FOREWORD INTRODUCTION

2,4-Diamino-6-phenyl-1,3,5-triazine

CAS N°: 91-76-9

SIDS Initial Assessment Report

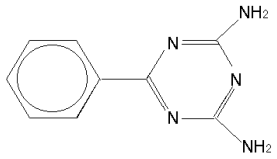
For

SIAM 13

Bern, Switzerland, 6-9 November 2001

1. Chemical Name:	2,4-Diamino-6-phenyl-1,3,5-triazine
2. CAS Number:	91-76-9
3. Sponsor Country:	Japan National SIDS Contact Points in Sponsor Country: Mr. Yasuhisa Kawamura, Ministry of Foreign Affairs
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	ICCA Initiative work lead by NIPPON SHOKUBAI CO.,LTD., Japan
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	
7. Review Process Prior to the SIAM:	
8. Quality check process:	
9. Date of Submission:	
10. Date of last Update:	
11. Comments:	History: The original IUCLID documents were prepared by European Commission. NIPPON SHOKUBAI CO.,LTD., Japan reviewed the Documents after incorporation of Japanese testing results. Testing: No testing (x) Testing ( )

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	91-76-9
Chemical Name	2,4-diamino-6-phenyl-1,3,5-triazine
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no available information on toxicokinetics and metabolism of this substance. The oral LD_{50} of rats was 933 mg/kg for males and 1231 mg/kg for females [OECD TG 401]. The major toxicity was edema in the forestomach. The LC_{50} value in the acute inhalation toxicity was 2.932 mg/L (4 hr, rat) [OECD TG 403]. This substance was not irritating to the skin in rabbits [OECD TG 404] and mildly irritating to the eyes in rabbits. There is no information on skin sensitization.

In the OECD combined repeat dose and reproductive/developmental toxicity screening test by gavage [OECD TG 422], this substance was given at 0, 4, 20 and 100 mg/kg/day to rats for at least 39 days. One male and one female rat died and the body weight gain was decreased in the 100 mg/kg group. Hematological and blood chemical examination showed decreases in the erythrocyte counts and hematocrit values with increased reticulocyte counts, and increases of GOT, GPT and total bilirubin with centrilobular hypertrophy of hepatocyte in the 100 mg/kg group. The severity of these changes, however, were toxicologically not significant or adaptive changes, except for the increase in reticulocyte count whose significance was equivocal. The NOAEL in this study was considered as 20 mg/kg/day.

In the 90-day feeding study of rats at 0, 1.9, 19.0, and 173.0 mg/kg/day [OECD TG 408], the body weight gain was decreased in the high dose group. In the histopathological examination, centrilobular hepatocyte enlargement, an increased severity of extramedullary hemopoiesis in the spleen and hemosiderin pigment accumulation in the kidneys and the spleen, hypertrophy and vacuolation of adrenal zona glomerulosa cells, and degeneration of pancreatic exocrine cells together with associated inflammatory cell infiltrates were observed in the high dose group. At the mid dose, the severity of hemosiderin pigment accumulation in the spleen was also increased moderately in males. This change in the spleen was considered not to be an adverse effect because no other changes were observed at this dose level. Therefore, the NOAEL in this study was considered to be 19 mg/kg/day.

On basis of these two studies, the NOAEL for repeated dose toxicity was considered to be 20 mg/kg/day.

For genotoxicity of this substance, there were two Ames tests, three non-bacterial *in vitro* studies, and two genotoxic *in vivo* studies reported. This substance was not mutagenic in bacteria [OECD TG 471 & 472]. It induced chromosomal aberration in CHL/IU cells with and without an exogenous metabolic activation system even under the soluble concentrations. It also gave a positive response in the human lymphocyte test [OECD TG 473] and the mouse lymphoma TK assay [OECD TG 476] but only under the insoluble dose levels. The cytogenetic effect observed in *in vitro* assays however, could not be reproduced in the micronucleus tests *in vivo* [OECD TG 474]. Based on the weight of evidence, it could be concluded that this substance was not genotoxic *in vivo*.

For carcinogenicity, two dietary studies using male rats and male/female mice for 18 months showed no tumorigenic activity of this substance. However, these studies were considered to be insufficient for assessment of the carcinogenicity because of insufficient testing protocol compared to current test guidelines.

In the OECD combined repeat dose and reproductive/developmental (one generation) toxicity screening test [OECD TG 422], this substance was given for 49 days from 14 days before mating in males and from 14 days before mating to day 3 of lactation in females. At 100 mg/kg, one female died in gestation and another female was not impregnated. Birth index was decreased with increase in stillborns at 100 mg/kg. All pups of two dams at 20 mg/kg and seven dams at 100 mg/kg died due to the lack of nursing activity, and the viability index on day 4 after birth was consequently decreased in these groups. The body weights of pups were also decreased at birth and at day 4 of lactation in the 100 mg/kg group. The decrease of litter size observed at 100 mg/kg seems to be the chemical-induced effect although it is not statistically significant. No malformations or variations were observed in the pups.

From these results, the parental NOAEL of reproductive toxicity was considered to be 100 mg/kg/day for males, and 4 mg/kg/day for females, based on the lack of nursing activity, and the NOAEL of developmental toxicity was considered to be 20 mg/kg/day, based on the decrease of birth index and body weight of pups.

Environment

This substance (2,4-diamino-6-phenyl-1,3,5-triazine) is slightly soluble in water (320 mg/L at 25°C). The vapour pressure of this substance is estimated as very low ($1.6x10^{-5}$Pa at 25°C). This substance would be released into the aquatic environment from waste water, and distributed almost entirely in the water compartment from the calculation using the fugacity model [Mackey level III]. Although this substance is stable in water biotically and abiotically, this substance has a low potential of bioaccumulation based on BCF = 6.4, estimated from log Pow = 1.38.

In acute toxicity to aquatic species, the toxicity to algae [OECD TG 201] was 53.7 mg/L for EC50 (72 hr, *Selenastrum capricornutum*, biomass) and the toxicity to daphnids [OECD TG 202] was 52.0 mg/L for EC50 (48 hr, *Daphnia magna*, immobility). The toxicity to fish [other method] was 99 mg/L for LC_{50} (48 hr, *Leuciscus idus* (L.)).

In chronic toxicity to aquatic species, the toxicity to daphnids [OECD TG 211] was 1.91 mg/L for NOEC (21 day, *Daphnia magna*, reproduction). The toxicity to algae [OECD TG 201] was 24.4 mg/L for NOEC (72 hr, *Selenastrum capricornutum*, biomass).

PNEC = 0.0191 mg/L for the aquatic organisms was calculated from the 21 day – NOEC (1.91 mg/L) for *Daphnia magna* using an assessment factor of 100, because two chronic data (*Daphnia magna* and alga) were available.

Exposure

Production volume of this substance (2,4-diamino-6-phenyl-1,3,5-triazine or benzoguanamine) is estimated 3,000 t/y in Japan and 5,000 t/y world-wide in 2000. The producing countries are Japan, Germany and the People's Republic of China. This substance can be produced in closed systems. The main use is as an intermediate in benzoguanamine-formaldehyde resins whose applications are coatings, paints, thermosetting resins and others. In the case of coatings, the resins are used as outside and/or inside coatings of cans for storing foods and beverages.

The fugacity model suggests that if released from air or soil, the majority of this substance would distribute into the water and soil. It would not distribute into the air and soil from water. From the uses and properties of this substance, estimated exposures are considered in the following three scenarios. The effects are as follows:

(1) Occupational exposure scenario: inhalation of dust without breathing protection in the factory;
Dust level was 0.25 mg/m^3 by measurement at the packing workplace;
EHEinh = 0.027 mg/kg/day and EHEder = 1.7 mg/kg/day (estimate).

In Japan, this substance has been manufactured since 1964, and no persons handling or contacting this substance have experienced any adverse symptoms regarding skin or respiratory organs.

(2) Environmental exposure scenario: emission to aquatic compartment from waste water;
PEClocal water = 0.0176 mg/L (calculation).

(3) Consumer use exposure scenario: intake through migration from can coating of benzoguanamine-formaldehyde resins for storing foods and beverages;
EHE for consumer use was calculated as 0.076 mg/kg/day at the worst scenario based on the migration tests.

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

FULL SIDS SUMMARY

CAS NO: 91-76-9		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Unknown	228 °C
2.2	Boiling Point		OECD TG 103	> 350 °C (at 1,013 hPa)
2.3	Density		Unknown	1.425 g/cm^3 (at 15 °C)
2.4	Vapour Pressure		OECD TG 104	$<4.1x10^{-5}$ Pa (at 100 °C) 1.6×10^{-5} Pa (at 25 °C) estimate
2.5	Partition Coefficient		OECD TG 107	Log Pow = 1.38 (at 25 °C)
2.6 A.	Water Solubility		OECD TG 105	320 mg/L (at 25 °C)
B.	pH		Unknown	6.5 (at 20°C, 300 mg/L)
	pKa		OECD TG 112	3.91 (at 25 °C)
2.12	Henry's Law constant		Unknown	$4.1x10^{-11}$ $atm\text{-}m^3$ /mol (at 25 °C) estimate
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Unknown	$t_{1/2}$ = 4.4 day in air (calculation)
3.1.2	Stability in Water		OECD TG 111	Stable ($t_{1/2}$ > 5 day at 50 °C, pH 4, 7 and 9)
3.2	Monitoring Data			No data
3.3	Transport and Distribution		Fugacity Model (Mackay level III)	Distribution to the compartment (estimate) Release 100% ; to air / to water / to soil air 0.0% / 0.0% / 0.0% water 29.3% / 99.5% / 24.9% soil 70.5% / 0.0% / 75.0% sediment 0.2% / 0.5% / 0.1%
			PEClocal.water	PEClocal.water = 0.0176 mg/L
3.5	Biodegradation		OECD TG 301C	Not readily biodegradable (2% based on BOD)
3.7	Bioaccumulation			BCF = 6.4 (calculation)
ECOTOXICOLOGY				
4.1	Acute/Prolonged toxicity to Fish	*Oryzias latipes*	OECD TG 203	**LC_{50}** (96 hr) > 100 mg/L
		Leuciscus idus (L.)	DIN38412 part 15	**LC_0** (48 hr) = 56 mg/L **LC_{50}** (48 hr) = 99 mg/L **LC_{100}** (48 hr) = 180 mg/L
4.2	Acute Toxicity to aquatic Invertebrates	*Daphnia magna*	OECD TG 202	**EC50** (24 hr) = 112 mg/L **EC50** (48 hr) = 52 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	*Scenedesmus subspicatus*	Unknown	**EC50** (72 hr) = 22 mg/L
		Selenastrum capricornutum	OECD TG 201	**EC50** (72 hr) = 53.7 mg/L **NOEC** (72 hr) =24.4 mg/L
4.5.2	Chronic Toxicity to aquatic Invertebrates	*Daphnia magna*	OECD TG 211	**EC50** (21 day, reproduction) = 5.91 mg/L **NOEC** (21 day, reproduction) = 1.91 mg/L **LOEC** (21day, reproduction) = 3.43 mg/L

