentages)		(0.6 $\pm$ 1.9)	(0)	(0.7 $\pm$ 2.1)	(0)	

Table 21 Incidence of visceral findings of rats treated orally with isocyanuric acid in the combined repeat dose and reproductive/developmental toxicity screening test

Findings	Dose (mg/kg)	0	10	40	150	600
Visceral	No. of pups examined	167	123	142	123	151
	No. of pups with visceral anomalies <sup>a</sup>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	No. of pups with visceral variations <sup>a</sup>	5 (3.1±4.5)	2 (1.7±3.2)	3 (2.2±6.7)	6 (4.2±8.3)	4 (2.8±4.8)
	Visceral variations <sup>a</sup>					
	Thymic remnant in neck	1 (0.6±1.8)	2 (1.7±3.2)	3 (2.2±6.7)	6 (4.2±8.3)	4 (2.8±4.8)
	Persistent left umbilical artery	3 (2.0±4.4)	0 (0)	0 (0)	0 (0)	0 (0)
	Dilatation of renal pelvis	1 (0.6±1.8)	0 (0)	0 (0)	0 (0)	0 (0)

a : No. of pups (Mean ± S.D. of individual litter percentages)

FOREWORD

INTRODUCTION

**ISOCYANURIC ACID**  
**CAS N°: 108-80-5**

# SIDS Initial Assessment Report

for

## 9th SIAM

(France, June 29-July 1, 1999)

Chemical Name: Isocyanuric acid  
CAS No: 108-80-5  
Sponsor Country: Japan

National SIDS Contact Point in Sponsor Country:

Mr. Kazuhide Ishikawa  
Ministry of Foreign Affairs, Japan

### HISTORY:

SIDS Testing Plan were reviewed in SIDS Review Process, where the following SIDS Testing Plan was agreed:

no testing ( )

testing (X) Water solubility, Vapour pressure, Octanol/water partition coefficient,  
Stability in water Biodegradation

Chronic toxicity to daphnia

Combined repeat dose and reproductive toxicity,

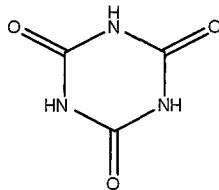
Chromosomal aberration test in vitro

Deadline for circulation: March 31, 1999

Date of Circulation: March 30, 1999

(To all National SIDS Contact Points and the OECD Secretariat)

## SIDS INITIAL ASSESSMENT PROFILE

CAS NO.	108-80-5
CHEMICAL NAME	Isocyanuric acid
Structural formula	
<u>RECOMMENDATIONS OF THE SPONSOR COUNTRY</u>	
The chemical is currently of low priority for further work.	
<u>SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE RECOMMENDATIONS</u>	
<p>Isocyanuric acid is not readily biodegradable (OECD 301C: 0% after 14-day) and stable in water. Bioconcentration factor to fish is low (&lt;0.5, in Carp for 6 weeks).</p> <p>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 <i>Daphnia magna</i>). 48-EC<sub>50</sub> for immobilisation of <i>Daphnia magna</i> was 1000 mg/l. For testing in fish, Medaka (<i>Oryzias latipes</i>), both 96-h LC<sub>50</sub> and 14-day LC<sub>50</sub> were more than 100 mg/l. For algal test (<i>Selenastrum capricornutum</i>), 72-h EC<sub>50</sub> and 72-h NOEC were 620.0 mg/l and 62.5 mg/l, respectively. No data are available for effects on terrestrial organisms.</p> <p>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 toxicity to the dams. No reproductive toxicity was observed (NOAEL: 600 mg/kg/day). A variety of <i>in vitro</i> and <i>in vivo</i> genotoxicity studies show this chemical is not genotoxic. Two years studies of rats and mice indicate this chemical has no carcinogenic potential.</p> <p>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.</p> <p>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.</p>	
<u>IF FURTHER WORK IS RECOMMENDED, SUMMARISE ITS NATURE</u>	

## FULL SIDS SUMMARY

CAS NO: 108-80-5		SPECIES	PROTOCOL	RESULTS
<b>PHYSICAL-CHEMICAL</b>				
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 <sup>-3</sup> 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			
<b>ENVIRONMENTAL FATE AND PATHWAY</b>				
3.1.1	Photodegradation			
3.1.2	Stability in Water		OECD TG 111	Stable at pH 4,7 and 9 pK <sub>1</sub> = 6.88, pK <sub>2</sub> = 11.40, pK <sub>3</sub> = 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
<b>ECOTOXICOLOGY</b>				
4.1	Acute/Prolonged Toxicity to Fish	<i>Oryzias latipes</i>	OECD TG 203	LC <sub>50</sub> (96hr) > 100 mg/l LC <sub>50</sub> (14 d) > 100 mg/l
4.2	Acute Toxicity to Aquatic Invertebrates <i>Daphnia</i>	<i>Daphnia magna</i>	OECD TG 202	EC <sub>50</sub> (48hr): 1000 mg/l
4.3	Toxicity to Aquatic Plants e.g. Algae	<i>Selenastrum capricornutum</i>	OECD TG 201	EC <sub>50</sub> (72hr) = 620 mg/l NOEC = 62.5 mg/l
4.5.2	Chronic Toxicity to Aquatic Invertebrates ( <i>Daphnia</i> )	<i>Daphnia magna</i>	OECD TG 202	EC <sub>50</sub> (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

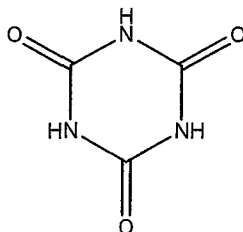
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Other (unknown)	LD <sub>50</sub> = 7700 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	Other (unknown)	Minimum toxic concentration = 612 mg/m <sup>3</sup>
5.1.3	Acute Dermal Toxicity	Rabbit	Other (unknown)	LD <sub>50</sub> = > 7940 mg/kg
5.2.1	Skin Irritation/Corrosion	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)	<i>S. typhimurium</i>	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:  $< 5.0 \times 10^{-3}$  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