CAS NO: 91-76-9		SPECIES	PROTOCOL	RESULTS
4.6.1	Toxicity to Soil Dwelling Organisms			No data
4.6.2	Toxicity to Terrestrial			No data
4.6.3	Plants			No data
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Unknown	**LD_{50}** = 1,050 mg/kg
		Rat	OECD TG 401	**LD_{50}** = 933 mg/kg (male) **LD_{50}** = 1,231 mg/kg (female)
		Rat	Other	**LD_{50}** = 1,470 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	OECD TG 403	**LC_{50}** (4 hr) = 2.932 mg/L
5.1.3	Acute Dermal Toxicity			No data
5.2.1	Skin Irritation	Albino rabbit	OECD TG 404	Not irritating, Primary irritating index = 0
5.2.2	Eye Irritation	Albino rabbit	Directive 84/ 449/EEC, B.5	Mildly irritating, Draize score = 4 (1 hr)
5.3	Skin Sensitization			No data
5.4	Repeated Dose Toxicity	Rat male 49 day Female 39-53 day	OECD TG 422 (gavage)	**NOAEL** = 20 mg/kg/day
		Rat 90 day	OECD TG 408 (dietary)	**NOAEL** = 19 mg/kg/day
5.5	Genotoxicity *in vitro*			
A.	Bacterial Test (Gene mutation)	S. typhimurium, E. coli	Japanese TG and OECD TG 471 & 472	- (With metabolic activation) - (Without metabolic activation)
		S. typhimurium	OECD TG 471	- (With metabolic activation) - (Without metabolic activation)
B.	Non-Bacterial *in vitro* Test (*Chromosomal aberrations*)	CHL cells	Japanese TG and OECD TG 473	+ (With metabolic activation) + (Without metabolic activation)
		Human lymphocyte	OECD TG 473	- (Without metabolic activation, within the solubility limit) + (Without metabolic activation, above the solubility limit)
	Test (Mammalian cell gene mutation)	Mouse lymphoma cells L5178Y	OECD TG 476	- (With metabolic activation, within the solubility limit) + (With metabolic activation, above the solubility limit) - (Without metabolic activation)
5.6	Genetoxicity *in vivo* (Micronucleus assay)	Mouse	Directive 92/69/ EEC, B.12	Inconclusive
		Mouse	OECD TG 474	Negative
5.7	Carcinogenicity	Male rat (18 month)	Other	No tumorigenicity
		Mouse (18 month)	Other	No tumorigenicity

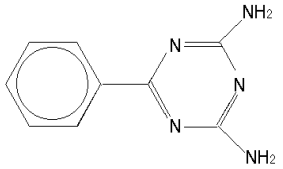
CAS NO: 91-76-9		SPECIES	PROTOCOL	RESULTS
5.8	Toxicity to Reproduction	Rat	OECD TG 422	**NOAEL** Parental = 100 mg/kg/day (male) **NOAEL** Parental = 4 mg/kg/day (female)
5.9	Developmental Toxicity/ Teratogenicity	Rat	OECD TG 422	**NOAEL** F_1 offspring = 20 mg/kg/day No external anomalies of pups
5.11	Experience with Human Exposure			No data

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 91-76-9
IUPAC Name: 2,4-Diamino-6-phenyl-1,3,5-triazine
Molecular Formula: $C_9H_9N_5$
Structural Formula:



Synonyms: (Chemical Names)
1,3,5-Triazine-2,4-diamine, 6-phenyl- (9CI)
2,4-Diamino-6-phenyl-1,3,5-triazine
2,4-Diamino-6-phenyl-s-triazine
2-Phenyl-4,6-diamino-1,3,5-triazine
4,6-Diamino-2-phenyl-s-triazine
6-Phenyl-1,3,5-triazine-2,4-diamine
Benzoguanamine
s-Triazine, 2,4-diamino-6-phenyl-

(Trade Names)
ENT 60118
USAF RH-5

1.2 Purity/Impurities/Additives

Purity: ≧ 98% weight/weight

Impurities:	Melamine	max. 2%
	Dicyandiamide	max. 0.1%
	Benzamide	ca. 0.01%

Additives: None

1.3 Physico-Chemical properties

Table 1: Summary of physico-chemical properties

Property	Protocol	Results
Melting Point	Unknown	228 °C
Boiling Point	OECD TG 103	> 350 °C (at 1,013 hPa)
Density	Unknown	1.425 g/m^3 (15 °C)
Vapor Pressure	OECD TG 104 Unknown	< 4.1 x 10^{-5} Pa (at 100 °C) 1.6 x 10^{-5} Pa (at 25 °C) (estimate)
Henry's Law constant	Unknown	4.1x10^{-11} atm-m^3 /mol (at 25 °C) (estimate)
Partition Coefficient (Log Pow)	OECD TG 107 (Flask shaking method)	1.38 (at 25 °C)
Water Solubility	OECD TG 105	320 mg/L (at 25 °C)
pH	Unknown	6.5 (at 20 °C, 300 mg/L)
pKa	OECD TG 112	3.91 (at 25 °C)

2 GENERAL INFORMATION ON EXPOSURE

Regarding the physical and chemical properties, this substance (2,4-diamino-6-phenyl-1,3,5-triazine or benzoguanamine) has a powder appearance and is slightly soluble in water. This substance is not readily biodegraded and stable in water. Its vapor pressure is very low.

The production volume of this substance is estimated to be 3,000 t/y in Japan and 5,000 t/y world-wide in 2000. The producing countries are Japan, Germany and the People's Republic of China. This substance can be produced in closed systems.

The main use is as an intermediate as benzoguanamine-formaldehyde resins whose applications are coatings, paints, varnishes, printing inks and thermosetting resins. In the case of coatings, the resins are used as outside and/or inside coatings of cans for storing foods and beverages which is the major existing usage.

In the case of thermosetting resins, this substance is a monomeric intermediate in order to produce several amino resins whose fine sphere particles can support dyes or pigments on this particle's surface. This method can be expected to reduce the usage volume of the colouring dyes and pigments. These amino resins are useful for plastics admixtures and LCD spacers. Migration test results based on THE FOOD SANITATION LAW in Japan show that these resins including coloured resins are in line with this law's requirement.

Pharmaceutical, herbicide and colouring agent usage volume are not identified in both Japan and Germany, however there were several patents showing medical actions such as antiulcer agent [USP 3629467] or stomatititis [JP H4-295427] by using this substance or its derivatives.

The exposures of the substance were mainly relevant to three scenarios as following.

(1) Occupational exposure: inhalation and dermal route by dusts in the factory

(2) Environmental exposure: emission to the aquatic environment from waste water

(3) Consumer use exposure: intake through migration from can coating of benzoguanamine-formaldehyde resins for storing foods and beverages

2.1 Environmental Exposure and Fate

A generic fugacity model (Mackay level III) suggests that if released to air or soil, the majority of this substance would distribute into soil and/or water. It would not distribute into the air and soil if released to water. These data are shown in Table 2 below.

Table 2: Environmental distribution using the fugacity model (Mackay level Ⅲ) for three emission scenarios

Compartment	Release: 100% to air	Release: 100% to water	Release: 100% to soil
Air	0.0%	0.0%	0.0%
Water	29.3%	99.5%	24.9%
Soil	70.5%	0.0%	75.0%
Sediment	0.2%	0.5%	0.1%

This substance would be released into the aquatic environment from waste water, and remain almost entirely in the water compartment based on the above calculation results.

This substance is not readily biodegraded (OECD TG 301C: 2% based on BOD and 0% based on HPLC analysis during 28 days) and stable in water [OECD TG 111]. The BCF = 6.4 estimated from log Pow = 1.38 suggests that the potential for bioaccumlation in aquatic organisms is low [HSDB 2000].

Some of this substance might be released from the production facility through the waste water. Based on data from Japan, a PEC (Predicted Environment Concentration) in the local surface water is calculated as 0.0176 mg/L (see Appendix 1**)**.

If released into soil, this substance is expected to have high mobility in soil based upon an estimated Koc of 130. It is not expected to volatilise from moist and dry soil surfaces based upon an estimated Henry's Law constant of 4.1×10^{-11} atm-m^3 /mol and this substance's vapor pressure, respectively [HSDB 2000].

If released into air, this substance (in its vapour phase) will be degraded in the atmosphere by reaction with photochemically produced hydroxyl-radical; the half time for this degradation reaction in air is estimated to be 4.4 days [HSDB 2000].

2.2 Human Exposure

2.2.1 Occupational Exposure

Occupational exposure to this substance's dust may occur by the inhalation and dermal route. This substance has a powder appearance and has an extremely low estimated vapour pressure (1.6×10^{-5} Pa), so that the vapour exposure is practically negligible.

The atmospheric concentration was measured at the Japanese production site in 1996. The monitored data is shown in Table 3.

Table 3: Workplace monitoring data for 2,4-diamino-6-phenyl-1,3,5-triazine

Industrial activity (country)	Sampling area (equipment)	Operating conditions (work time)	Monitoring data	Source
Manufacturing of this substance (Japan)	Packing workplace	The packing equipment was operated automatically for paper bags and semi-automatically for container bags. (6 hr /person/day)	0.25 mg/m^3 as respirable dust（smaller than 7.07 um)	Nippon Shokubai (1996), unpublished report

(Monitoring method)

Air sample was suctioned at the breathing zone (1.0 m in height) of the worker at a suction rate of 500 L/min for 5 or 10 min and was passed through a filter after an impactor. The substance collected on the filter was weighted with the filter.

The process is a closed batch system, both in Japan and Germany, the dust level can therefore be measured only at the packing workplace.

This dust level was 0.25 mg/m^3 as respirable dust (smaller than 7.07 um) at the packing workplace. When the sampling of dust is implemented without an impactor, the monitoring data might be higher than this measured level.

The EHE (Estimated Human Exposure) for inhalation is calculated as follows, using the measured dust level at the packing workplace, worker's body weight = 70 kg, respiratory volume = 1.25 m^3/hr, and exposure period = 6 hr/day;

EHEinh = 0.25 mg/m^3 x 1.25 m^3/hr x 6 hr/day / 70 kg = 0.027 mg/kg/day

The EHE for dermal exposure by means of the EASE model is estimated as follows using worker's body weight = 70 kg, open face area is 1180 cm^2, and an exposure of 0 - 0.1 mg/cm^2/day;

EHEder = 0.1 mg/cm^2/day x 1180 cm^2 / 70 kg = 1.7 mg/kg/day

Normally, workers wear protective clothing, gloves and breathing protection during the packing work. Hence, the EHEs are considered to be substantially lower than the calculated value.

In Japan, this substance has been manufactured since 1964, and no persons handling or contacting this substance have experienced any adverse symptoms regarding skin or respiratory organs.

Dust levels and EHEs at processing operations/formulators are estimated to be lower that at the packing place due to a lower number of operations.

2.2.2 Consumer Exposure

As for consumer products, this substance is used as chemical intermediate for amino resins including coloured amino resins such as benzoguanamine-formaldehyde resins, which is used as crosslinking agent in can coatings intended to come into contact with foods and beverages. After polimerisation into resins, release of this substance is low. The maximum migration of this substance is 0.53 mg/dm^2 and the EHE for consumers was calculated to be 0.076 mg/kg/day at the worst scenario based on migration tests (see Appendix 2).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There is no available information on toxicokinetics and metabolism of this substance.

3.1.2 Acute Toxicity

There is no available information on humans. Available studies are shown in Table 4.

Table 4: Acute toxicity of 2,4-diamino-6-phenyl-1,3,5-triazine in experimental animals

Route	Animals	Values	Type	References
Oral				
	Rat	933 mg/kg for male 1231 mg/kg for female	LD_{50}	MHW, Japan (1999c)
	Rat	1050 mg/kg	LD_{50}	Usden (1972)
	Rat	1470 mg/kg	LD_{50}	TNO (1972)
	Bird	100 mg/kg	LD_{50}	Schafer (1972)
Inhalation				
	Rat	2932 mg/L (4 hr)	LC_{50}	Hazleton U.K. (1989)

Among several oral acute toxicity studies shown in Table 3, the oral rat study [MHW, Japan (1999c)] was identified as the best quality and the key study because it was well conducted and described in detail.

In this study, this substance was studied for oral toxicity in rats in a single dose toxicity test at doses of 0, 250, 500, 1000, and 2000 mg/kg for both sexes. Deaths occurred in both sexes from the 1000 and 2000 mg/kg groups. In the dead animals, thickening of the mucosa in the forestomach, atrophy and decoloration in the thymus, atrophy of the spleen, and retention of dark green urine in the urinary bladder were noted at necropsy. Histopathological examination showed edema of the submucosal tissue in the forestomach and atrophy in the thymus and spleen.

In the surviving animals, white spots of the mucosa in the forestomach were noted at necroscopy, and histopathological examination showed hyperplasia of squamous epithelial cells. These changes were consistent with corrosivity at the stomach.

As a result, the oral LD50 values were 933 mg/kg (male rat) and 1231 mg/kg (female rat). The major toxicity was edema in the forestomach.

As for the acute inhalation study with 5 male and 5 female rats exposed for 4 hr, the LC50 value was 2.932 mg/L.

Conclusion

The lowest LD_{50} value by oral exposure routes in rats was 933 mg/kg (male) and 1231 mg/kg (female). The major oral toxicity was edema in the forestomach. The LC_{50} value by inhalation exposure was 2.932 mg/L (4 hr, rat).

3.1.3 Irritation

Mildly irritating to eyes in rabbits [RCC-NOTOX (1988c)]. In this study, 94 mg of this substance was instilled in one eye of three albino rabbits. The estimated Draize score was 4 (1 hr).

No skin irritation in rabbits was reported [RCC-NOTOX (1988d)]. Based on the study, the calculated primary irritation index was 0.

3.1.4 Sensitisation

There is no available information on sensitization.

3.1.5 Repeated Dose Toxicity

There is no available information on human toxicity. Two oral rat studies are available on 2,4-diamino-6-phenyl-1,3,5-triazine.

(Oral gavage) The first study is an OECD combined repeat dose and reproductive/developmental toxicity screening test [MHW, Japan (1999d)]. This substance was administered to three groups, each 12 males and 12 females Sprague-Dawley (Crj: CD) rats at doses of 0 (vehicle: 0.5% CMC-Na solution), 4, 20, 100 mg/kg/day respectively. Males were dosed for 49 days and females were dosed from 14 days before mating, throughout pregnancy to day 3 of lactation in females.

One male and female rat died, and the body weight gain was decreased in the 100 mg/kg group. Histopathological examination of dead animals revealed cellular infiltration of neutrophils and granulation in the ileum, atrophy and hemorrhage in the thymus, necrosis of the zona fasciculata to zona reticularis in the adrenals, erosion in the glandular stomach, and edema in the lung and atrophy in the spleen.

Increases of reticulocyte counts and the A/G ratio were observed in the survived males of the100 mg/kg group, and histopathological examination revealed centrilobular hypertrophy of the hepatocytes in both sexes given 100 mg/kg. The severity of these changes, however, were toxicologically not significant or adaptive change, except increase in reticulocyte count whose significance was equivocal.

A suppression of body weight gain and a decrease of food consumption were observed in both sexes of the 20 mg/kg or more groups. As the gains of body weight at the 20 mg/kg were not less than 90% compared by the control group, the toxicological meaning was less profound.

The NOAEL for repeated dose toxicity by oral gavage was considered to be 20 mg/kg (rat, male 49 day, female 39-53 day, gavage).

(Oral dietary) The second study is a repeat dose oral toxicity 90-day test conducted by OECD TG 408 [SafePharm (1993)]. The substance was administered to three groups of 10 male and 10 female Sprague-Dawley (CD strain) rats at dietary concentrations of 0 (vehicle; basal laboratory diet), 25, 250 and 2000 ppm (equivalent to a mean achieved dosage of 0, 1.9, 19 and 173 mg/kg/day respectively).

There were no deaths during the study. At the high dose (173 mg/kg/day), hunched posture and pilo-erection were observed, and a substantially lower body weight gain and lower food consumption were observed compared to the control during the treatment in either sex.

Many changes such as clinical observations, hematology/blood chemistry and necropsy/histopathology were observed. In blood chemistry, in either sex, slight but statistically significant increases in plasma alanine aminotransferase and bilirubin were shown compared with

controls. Regarding organ weights, in females, a statistically significant increase in liver weight was shown, relative to body weight, compared with controls. In the histopathology, centrilobular hepatocyte enlargement, an increased severity of splenic extramedullary hemopoiesis, hypertrophy and vacuolation of adrenal zona glomerulosa cells, and degeneration of pancreatic exocrine cells together with associated inflammatory cell infiltrates were shown.

An increased severity and/or incidence of hemosiderin pigment accumulation was observed in both the kidneys and the spleen of either sex.

At the dose of 19 mg/kg/day, in the histopathology, the sole treatment-related change was confined to males and identified as an increase in the severity of hemosiderin pigment accumulation in the spleen. Because such changes were graded up to moderate changes other substantial hematopoietic spleen changes subsided, the change was considered unlikely to be indicative of any damage to the health of the animals because no other changes were observed at this dose level.

Based on the above results, the NOAEL for repeated dose toxicity by oral diet was considered to be 19 mg/kg/day (rat, 90 day, dietary).

Conclusion

On basis of these two studies, the NOAEL for repeated dose toxicity was considered to be 20 mg/kg/day.

3.1.6 Mutagenicity

There are two bacterial studies, three non-bacterial *in vitro* studies, and two genotoxic *in vivo* studies available with 2,4-diamino-6-phenyl-1,3,5-triazine. The summary of the results is shown in Table 5.

Table 5: Summary of genotoxicity studies of 2,4-diamino-6-phenyl-1,3,5-triazine

Genotoxicity	Species	Protocol	Dose	MA*	Result	Reference
Bacterial test						
Ames test	S. typh. (strains TA98, TA100, TA1535, TA1537) E. coli WP2uvrA	Japanese TG OECD TG 471 & 472	Up to 5,000 ug/plate	+	Negative	MHW, Japan (1999a)
				-	Negative	
Ames test	S. typh. (strains TA98, TA100, TA1535, TA1537, TA1538)	OECD TG 471	Up to 5000 ug/plate	+	Negative	Microtest Res. (1988)
				-	Negative	
Non-bacterial in vitro test						
Chromosomal aberration test	CHL/IU cells	OECD TG 473	Up to 5000 ug/ml	+	Positive	MHW, Japan (1999b)
				-	Positive	
	Human lymphocyte	OECD TG 473	Up to 1250 ug/ml	+	Negative	SafePharm (1994a)
				-	Negative within solubility	
				-	Positive above solubility	
Mammalian cell gene mutation	Mouse lymphomacells (L5178Y)	OECD TG 476	Up to 1250 ug/ml	+	Negative within solubility	SafePharm (1994b)
				+	Positive above solubility	
				-	Negative	
In vivo test						
Micronucleus test	Mouse	92/69/EEC, B.12	Up to 500 mg/kg bw		Inconclusive	SafePharm (1996)
	Mouse	OECD TG 474	Up to 300 mg/kg bw		Negative	RCC (2000)

*MA: metabolic activation

Key studies on 2,4-diamino-6-phenyl-1,3,5-triazine are described below because they are well conducted and give detailed information.

In vitro Studies

Bacterial test

The study by MHW, Japan (1999a) was well conducted and according to Japanese Guideline for Screening Mutagenicity Testing of Chemicals, and OECD TG 471 & 472. All results were negative in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *Escherichia coli.* WP2 uvrA with and without an exogenous metabolic activation system.

Non-bacterial in vitro test

In the chromosomal aberration test with CHL cells [MHW, Japan (1999b)], this substance induced structural chromosomal aberrations under the 48 hr continuous treatment (0.2, 0.4 and 0.8 mg/ml, 11.0, 35.5 and 29.1%) and with a short-term treatment with an S9 mix (0.0781 mg/ml, 41.5%).

There were many metaphases that showed c-mitosis at the dose of 0.8 mg/ml for a 48 hr continuous treatment, and some spreads showed polyploidy. Accordingly a confirmative examination was conducted. Chromosome preparations were made after 24 hr recovery subsequent to the 48 hr

exposure. As a result, polyploidy was induced dose-dependently (0.8 and 1.6 mg/ml, 11.5% and 14.5%). In this study, visible precipitation was shown at the end of exposure period at about 400 ug/ml or more.

In the chromosomal aberration test with Human lymphocytes [SafePharm (1994a)], the dose range was 78.125, 156.25, 312.5, 625, 1250 ug/ml and additionally 2500 ug/ml for the 20 hr and 30 hr cell harvest with and without metabolic activation.

As a result, this substance did not induce chromosomal aberrations at doses within the solubility limit of the substance. It produced a statistically significant but modest increase in the frequency of cells with chromosomal aberrations at dose levels of 625 ug/ml or more (exceeding the solubility) limit without S9 mix.

In the genotoxicity test with Mouse lymphoma cells [SafePharm (1994b)], the dose range was selected on the preliminary toxicity test and was 78.1, 156.25, 312.5, 625, and 1250 ug/ml in the first experiment. In the second experiment the dose range was 156.25, 312.5, 625, 1250, and 2500 ug/ml.

The results were negative within the solubility limits of the substance but modestly positive only at dose levels of 625 ug/ml or more (exceeding the solubility limit) with S9 mix.

In vivo Studies

A first micronucleus assay with bone marrow cells of the mouse according to directive 92/69/EEC, B12 [SafePharm (1996)] was performed with sampling times of 24 and 48 hr, dosing of 125, 250 and 500 mg/kg based on a range-finding toxicity study and scoring of 1000 Polychromatic erythrocytes (PCEs).

In this test, the test result was inconclusive for two reasons:

Firstly, there were small deviations in the value of PCEs with micronuclei/1000PCEs = 2.1, 2.4 at the 48 hr in the 500, 250 mg/kg groups respectively.

Secondly, the mean value of positive control had two low scores which were very much lower than SafePharm's historical control values conducted by the further evaluation of the replica slides.

The above test result was inadequate as advised by the Scientific Committee on Food (SCF) of the European Commission (EC); SCF/CS/PM (GEN) 3334 final, adopted at the 118th SCF meeting on September 23 1999.

Accordingly, the second study by OECD TG 474 [RCC (2000)] was performed with sampling times of 24, 48 and 72 hr, dosing of 75, 150 and 300 mg/kg male mice, 50, 100 and 200 mg/kg female mice based on five studies of range-finding toxicity and scoring of at least 2000 PCEs per animal.

As a result, the number of NCEs was not substantially increased as compared to the mean value of NCEs of the control thus indicating that this substance at the indicated concentrations had no cytotoxic effects in the bone marrow. There was no biologically and statistically relevant enhancement in the frequency of the detected micronuclei after administration of this substance at any dose level or sampling time as compared to the vehicle control.

In conclusion, this substance did not induce micronuclei as determined by the micronucleus test with bone marrow cells of the mouse.

Based on the above results, the micronucleus test with bone marrow of mouse was negative

Conclusion

This substance was not mutagenic in bacteria [OECD TG 471 & 472]. It induced chromosomal aberration in CHL/IU cells with and without an exogenous metabolic activation system even at soluble concentrations. It also gave a positive response in the human lymphocytes test [OECD TG 473] and the mouse lymphoma TK assay [OECD TG 476] but only at insoluble dose levels. The cytogenetic effect observed in *in vitro* assays however, could not be reproduced in the micronucleus tests *in vivo* [OECD TG 474].

Based on the weight of evidence, it can be concluded that this substance is not genotoxic *in vivo*.

3.1.7 Carcinogenicity

In vivo Studies in Animals

Two chronic toxicity studies of 18 months were available as shown in Table 6. These studies were reported from the early National Cancer Institute program, currently the National Toxicology Program in the US. However, these studies were considered to be insufficient for assessment of the carcinogenicity because of insufficiencies of the testing protocol compared to current test guidelines (half the number of animal in each dose group, shorter exposure period in the rat study, only males used in the rat study).

Table 6: Carcinogenicity of 2,4-diamino-6-phenyl-1,3,5-triazine

Oral	Animal	Period (month)	Doses (mg/kg/day)	Toxic effects Tumorigenicity	Reference
Dietary	Rat male	18 (dose) 4 - 6 (post dosing)	0, 37.5, 75	Negative	Weisburger et al. Bio-Reserch (1973)
Dietary	Mouse male & female	18 (dose) 4 –6 (post dosing)	0, 300, 600	Negative	Weisburger et al. Bio-Reseach (1973)

The first [Weisburger et al. (1973)] was a study with male Charles River CD rats (25/sex/dose). This substance was fed at levels of 0 (control), 500 and 1000 ppm (0, 37.5, 75 mg/kg/day). Feeding was stopped after 18 months. The survival curve was not affected although there was a dose-related inhibition of growth. The incidence of tumors was no greater than in controls. Four tumors were seen which had not been observed in the simultaneous control. These events, however, have no significant frequency.

The second [Weisburger et al. (1973)] was a study with male and female albino CD-1 mice (25/sex/dose) fed at levels of 0 (control), 2000, 4000 ppm (0, 300, 600 mg/kg/day) for 18 months. This substance had no significant effects on survival and body weight gain, and did not cause a significant number of tumors including mammary tumors and bladder tumors.

Studies in Humans

There is no information available on humans.

Conclusion

Two dietary studies using male rats and male/female mice for 18 months showed no tumorigenic activity of this substance. However, these studies were considered to be insufficient for assessment of the carcinogenicity because of insufficiencies of the testing protocol compared to current test guidelines.

3.1.8 Toxicity for Reproduction/Development

One study [MHW 1999d] is considered to be a key study as shown in Table 7. The study was conducted according to a well-designed protocols (an OECD combined repeat dose and reproductive/developmental toxicity screening test), and is provides detailed information.

Table 7: Reproductive/developmental toxicity of 2,4-diamino-6-phenyl-1,3,5-triazine

Toxicity	**Item**		**Dose (mg/kg)**			
			0	4	20	100
Reproductive	No. of copulated	Male	12	12	12	12
		Female	12	12	12	12
	No. of impregnated	Female	11	12	12	11
	No. of dams	Dam	11	12	12	10
	No. of poor nursing dams	Day 0	0	0	0	2[1)]
		Day 4	0	0	2[2)]	7[2)]
Developmental	Gestation index	#a)	100%	100%	100%	91%
	Mean no. of litter size	#b)	15.5	14.4	13.3	10.9
	S.D. of no. of litter size		3.1	1.6	3.5	5.1
	Birth index	#c)	100%	98%	98%	72%**
	Body weight of pups	Day 0	6.2 g	6.7g	6.0g	4.9g**
		Day 4	9.4g	10.4g	9.6g	6.3g**
	Viability index	#d)	99%	99%	76%*	12%**
	No. of external anomalies	Pups	0	0	0	0

* : P<0.05; ** : P<0.01

#a): Gestation index = (Number of dams with live newborns/Number of pregnant females) x 100

#b): No. of litter size = Number of live newborns pups/litter

#c): Birth index = (Number of live newborns/Number of (stillborns + live newborns)) x 100

#d): Viability index = (Number of live newborns on day 4 after birth/Number of live newborns) x 100

[1)]: All newborns were dead and counted as stillborn

[2)]: All newborns were dead before day 4 of lactation

2,4-Diamino-6-phenyl-1,3,5-triazine was administered to each 12 male and 12 female Sprague-Dawley (Crj: CD) rats by gavage at doses of 0 (vehicle; 0.5% CMC-Na solution), 4, 20 and 100 mg/kg from 14 days before mating to 14 days after mating in males, and from 14 days before mating to day 3 of lactation in females [MHW, Japan (1999d)]. At 100 mg/kg, one female died during gestation and another female was not impregnated.

As for reproductive performance, no effects related to this substance were observed for the estrous cycle, numbers of corpora lutea and implantation, copulation index, conception index and duration of mating. On the findings of delivery of F_0 dams in the 100 mg/kg group, decreases of birth index and viability index on day 4 of lactation due to poor nursing of seven dams out of 10 were observed. The body weights of pups were also decreased at birth and day 4 of lactation in the 100 mg/kg group.

A dose-related decrease of litter sizes (number of live newborn pups/litter) was observed. However, the value at 20 mg/kg group is within the historical control values (13.67 +/- 3.08, 14.25

+/- 1.22, 14.73 +/- 2.65, 13.83 +/- 1.40). Therefore, the decrease at 4 and 20 mg/kg is not considered to be due to chemical-related effects.

The decrease of litter size observed at 100 mg/kg seems to be a chemical-induced effect although it is not statistically significant. In the 20 mg/kg group, a decrease in the viability index due to poor nursing on two dams out of 12 was observed. All live newborns of poor nursing dams died after three days.

There were no external anomalies of pups.

From these results, the parental NOAEL of reproductive toxicity was considered to be 100 mg/kg/day for males, and 4 mg/kg/day for females, based on the lack of nursing activity. And the NOAEL for developmental toxicity was considered to be 20 mg/kg/day, based on decrease of birth index and body weight of pups.

There is no available information on humans.

Conclusion

The parental NOAEL of reproductive toxicity was considered to be 100 mg/kg/day for males, and 4 mg/kg/day for females, based on the lack of nursing activity. And the NOAEL of developmental toxicity was considered to be 20 mg/kg/day, based on decreases of birth index and body weight of pups.

3.1.9 Information of structure-toxicity relationship (Triazine compounds)

Triazine compounds such as metribuzin (4-amino-6-t-butyl-3-methylthio-1,2,4-triazine-5(4H)-one), simazine (2-chloro-4,6-bis(ethylamino)-1,3,5-triazine), or atrazine (2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine) are suspected to be endocrine disruptors, although no toxicological information hinting at endocrine disruption is available in this substance (2,4-diamino-6-phenyl-1,3,5-triazine).

The skeletal structure (1,2,4-triazine-5(4H)-one) of metribuzin is considered to be chemically different from the skeletal structure (1,3,5-triazine) of this substance.

Chloro-1,3,5-triazine-triazine compounds such as atrazine and simazine are reported to affect mammary tumors in rat [Wetzel, L.T. et al], and also a long-term carcinogenicity study (test period was more than 24 month) on herbicide atrazine has been published [Pinter,A, et al].

3.2 Initial Assessment for Human Health

In the acute toxicity studies [OECD TG 401] for acute oral toxicity for rat, the dead animals showed thickening of the mucosa in the forestomach and edema in submucosal tissue of forestomach. These changes were consistent with corrosivity at the stomach and thought to be the case of death. The value of LD50 of this substance (2,4-diamino-6-phenyl-1,3,5-triazine) was 933 mg/kg (male) and 1231 mg/kg (female). The major oral toxicity was edema in the forestomach. The LC50 value in acute inhalation toxicity was 2.932 mg/L (4 hr, rat) [OECD TG 403]. , This substance was not irritating to the skin of rabbits [OECD TG 404].It is mildly irritating to the eyes in rabbits. There is no information on skin sensitisation.

In the OECD combined repeat dose and reproductive/developmental toxicity screening test by gavage [OECD TG 422], this substance was given at 0, 4, 20 and 100 mg/kg/day to rats for at least 39 days. One male and female rats died, and the body weight gain was decreased in the 100 mg/kg group. Hematological and blood chemical examination showed decreases in the erythrocyte counts

and hematocrit values with increased reticulocyte counts, and increases of GOT, GPT and total bilirubin with centrilobular hypertrophy of hepatocyte in the 100 mg/kg group. The severity of these changes, however, were toxicologically not significant or they were adaptive changes, except for the increase in reticulocyte count whose significance was equivocal. The NOAEL in this study was considered as 20 mg/kg/day.

In the 90-day feeding study with rats at 0, 1.9, 19.0, and 173.0 mg/kg/day [OECD TG 408], the body weight gain was decreased in the high dose group. In the histopathological examination, centrilobular hepatocyte enlargement, an increased severity of extramedullary hemopoiesis in the spleen and hemosiderin pigment accumulation in the kidneys and the spleen, hypertrophy and vacuolation of adrenal zona glomerulosa cells, and degeneration of pancreatic exocrine cells together with associated inflammatory cell infiltrates were observed in the high dose group. At the mid dose, the severity of hemosiderin pigment accumulation in the spleen was also increased moderately in males. This change in the spleen was considered not to be adverse effect because no other changes were observed at this dose level. Therefore, the NOAEL in this study was considered to be 19 mg/kg/day.

On basis of these two studies, the NOAEL for repeated dose toxicity was considered to be 20 mg/kg/day.

Regarding the genotoxicity of this substance, there were two Ames tests, three non-bacterial in vitro studies, and two genotoxic in vivo studies reported. This substance was not mutagenic in bacteria [OECD TG 471 & 472]. It induced chromosomal aberration in CHL/IU cells with and without an exogenous metabolic activation system even at soluble concentrations. It also gave a positive response in the human lymphocytes test [OECD TG 473] and the mouse lymphoma TK assay [OECD TG 476] but only at insoluble dose levels. The cytogenetic effect observed in in vitro assays however, could not be reproduced in the micronucleus tests in vivo [OECD TG 474].

Based on the weight of evidence, it could be concluded that this substance was not genotoxic in vivo.

Two dietary studies using male rats and male/female mice for 18 months showed no tumorigenic activity of this substance. However, these studies were considered to be insufficient for assessment of the carcinogenicity because of insufficiencies of the testing protocol compared to current test guidelines.

In the OECD combined repeat dose and reproductive/ developmental (one generation) toxicity screening test [OECD TG 422], this substance was given for 49 days from 14 days before mating in males and from 14 days before mating to day 3 of lactation in females. At 100 mg/kg, one female died in gestation and another female was not impregnated. Birth index was decreased with increase in stillborns at 100 mg/kg. All pups of two dams at 20 mg/kg and seven dams at 100 mg/kg died due to the lack of nursing activity, and the viability index on day 4 after birth was consequently decreased in these groups. The body weights of pups were also decreased at birth and day 4 of lactation in the 100 mg/kg group. The decrease of litter size observed at 100 mg/kg seems to be the chemical-induced effect although it is not statistically significant. No malformations or variations were observed in the pups.

From these results, the parental NOAEL of reproductive toxicity was considered to be 100 mg/kg/day for males, and 4 mg/kg/day for females, based on the lack of nursing activity, and the NOAEL of developmental toxicity was considered to be 20 mg/kg/day based on decreases of birth index and body weight of pups.

As for other human related information, this substance was not irritating to the skin and mildly irritating to the eyes in rabbits. There is no available information on toxicokinetics and metabolism of 2,4-diamino-6-phenyl-1,3,5-triazine.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The most relevant results from acute and chronic tests with aquatic organisms are shown in Table 8.

Table 8: Aquatic toxicity of 2,4-diamino-6-phenyl-1,3,5-triazine

Organism	Test method	Result (mg/L)	Reference
Algae			
Green alga (*Selenastrum capricornutum* ATCC 22662)	OECD TG 201 72 hr (cl)	EC50 (72 hr, bms) = 53.7 (nc*) NOEC (72 hr, bms) = 24.4 (nc*) EC50 (24-48 hr, gr) = 68.2 (nc*) EC50 (24-72 hr, gr) = 69.3 (nc*) NOEC (48 hr, gr) =39.1(nc*) NOEC (72 hr, gr) =39.1(nc*)	MOE, Japan (1999c)
(*Scenedesmus subspicatus*)	Unknown	EC50 (72 hr) = 22	KBwS (1991)
Invertebrates			
Water flea (*Daphnia magna*)	OECD TG 202 24, 48 hr (op,s)	EC50 (24 hr, imm) = 112 (mc) EC0 (48 hr, imm) = 7.68 (mc) EC50 (48 hr, imm) = 52.0 (mc) EC100 (48 hr, imm) = 300 (mc)	MOE, Japan (1999b)
	OECD TG 211 21 d (op, ss)	LC50(21 d, par)=13.4 (mc) EC50 (21 d, rep) = 5.91 (mc) NOEC (21 d, rep) = 1.91 (mc) LOEC (21 d, rep) = 3.43 (mc)	MOE, Japan (1999d)
Fish			
Medaka (*Oryzias latipes*)	OECD TG 203 96 hr (op, ss)	LC_0 (96 hr) = 50 (nc*) LC_{50} (96 hr) > 100 (nc*) LC_{100} (96 hr) > 100 (nc*)	MOE, Japan (1999a)
Goldorfe (*Leuciscus idus* (L.))	DIN 38412 Teil 15 48 hr (op,s)	LC_0 (48 hr) = 56 (nc) LC_{50} (48 hr) = 99 (calc) LC_{100} (48 hr) = 180 (nc)	TNO (1988)

cl; closed system, op; open system s; static, ss; semi-static nc; nominal concentration (actual concentration not measured), mc; measured concentration, nc*; nominal concentration (actual concentration measured and greater than 80% of the nominal), calc; calculated concentration using parametric model developed by Kooijiman, bms; biomass, gr; growth rate, imm; immobility, rep; reproduction, par;parental,

There are two additional results regarding toxicity to microorganisms e.g. Bacteria. One test with *Photobacterium phosphoreum* reported a EC50 = 210 mg/L [KBwS 1991]. The other test with *Pseudemonas putida* reported a EC10 = 3.4 mg/L (18hr) [RCC-NOTOX(1988a)].

There is no available information on the toxicity towards sediment dwelling organisms.

4.2 Terrestrial Effects

There is no available information.

4.3 Other Environmental Effects

There is no available information.

4.4 Initial Assessment for the Environment

This substance (2,4-diamino-6-phenyl-1,3,5-triazine) would be released into the aquatic environment from waste water, and remain almost entirely in the water compartment according to a calculation using the fugacity model [Mackey level III]. Although this substance is stable in water biotically and abiotically, this substance has a low potential of bioaccumulation (BCF = 6.4), estimated from the log Pow (1.38).

Regarding acute toxicity to aquatic species, the toxicity to algae [OECD TG 201] was 53.7 mg/L for EC50 (72 hr, *Selenastrum capricornutum*, biomass) and the toxicity to daphnids [OECD TG 202] was 52.0 mg/L for EC50 (48 hr, *Daphnia magna*, immobility). The toxicity to fish [other method] was 99 mg/L for LC_{50} (48 hr, *Leuciscus idus* (L.)).

Regarding chronic toxicity to aquatic species, the toxicity to daphnids [OECD TG 211] was 1.91 mg/L for NOEC (21 day, *Daphnia magna*, reproduction). The toxicity to algae [OECD TG 201] was 24.4 mg/L for NOEC (72 hr, *Selenastrum capricornutum*, biomass).

A PNEC = 0.0191 mg/L (Predicted No Effect Concentration) for the aquatic organisms was calculated from the 21 d - NOEC (1.91 mg/L) for *Daphnia magna* using an assessment factor of 100 according to the ICCA HPV guidance, because two chronic data (*Daphnia magna* and alga) and one acute data (*Daphnia magna)* were available.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

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APPENDIX 1: PREDICTED EMISSION CONCENTRATION (PEC) FROM WASTE WATER TO LOCAL SURFACE WATER ESTIMATED IN JAPAN AND CALCULATED PEC/PNEC RATIO

PEC

PEClocal.water described in section 2.1. is calculated to be 0.0176 mg/L as follows;

PEClocal.water = 3000 t/y x 0.00019 t/t x (1 - 0.01) / (200 d/y x 4000 m^3/d x 4 x 10) x 10^6

= 0.0176 mg/L

Remark;

3000 t/y	production volume of Benzoguanamine in Japan
0.00019 t/t	emission unit versus production volume
0.01	elimination based on biodegradable portion
200 d/y	annual production days
4000 m^3/d	flow rate per day of waste water in the treatment plant
4	internal dilution factor
10	dilution factor in surface water

PNEC

PNEC described in section 2.1. is calculated to be 0.0191 mg/L as follows;

PNEC = 0.0191 mg/L for the aquatic organisms was calculated from the 21 d – NOEC (1.91 mg/L) for *Daphnia magna* using an assessment factor of 100 according to the ICCA HPV guidance, because two chronic data (*Daphnia magna* and alga) and one acute data (*Daphnia magna)* were available.

PEC/PNEC

PEC/PNEC ratio is below 1 as follows:

PEClocal.water = 0.0176 mg/L

PNEC = 0.0191 mg/L

Hence, PEC/PNEC = 0.92, and this ratio is close to one but below 1.

APPENDIX 2: ESTIMATED HUMAN EXPOSURE (EHE) FOR CONSUMER USE BY INTAKE THROUGH MIGRATION FROM COATING CAN

(1) Sample of coating:

Base metal ; tin and silver foils

Dry conditions; 200°C、15 min

Coating resin ; No.1 Epoxy resin/Benzoguanamine resin = 80/20

No.2 Polyester resin/Benzoguanamine resin = 80/20

No.3 Polyester resin/Epoxy resin/Benzoguanamine-formaldehyde resin = 55/20/25

Coating weight; 8-9 g/m

(2) Test condition

Solvent extraction tests:

Area of coated sample ; 2 dm^2

Solvent ; Methanol, 400 ml

Extraction ; Reflux during 2 hr

Migration tests:

Area of coated sample ; 2 dm^2

(3) Result of Migration tests

Foods	Condition for migration	Results of migration (mg/dm^2)		
Simulates	Temperature, Time	No.1	No.2	No.3
Distilled water	121°C, 30 min + 40°C, 10 day	0.04	0.04	0.04
3% acetic acid	121°C, 30 min + 40°C, 10 day	0.53	0.05	0.29
15% ethanol	121°C, 30 min + 40°C, 10 day	0.14	0.03	0.05
50% ethanol	40°C, 10 day	0.24	0.07	0.07

(4) EHE for consumer use is calculated to be 0.076 mg/kg/day as follows;

EHEconsumer = 0.53 mg/dm^2 x 5 dm^2/L x 2 L/day / 70 kg

= 0.076 mg/kg/day

Remark;

0.53 mg/dm^2	maximum migration of Benzoguanamine	(at as shown above)
5 dm^2/L	area of contact to food in coated can	(default)
2 L/day	daily drinking volume	(default)
70 kg	adult body weight	(default)

SIDS Dossier

Existing Chemical	:	ID: 91-76-9
CAS No.	:	91-76-9
EINECS Name	:	6-phenyl-1,3,5-triazine-2,4-diyldiamine
EINECS No.	:	202-095-6
TSCA Name	:	1,3,5-triazine-2,4-diamine, 6-phenyl-
Molecular Formula	:	C9H9N5

Producer Related Part

Company	:	NIPPON SHOKUBAI CO., LTD.
Creation date	:	29.11.2000

Substance Related Part

Company	:	NIPPON SHOKUBAI CO., LTD.
Creation date	:	29.11.2000
Memo	:	2,4-diamino-6-phenyl-1,3,5-triazine
Printing date	:	04.05.2001
Revision date	:	13.09.2001
Date of last Update	:	08.02.2002
Number of Pages	:	60
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 8
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4, 5
Flags (profile)	:	Flags: SIDS

1.0.1 OECD AND COMPANY INFORMATION

Type : lead organisation
Name : NIPPON SHOKUBAI CO., LTD.
Partner : SKW Trostberg AG
Date : 24.08.2001
Street : 4-1-1, Koraibashi, Chuo-ku
Town : Osaka 541-0043
Country : Japan
Phone : +81-6-6223-9166
Telefax : +81-6-6202-1766
16.01.2001

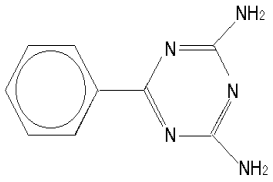
1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

Name of recipient : Mr. Koji Tomita, Ministry of Foreign Affairs, Economic Affairs Bureau, Second International Organisations Div.
Street : 2-2-1 Kasumigaseki, Chiyodaku
Town : 100 Tokyo
Country : Japan
Phone : +81-3-3581-0018
Telefax : +81-3-3581-9470
25.12.2000

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : Organic
Physical status : Solid
Purity : >= 98% w/w
Remark :
Source : COMPANY: SKW Trostberg AG Trostberg
Attached doc. :



04.05.2001 (21)

1.1.0 DETAILS ON TEMPLATE

Production : Production volume and emission rate in 2000.

Contry	Company	Production (T/y)	Process	Emmision (g/T)
Japan	Nippon Shokubai	3,000	Closed batch	190
Germany	SKW	1,500	Closed batch	
China	Shanghai	200+		
		5,000		

Source : COMPANY: NIPPON SHOKUBAI CO., LTD. Osaka

08.02.2002 (32)

1.1.1 SPECTRA

Type of spectra : IR
Remark : NO.: 6423 (Coblentz Society Spectral Collection)
Source : HSDB (2001)
12.02.2001 (56)

Type of spectra : UV
Remark : NO.: 3855 (Sadtler Research Laboratories Spectral Collection)
Source : HSDB (2001)
12.02.2001 (56)

Type of spectra : NMR
Remark : NO.: 544(Sadtler Research Laboratories Spectral Collection)
Source : HSDB (2001)
12.02.2001 (56)

Type of spectra : mass spectrum
Remark : NO.: 1005 (National Bureau of Standards EPA-NIH Mass Spectra Data Base, NSRDS-NBS-63)
Source : HSDB (2001)
12.02.2001 (56)

Type of spectra : IR
Result : SPECTROSCOPIC DATA (KBR): 3507(w), 3411(m), 3299(m), 3180(m), 1624(s), 1529(w), 1539(s), 1493(sh), 1452(w), 1393(s), 825(m), 777(w), 691(m), 679(sh), 618(w) /cm
20.02.2001 (47)

Type of spectra : UV
Result : UV max absorption (ethanol): 249 nm (epsilon. 25,000)
20.02.2001 (51)

1.2 SYNONYMS

1,3,5-Triazine-2,4-diamine, 6-phenyl-
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
05.08.1993

1,3,5-Triazine-2,4-diamine, 6-phenyl- (9CI)
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

2,4-diamino-6-phenyl-1,3,5-triazine
Source : TRANSOL Chemicals BV Ridderkerk
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
17.09.1997

2,4-Diamino-6-phenyl-1,3,5-triazine
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

2,4-Diamino-6-phenyl-s-triazine

Source : BASF AG Ludwigshafen
SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

2-Phenyl-4,6-diamino-1,3,5-triazine
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
05.08.1993

4,6-Diamino-2-phenyl-s-triazine
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
05.08.1993

6-Phenyl-1,3,5-triazin-2,4-diamin
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
05.08.1993

6-Phenyl-1,3,5-triazin-2,4-diylamin
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
05.08.1993

6-Phenyl-1,3,5-triazine-2,4-diamine
Source : BASF AG Ludwigshafen
SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

6-Phenyl-1,3,5-triazine-2,4-diyldiamine
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
05.08.1993

Benzoguanamin
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
05.08.1993

benzoguanamine
Source : DSM Resins BV Zwolle
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.04.1998

Benzoguanamine
Source : BASF AG Ludwigshafen
SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

ENT 60118
Source : BASF AG Ludwigshafen
SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

s-Triazine, 2,4-diamino-6-phenyl-
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

05.08.1993

s-Triazine, 2,4-diamino-6-phenyl- (6Cl, 8Cl)
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
29.08.1996

USAF RH-5
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
05.08.1993

1.3 IMPURITIES

CAS-No : 461-58-5
EINECS-No : 207-312-8
EINECS-Name : dicyandiamide
Contents : < 0.1% w/w
Reliability : (2) valid with restrictions
03.05.2001 (42) (47)

CAS-No : 108-78-1
EINECS-No : 203-615-4
EINECS-Name : melamine
Contents : <= 2% w/w
18.12.2000 (43) (47)

CAS-No : 55-21-0
EINECS-No : 200-227-7
EINECS-Name : benzamide
Contents : ca. 0.01% w/w
03.05.2001 (27)

1.4 ADDITIVES

1.5 QUANTITY

Quantity produced : 5,000 tonnes in 2000
12.02.2001
Source : NIPPON SHOKUBAI CO., LTD. Osaka
04.05.2001 (32)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Symbols : Xn
Nota :
Specific limits : no data
R-Phrases : (22) harmful if swallowed
(52/53) harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-Phrases : (2) keep out of reach of children
(61) Avoid release to the environment. Refer to special instructions/safety data sets.
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)

03.05.2001

1.6.2 CLASSIFICATION

Classification : as in Directive 67/548/EEC
Class of danger : harmful
R-Phrases : (22) harmful if swallowed
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
03.05.2001

Classification : as in Directive 67/548/EEC
Class of danger :
R-Phrases : (52) harmful to aquatic organisms
(53) may cause long-term adverse effects in the aquatic environment
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
11.02.2000

1.7 USE PATTERN

Type : industrial
Category : chemical intermediate: amino resins
Source : NIPPON SHOKUBAI CO., LTD. Osaka
08.02.2002 (32)

Type : industrial
Category : chemical intermediate: coloured amino resins
Source : NIPPON SHOKUBAI CO., LTD. Osaka
08.02.2002 (32)

Type : industrial
Category : chemical intermediate: materials for fine sphere particle
Source : NIPPON SHOKUBAI CO., LTD. Osaka
08.02.2002 (32)

Type : industrial
Category : chemical intermediate: materials for coloured fine sphere particle
Source : NIPPON SHOKUBAI CO., LTD. Osaka
08.02.2002 (32)

Type : industrial
Category : chemical intermediate: support materials for dye or pigment
Source : NIPPON SHOKUBAI CO., LTD. Osaka
08.02.2002 (32)

Type : industrial
Category : chemical intermediate: materials for plastics admixture
Source : NIPPON SHOKUBAI CO., LTD. Osaka
08.02.2002 (32)

Type : industrial
Category : chemical intermediate: materials for liquid crystal display spacer
Source : NIPPON SHOKUBAI CO., LTD. Osaka
08.02.2002 (32)

Type : industrial
Category : chemical intermediate: materials for coating, paint, vanish and printink
Source : NIPPON SHOKUBAI CO., LTD. Osaka
08.02.2002 (32)

Type : Industrial
Category : chemical intermediate: materials for can coatings
Source : NIPPON SHOKUBAI CO., LTD. Osaka
08.02.2002 (32)

Type : type
Category : non dispersive use
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
11.02.2000

Type : industrial
Category : basic industry: basic chemicals
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
11.02.2000

Type : industrial
Category : chemical industry: used in synthesis
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
11.02.2000

Type : industrial
Category : other: Aminoplastharzmodifizierung
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
11.02.2000

Type : use
Category : Colouring agents
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
11.02.2000

Type : use
Category : pharmaceuticals
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
11.02.2000

Type : use
Category : other: Lackrohstoffe für Härter, für Klebe- und Bindemittel
Source : EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
09.12.2000

1.7.1 TECHNOLOGY PRODUCTION/USE

Type : production
Remark : This substance (2,4-diamino-6-phenyl-1,3,5-triazine or benzoguanamine) can be produced by the reaction of benzonitrile (C6H5-CN: CAS No. 100-47-0) and dicyandiamide (NH2C(=NH)-NHCN: CAS No. 461-58-5) in Japan.
Source : NIPPON SHOKUBAI CO., LTD. Osaka
04.05.2001 (32)

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : BAT (DE)
Limit value :
Remark : Kein MAK-Wert festgelegt
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ipra (VA)

30.04.2001 (53)

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 2 (water polluting)
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
09.12.2000

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 2 (water polluting)
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
21.02.2001 (46) (48)

1.14.2 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : no
No. in directive :
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
19.11.1997 (49)

1.14.3 AIR POLLUTION

Classified by : other: SKW Trostberg AG Trostberg
Labelled by : other: SKW Trostberg AG Trostberg
Number : 3.1.7 (organic substances)
Class of danger : III
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

05.08.1993

1.15 ADDITIONAL REMARKS

Memo : imupurities of sample; lot no. 93/12840 of SKW Trostberg AG
Result : contents;
- sample; batch no.2315/02 of SKW Trostberg AG

CAS No.	Chemical name	Contents
91-76-9	benzoguanamine	98.2 wt%
108-78-1	melamine	0.91 wt%
461-58-5	dicyandiamide	0.04 wt%

30.04.2001 (42) (43)

Memo : imupurities of sample; lot no. 7P11 of NIPPON SHOKUBAI CO.,LTD.
Result : contents;
- sample; lot no. 7P11 of NIPPON SHOKUBAI CO.,LTD.

CAS No.	Chemical name	Contents
91-76-9	benzoguanamine	more than 98 wt%
108-78-1	melamine	0.1-0.2 wt%
461-58-5	dicyandiamide	0.04 wt%
55-21-6	benzamide	0.01 wt%

30.04.2001 (30)

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value : = 226.5°C
Source : SRC (2001)
04.05.2001 (50)

Value : = 227-228°C
Source : HSDB (2000)

Value : = 227°C
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
21.02.2001 (48)

Value : = 228°C
Sublimation : No
Method :
Year : 1999
GLP :
Test substance : other TS: Wako Chemical Co.
Source : METI Japan
Test substance : Purity: 100%
Flag : Critical study for SIDS endpoint
04.05.2001 (6)

2.2 BOILING POINT

Value : > 350°C at 1,013 hPa
Decomposition :
Method : OECD Guide-line 103 "Boiling Point/boiling Range"
Year : 1999
GLP : Yes
Test substance : other TS: Wako Chemical Co.
Source : METI Japan
Test substance : Purity: 100%
Flag : Critical study for SIDS endpoint
04.05.2001 (6)

2.3 DENSITY

Type : density
Value : = 1.425 g/cm3 at 15°C
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Flag : Critical study for SIDS endpoint
21.02.2001 (48)

Type : density
Value : = 1.4 g/cm3 at 25°C
Source : Merck (2001)
04.05.2001 (51)

Type : bulk density
Value : = 680 kg/m3
Method :
Year :

GLP :
Test substance : other TS
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
21.02.2001 (48)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : 1.6x10E-5 Pa at 25°C
Method other (calculated)
Source : HSDB (2001)
Flag : Critical study for SIDS endpoint
02.04.2001 (20)

Value : < 4.1x10E-5 Pa at 100°C
Decomposition : no
Method OECD Guide-line 104 "Vapour Pressure Curve"
Year : 1999
GLP : yes
Test substance : other TS: Wako Chemical Co.
Decomposition : no
Source : METI Japan
Test condition : number of apparatus: n = 1
flow rate: 37.9 ml/min
solvent for absorption: pure water ; carrier gas: extra pure (99.99%)
Test substance : purity: 100%
Conclusion less than the limmit of the quantity (= 0.000041 Pa)
Flag : Critical study for SIDS endpoint
04.05.2001 (6)

2.5 PARTITION COEFFICIENT

Log Pow : = 1.36
Method other (measured): Flask Shaking Mesthod
Year : 1980
GLP : no
Test substance :
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
30.01.2001 (18) (34)

Log Pow : = 1.36
Test substance : other TS
Source : HSDB (2001)
12.02.2001 (13)

Log Pow : = 1.38 at 25°C
Method OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1999
GLP : yes
Test substance : other TS: Wako Chemical Co.
Method : flask-shaking method
Result :

Log Pow;

Test	A pH	A Log Pow	B pH	B Log Pow	Average Log Pow
1	6.3	1.41	6.3	1.39	1.38
2	6.2	1.36	6.2	1.37	
3	6.1	1.38	6.1	1.38	

reference: ( ) is pH at water layer

Source : METI Japan
Test condition : sample weight: 5.10 mg (= 5 ml x 1020 mg/L)
component of test solution:

Case	No.1 ml	No.2 ml	No.3 ml
1-octanol saturated by water	5	10	20
water saturated by 1-octanol	30	25	15

temperature: 25 (24-26) °C
revolution: 20/min x 5 min
number of replicate: 2
analysis: HPLC

Test substance : purity: 100%
Flag : Critical study for SIDS endpoint
04.05.2001 (6)

Log Pow : = 1.48 at 20°C
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1988
GLP : yes
Test substance : as prescribed by 1.1-1.4
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
02.04.2001 (38)

2.6.1 WATER SOLUBILITY

Value : = 600 mg/L at 22°C
Source : HSDB (2001)
21.02.2001 (51)

Value : = 300 mg/L at 25°C
pH : = 6.5 at 300 mg/L and 20°C
Source : SKW Trostberg AG Trostberg
21.04.2001 (48)

Value : = 320 mg/L at 25°C
pKa : = 3.91 at 25°C
Method : OECD Guide-line 105 "Water Solubility"
Year : 1999
GLP : yes
Test substance : other TS: Wako Chemical Co.
Result : solubility (at 25°C)

Shaking time (hr)	Concentration (mg/L)	Average (mg/L)	Total average (mg/L)
24	310	320	320
	320		
48	310	320	
	320		

72	310 320	320	

Source : METI Japan
Test condition : pre-shaking: 24 hr, 48 hr, 72 hr at 30°C
shaking: 24 hr at 25°C ; vessel: flask with a plug ; number of replicate: 2
Test substance : purity: 100%
Flag : Critical study for SIDS endpoint
04.05.2001 (6)

Value : = 1 g/L at 40°C
pH : = 5.6 at 80.5 mg/L and 20°C
Year :
GLP : none
Test substance : other TS: NIPPON SHOKUBAI CO., LTD. Osaka
Source : NIPPON SHOKUBAI CO.,LTD. Osaka
12.02.2001 (32)

Value : = 6 g/L at 100°C
Source : HSDB (2001)
21.02.2001 (51)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Method : other: Haltman
Year : 1994
GLP : no data
Result : other: lower limmit of explosion; 25 g/m3
Remark : electrified quantity of static electricity: 1.4x10E-9 c/g
conductivity: 2.0x10E-14 S/m
Test substance : particle size: 200 mesh pass
other TS: NIPPON SHOKUBAI CO.,LTD. Osaka
Source : NIPPON SHOKUBAI CO.,LTD. Osaka
04.05.2001 (33)

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

Memo : Henry's Law constant = 4.1x10E-11 atm-m3/mol (at 25°C)
Method : estimation by the bond contribution method developed by Meylan and Howard (1991)

Source : SRC (2001), HSDB (2001)
02.04.2001 (24)

Memo : solubility in organic solvents (1)
Remark
in acetonitrile	; more than 1 g/L
in tetrahydrofuran	; more than 10 g/L
in 1-octanol	; more than 1 g/L

Source : METI Japan
04.05.2001 (23)

Memo : solubility in organic solvents (2)
Remark :
in acetone	; 18.0 g/L at 20°C
in benzene	; 0. 3 g/L at 20°C
in dimethylformamide	; 120.0 g/L at 20°C
in ethanol	; more than 10%
in ethyl ether	; more than 10%
in dilute hydrochloric acid	; soluble
in Methyl Cellosolve	; soluble
in chloroform	; practically insoluble
in ethyl acetate	; practically insoluble
in trifluoroacetic acid	; slightly soluble

Source : HSDB (2000)
03.02.2001 (15)

Memo : solubility in organic solvents (3)
Remark : solubility (g/100g, 25°C)
in water	; 0
in heptane	; 0
in benzene	; 0.04
in methylenedichloride	; 0.08
in ethyl ether	; 0.2
in butyl acetate	; 0.7
in methanol	; 1.4
in acetone	; 1.8
in tetrahydrofuran	; 8.8
in dimethylformamide	; 12.0
in Methyl Cellosolve	; 13.7

Source : NIPPON SHOKUBAI CO.,LTD. Osaka
29.01.2001 (32)

Memo : solubility in methanol; 14 g/L (at 25°C)
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
21.02.2001 (48)

Memo : pKa = 3.7 by spectrophotometric method
Source : Weber, J. B. 1967. Spectrochimica Acta 23A: 458-461.
03.04.2001 (57)

Memo : pKa = 3.86
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
Test condition : temperature: 25°C
28.04.2001 (17)

Memo : pKa = 3.91 by spectrophotometric method
Method : OECD TG 112 “Spectrophotometry Method”
Source : METI Japan
Test condition : concentration: 10.0 mg/L (0.0534 mol/L)
temperature: 25°C
30.04.2001 (6)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	sun light
Light spect.	:	
Rel. intensity	:	based on intensity of sunlight
Conc. of subst.	:	at 25°C
Result	:	indirect photolysis - type of sentitizer: OH - concentration of sentitizer: 50,000 hydroxyl radical/cm3 - rate constant: 3.7x10E-12 cm3/molecule-sec at 25°C - half-life of degradation: 4.4 day by calclulation
Remarks	:	no decomposition information
Source	:	HSDB (2000)
Flag	:	Critical study for SIDS endpoint

04.05.2001 (15)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 5 day at 50°C
t1/2 pH7	:	> 5 day at 50°C
t1/2 pH9	:	> 5 day at 50°C
Deg. Product	:	no
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	1998
GLP	:	yes
Test substance	:	other TS: Wako Chemical Co.
Result	:	stable at pH 4, 7 and 9 (t1/2 > 5 day at 50°C)
Source	:	METI Japan
Test condition	:	concentration of test substance: 100 mg/L temperature: 50 (49-51) °C vessel: flask with a plug number of replicate: 2 period: 5 day
Test substance	:	purity: 100%
Flag	:	Critical study for SIDS endpoint

04.05.2001 (23)

3.1.3 STABILITY IN SOIL

Type	:	
Radiolabel	:	
Concentration	:	
Soil temp.	:	
Soil humidity	:	
Soil classif.	:	
Year	:	
Remark	:	The Koc of 2,4-diamino-6-phenyl-1,3,5-triazine is estimated as approximately 130, using a log Pow of 1.36 and a regression-derived equation. According to a classification scheme, this estimated Koc values suggestes that this substance is expected to have high mobility in soil. Adsorption of this substance, 5x10E-5 M, by Na-montmorillonaite at four pH levels was approximately pH 1 ------ 310 umol/g pH 2 ------ 460 umol/g

pH 4 ------ 475 umol/g
pH 6.5 --- 200 umol/g
and maximum adsorption by the clay occured at pH levels in the vicinity of the pKa 3.7. This substance's pKa of 3.7, indicates it will exist predominantly in the unionized form under environmental pHs. Weak bases, such as benzoguanamine, are more mobile in alkaline solids because cations are much more strongly absorbed by ion exchange on organic and inorganic surfaces than the unionized bases are by organic matter.

Source : HSDB (2000)
03.05.2001 (15)

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

Media : air-biota-sediment(s)-soil-water
Method : a generic fugacity model (Mackay level III)
Year : 2001
Result :

Compartment	Amount % Release 100% to air	Release 100% to water	Release 100% to soil
Air	0.0	0.0	0.0
Water	29.3	99.5	24.9
Soil	70.5	0.0	75.0
Sediment	0.2	0.5	0.1

Cited from Appendix 8.

Appendix 8. The Fugacity Model (Mackay level III)
Source : CERI Japan
Flag : Critical study for SIDS endpoint
04.05.2001 (7)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge
Concentration : 100 mg/L related to test substance
Contact time : 28 day
Degradation : = 2% after 28 day (BOD)
Result : under test conditions no ready biodegradation observed
Kinetic of test substance : mean 2%, (2%, 3%, 0%, n = 3)
Control substance : aniline
Kinetic : 66% (7 day), 77% (14 day)
Method : OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year : 1998
GLP : yes
Test substance : other TS: Wako Chemical Co.
Source : METI Japan

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.05.2001 (5)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF : = 6.4
Test substance : as prescribed by 1.1-1.4
Result : An estimated BCF of 6.4 was calculated for 2,4-diamino-6-phenyl-1,3,5-triazine, using a log Pow of 1.36 and regression-derived equation.
Source : HSDB (2000)
Flag : Critical study for SIDS endpoint
22.04.2001 (15)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : semi-static
Species : Medaka (Oryzias latipes)
Exposure period : 96 hr
Unit : mg/L
Analytical monitoring : yes
LC50 : c > 100
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1993
GLP : yes
Test substance : other TS: Wako Chemical Co.
Result : RESULTS: EXPOSED
- nominal/measured concentrations:

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percentage of nominal) 0 hr[a)]		48 hr[b)]		Mean[c)]	
Control	n.d.		n.d.		n.d.	
25.0	25.9	(104)	25.0	(100)	25.5	(102)
50.0	50.8	(102)	49.9	(99.9)	50.4	(101)
100	102	(102)	100	(100)	101	(101)

Remark: n.d.; less than 1.00 mg/L
a); fresh solutions
b); expired solutions
c); The values are expressed at time-weighted means calculated by the following equation:
$(C_0-C_{48})/lnC_0-lnC_{48})$
where C_0: the measured concentration at 0 hr
C_{48}: the measured concentaration at 48 hr

- effect data (mortality):
96 hr LC50 > 100 mg/L
Highest test substance concentration resulting in 0% mortality = 50.0 mg/L
Lowest test substance concentration resulting in 100% mortality > 100 mg/L

Nominal concentration (mg/L)	Cumulative number of dead fish mortality(%) vs time 24 hr		48 hr		72 hr		96 hr	
control	0	(0)	0	(0)	0	(0)	0	(0)
25.0	0	(0)	0	(0)	0	(0)	0	(0)
50.0	0	(0)	0	(0)	0	(0)	0	(0)
100.0	0	(0)	0	(0)	1	(10)	3	(30)

- other effects:

Nominal concentration (mg/L)	Symptom 3 hr	24 hr	48 hr	72 hr	96 hr
control	-	-	-	-	-
25.0	-	-	-	-	-
50.0	-	-	-	AB	AB
100.0	AB	AB	AB	AB	AB, AR

AB; abnormal behavior
AR; abnomal respiration

RESULTS: CONTROL: not described
RESULTS: TEST WITH REFERENCE SUBSTANCE
- concentrations: pure CuSO4·5H2O
- results: 96 hr LC50 = 1.22 mg/L

Source : NIPPON SHOKUBAI CO.,LTD.

Test condition : TEST ORGANISMS
- strain: not described
- supplier: Nakajima fish farm (Kumamoto, Japan)
- size/weight: 20 mm (18-21 mm), n = 10/0.11 g (0.083-0.13 g), n = 10
- feeding: "TETRAMIN" (TETRABERKE Co.)
- pretreatment: acclimated for 12 days before testing
- feeding during test: none

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- dispersion: irradiation of ultrasound
- vehicle, solvent: no solvent was used

REFERENCE SUBSTANCE: CuSO4·5H2O
DILUTION WATER
- source: dechlorinated tap water
- aeration: none
- alkalinity: 33.0 mg/L
- hardness: 52.0 mg/L as CaCO3
- chlorinity: less than 0.02 mg/L as Cl
- pH: 7.5
- oxygen content: not described

TEST SYSTEM
- concentrations: 0, 25.0, 50.0, 100 mg/L
- dosing rate: semi-static
- renewal of test solution: 48 hr
- exposure vessel type: size; 2.5 L test solution in a 3 L glass vessel (16cm diameter, 17 cm height) aeration; none
- number of replicates, fish per replicate: 2, 5
- test temperature: 24.0-24.5 °C
- dissolved oxygen: 6.8-8.3 mg/L
- pH: 7.2-7.3
- Intensity of irradiation: room light
- photoperiod: 16 hr-8 hr light-dark cycle

DURATION OF THE TEST: 96 hr
TEST PARAMETER: mortaliy, abnormal behavior, abnormal respiration
SAMPLING: at 0 hr and 48 hr
MONITORING OF TEST SUBSTANCE CONCENTRATION: measured by HPLC

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

28.04.2001 (9)

Type :
Species : Leuciscus idus (L.) (Goldorfe)
Exposure period : 48 hr
Unit : mg/L
Analytical monitoring :
LC0 : = 56
LC50 : = 99
LC100 : = 180
Method : other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil15
Year : 1988
GLP : yes
Test substance : as prescribed by 1.1-1.4

Result : RESULTS: EXPOSED
- effect data (mortality):
24 hr LC50 = 99 mg/L (mortality)
48 hr LC50 = 99 mg/L (mortality)
48 hr LC100 =180 mg/L (mortality)
48 hr NOEC = 56 mg/L (mortality, = 48 hr LC0)
48 hr NOEC = 32 mg/L (swimming behaviour)

Nominal concentration (mg/L)	Cumulative number of dead fish Mortality (%) 0 hr		2 hr		24 hr		48 hr		swimming behaviour 48 hr	
control	0	(0)	0	(0)	0	(0)	0	(0)	normal	*1)
10	0	(0)	0	(0)	0	(0)	0	(0)	normal	*2)
18	0	(0)	0	(0)	0	(0)	0	(0)	normal	*2)
32	0	(0)	0	(0)	0	(0)	0	(0)	normal	*2)
56	0	(0)	0	(0)	0	(0)	0	(0)	poor	*3)
100	0	(0)	0	(0)	6	(60)	6	(60)	very poor	*2)
180	0	(0)	10	(100)	10	(100)	10	(100)	-	

*1) normal (= good)
*2) equal to that the control fishes
*3) poorer than that of control fishes; they swam slowly and their reaction was poor; the conditions of two fishes wasvery poor and they swam upside-down
*4) very poor; their reaction to stimulus was almost non-existant and they swam upside-down.

- test substance solubility: 300 mg/L

RESULTS: CONTROL
- number/percentage of animals showing adverse effects: none
- nature of adverse effects: none

Source : SKW Trostberg AG Trostberg

Test condition : TEST ORGANISMS
- strain: Leuciscus idus
- supplier: P. Eggers
- size, weight, korpulenzfactor: 5.6±0.3 cm, 1.5±0.3 g, 0.9±0.05 g/cm3
- pretreatment: 15 days
- feeding during test: none
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- vehicle, solvent: no solvent was used
STABILITY OF THE TEST CHEMICAL SOLUTIONS:
REFERENCE SUBSTANCE:
DILUTION WATER
- pH: 7.6
- oxygen content: 8.9 mg/L
- holding water: 10 L
TEST SYSTEM
- concentrations: 0, 10, 18, 32, 56, 100, 180 mg/L
- renewal of test solution: none
- exposure vessel type: 10 L test solution in a 12 L all-glass aquaria
- number of replicates, fish per replicate: 1, 10
- test temperature: 20±1°C
- dissolved oxygen: 5.4-8.9 mg/L
- pH: 7.1-7.7
- photoperiod: 12 hr-12 hr light-dark cycle
DURATION OF THE TEST: 48 hr
TEST PARAMETER: mortality
SAMPLING: 0, 2, 24, 48 hr
MONITORING OF TEST SUBSTANCE CONCENTRATION: not determined by chemical analysis

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint
18.02.2001 (52)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hr
Unit : mg/L
Analytical monitoring : yes
EC50 : m = 52
EC100 : m >= 300
Method : OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilization Test"
Year : 1999
GLP : yes
Test substance : other TS: Wako Chemical Co.
Result : RESULTS: EXPOSED
- nominal/measured concentrations:

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percentage of nominal) 0 hr[a)]		48 hr[b)]		Mean[c)]	
Control	n.d.		n.d.		n.d.	
7.68	7.65	(99.6)	7.40	(96.4)	7.52	(98.0)
19.2	19.1	(99.5)	18.3	(95.3)	18.7	(97.4)
48.0	47.1	(98.2)	46.0	(95.9)	46.6	(97.0)
120	119	(99.5)	116	(96.3)	118	(97.9)
300	296	(98.5)	286	(95.4)	291	(96.9)

Remark: n.d.; less than 1.00 mg/L
a); fresh solutions
b); expired solutions
c); The values are expressed at time-weighted means calculated by the following equation:
$(C_0\text{-}C_{48})/(\ln C_0\text{-}\ln C_{48})$
where C_0: the measured concentration at 0 hr
C_{48}: the measured concentaration at 48 hr

effect data (immobilization):
24 hr EiC50 = 112 mg/L (95% c.l. = 87.6-143 mg/L)
48 hr EiC50 = 52 mg/L (95% c.l. = 40.8-67.0 mg/L)
48 hr NOECi = 7.68 mg/L

Nominal concentration (mg/L)	Cumulative number of Immobilized *Daphnia* (Percent immobility) 24 hr		48 hr	
Control	0	(0)	0	(0)
7.68	0	(0)	0	(0)
19.2	0	(0)	1	(5)
48.0	2	(10)	8	(40)
120	9	(45)	19	(95)
300	20	(100)	20	(100)

The value include dead *Daphnia*

RESULTS CONTROL:
RESULTS: TEST WITH REFERENCE SUBSTANCE
- concentrations: K2Cr2O7 pure grade
- results: 48 hr EiC50 = 0.135 mg/L

Source : MOE Japan
Test condition : TEST ORGANISMS
- source/supplier: Sheffield University (United Kingdom)

- age: Juvenile Daphnia magna less than 24 hr old
- feeding in acclimation: Chlorella vulgaris, 0.1-0.2 mgC/day/indivisual
- pretreatment: 2-4 weeks
- feeding during test: none

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- vehicle, solvent: no solvent was used

REFERENCE SUBSTANCE: K2Cr2O7

DILUTION WATER
- source: dechlorinated tap water
- alkalinity: not described
- hardness: 57.5 mg/L (as CaCO3)
- chlorinity: less than 0.02 mg/L (as Cl)
- TSS: none
- pH: 7.8
- oxygen content: saturated with aeration

TEST SYSTEM
- concentrations: 0, 7.68, 19.2, 48.0, 120, 300 mg/L
- renewal of test solution: none
- exposure vessel type: size; 200 ml test solution in a 300 ml tall vessel (8.5 cm diameter, 5.7 cm height)
- number of replicates, individuals per replicate: 4, 5
- test temperature: 20.2-20.3°C
- dissolved oxygen: 7.9-8.8 mg/L
- pH: 7.6-7.7
- intensity of irradiation: room light
- photoperiod: 16 hr-8 hr light-dark cycle

DURATION OF THE TEST: 48 hr

TEST PARAMETER: immobility

SAMPLING: at start and end of test

MONITORING OF TEST SUBSTANCE CONCENTRATION: measured by HPLC

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
18.02.2001 (10)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Type
Species : Selenastrum capricornutum (Algae)
Endpoint : growth inhibition
Exposure period : 72 hr
Unit : mg/L
Analytical monitoring : yes
NOEC : m = 24.4
EC50 : m = 53.7
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1999
GLP : yes
Test substance : other TS: Wako Chemical Co.
Result : RESULTS: EXPOSED
- nominal/measured concentrations:

Nominal concentration (mg/L)	Measured concentration (mg/L) (Percentage of nominal) 0 hr[a)]		72 hr[b)]		Mean[c)]	
Control	n.d.		n.d.		n.d.	
15.3	14.8	(96.5)	15.6	(102)	15.2	(99.4)
24.4	23.8	(97.6)	24.5	(101)	24.2	(99.1)
39.1	39.2	(100)	39.5	(101)	39.4	(101)
62.5	62.1	(99.4)	61.7	(98.7)	61.9	(99.0)

100	98.4	(98.4)	95.6	(95.6)	97.0	(97.0)

Remark: n.d.; less than 1.00 mg/L
a); initial
b); final
c); The values are expressed at time-weighted means calculated by the following equation:
$(C_0-C_{72})/(\ln C_0-\ln C_{72})$
where C_0: the measured concentration at 0 hr
C_{72}: the measured concentaration at 72 hr

- effect data/element values:
area method
EbC50 (0-72 hr) = 53.7 mg/L (95% c.l.: none)
NOECb (0-72 hr) = 24.4 mg/L
rate method
ErC50 (24-48 hr) = 68.2 mg/L (95% c.l.: 59.0-78.8 mg/L)
NOECr (24-48 hr) = 39.1 mg/L
ErC50 (24-72 hr) = 69.3 mg/L (95% c.l.: none)
NOECr (24-72 hr) = 39.1 mg/L

- average cell density of *Selenastrum capricornutum* during 72 hr exposure to 2,4-diamino-6-phenyl-1,3,5-triazine:

Nominal Concentaration	Cell density (x10E+4 cells/ml)			
(mg/L)	0 hr	24 hr	48 hr	72 hr
Control	1.0	4.2	27.6	113.1
15.3	1.0	4.2	29.5	120.0
24.4	1.0	3.6	27.1	117.4
39.1	1.0	3.4	22.8	105.1
62.5	1.0	2.6	7.6	13.7
100	1.0	1.2	1.7	2.5

- growth Inhibition:

Nominal Concentaration (mg/L)	Inhibition area method (0-72 hr) %	Inhibition growth rate (24-48 hr) %	Inhibition growth rate (24-72 hr) %
15.3	-6.15	-4.03	-1.90
24.4	-1.18	-8.63	-6.50
39.1	11.3	-2.03	-4.73
62.5	83.1	43.4	49.6
100	98.1	84.6	78.0

RESULTS: TEST WITH REFERENCE SUBSTANCE
- results: K2Cr2O7 pure grade; EbC50 (0-72 hr) = 0.295 mg/L

Source : MOE Japan

Test condition : TEST ORGANISMS
- strain: ATCC 22662
-source/supplier: American Type Culture Collection
- pretreatment: 3 day
- iniitial cell concentration: 1x10E+4
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- vehicle, solvent: no solvent was used
REFERENCE SUBSTANCE: K2Cr2O7 pure grade
GROWTH/TEST MEDIUM CHEMISTRY: OECD medium
TEST SYSTEM
- exposure vessel type: size; 100 ml medium in a 500 ml conical flask with a cap which allow ventilation
- number of replicates: triplicate
- concentrations: 0, 15.3, 24.4, 39.1, 62.5, 100 mg/L
- test temperature: 24.6-24.9°C

- pH: 7.8-7.9 at start and 8.4-10.3 at end of the test
- intensity of irradiation: 4,400-4,500 lux
- photoperiod: continuous
- shaking: 100 rpm

TEST PARAMETER: cells/ml
MONITORING OF TEST SUBSTANCE CONCENTRATION

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
12.02.2001 (11)

Type
Species : Scenedesmus subspicatus (Algae)
Endpoint :
Exposure period : 72 hr
Unit : mg/L
Analytical monitoring :
EC10 : = 13 mg/L
EC50 : = 22 mg/L
Method : other: Zellvermehrungshemmtest
Year : 1991
GLP : No
Test substance : as prescribed by 1.1-1.4
Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)
Reliability :
14.01.2001 (16)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type :
Species : activated sludge, domestic
Exposure period : 4 hr
Unit : mg/L
EC20 : = 100
Method : ISO DIS 9509 "Method for assessing the inhibition of nitrification of activated sludge microorganisms by chemicals and waste waters"
Year : 1991
GLP : No
Test substance : as prescribed by 1.1-1.4
Source : SKW Trostberg AG Trostberg
21.04.1994 (16)

Type :
Species : Photobacterium phosphoreum (Bacteria)
Unit : mg/L
EC50 : = 210
EC20 : = 80
Method : other: Hemmung der Photolumineszenz
Year : 1991
GLP : No
Test substance : as prescribed by 1.1-1.4
Source : SKW Trostberg AG Trostberg
16.01.2001 (16)

Type :
Species : Pseudomonas putida (Bacteria)
Exposure period : 18 hr
Unit : mg/L
EC10 : = 3.4
Method : other: Zellvermehrungshemmtest (Truebungstest)

Year : 1988
GLP : Yes
Test substance : as prescribed by 1.1-1.4
Remark : Niedrigste Konzentration, bei der eine beginnende Hemmung der Zellvermehrung zu beobachten war.
Source : SKW Trostberg AG Trostberg
Test condition : 25 Grad C
30.01.2001 (37)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type
Species : Daphnia magna (Crustacea)
Endpoint : reproduction
Exposure period : 21 day
Unit : mg/L
Analytical monitoring : Yes
NOEC : m = 1.91 (21 day)
LOEC : m = 3.43 (21 day)
EC50 : m = 5.91 (21 day)
LC50 : m = 13.4 (21 day)
Method : Other: OECD Guide-line 211 "Daphnia sp., Reproduction Test"
Year : 1999
GLP : Yes
Test substance : Other TS: Wako Chemical Co.
Result : RESULTS: EXPOSED
- nominal/measured concentrations:

Nominal concentration	Measured concentration (mg/L) (Percent of nominal)						Time-weighted mean [c]
(mg/L)	0day[a]	2day[b]	10day[a]	13day[b]	15day[a]	17day[b]	(mg/L)
control	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1.91	1.91 (100)	1.88 (98.2)	1.85 (97.1)	1.83 (96.0)	1.77 (92.8)	1.75 (91.7)	1.83 (96.1)
3.43	3.47 (101)	3.40 (99.0)	3.33 (97.1)	3.31 (96.5)	3.19 (93.1)	3.14 (91.7)	3.31 (96.5)
6.17	6.14 (99.6)	5.96 (96.7)	5.93 (96.0)	5.97 (96.7)	5.84 (94.7)	5.75 (93.2)	5.93 (96.2)
11.1	11.0 (99.3)	10.8 (97.1)	10.7 (96.2)	10.6 (95.5)	10.3 (93.0)	10.3 (92.8)	10.6 (95.7)
20.0	20.0 (100)	19.3 (96.5)	-	-	-	-	19.7 (98.3)

Remark: n.d.; less than 0.200 mg/L
a); fresh solutions
b); expired solutions
c); The values are expressed at time-weighted means calculated by the following equation:
$\{2(C_0-C_2)/(\ln C_0-\ln C_2)+3(C_{10}-C_{13})/(\ln C_{10}-\ln C_{13})+2(C_{15}-C_{17})/(\ln C_{15}-\ln C_{17})\} / 7$
where C_x: the measured concentration at X-day
$\ln C_x$: the natural logarithm of C_x

- effect data (reproduction):
  21 day LC50 = 13.4 mg/L (95% c.l.: 6.17-20.0 mg/L)
  21 day EC50 = 5.91 mg/L (95% c.l.: 5.48-6.37 mg/L)
  21 day NOEC = 1.91 mg/L
  21 day LOEC = 3.43 mg/L
- concentration/response curve:
- cumulative reproduction:

(1) Cumulative number of dead parental *Daphnia* and mortality after exposure of 21day

Nominal concentration (mg/L)	Number of dead parentals	Mortality (%)	Comment
control	0	0	at 21th day
1.91	0	0	at 21th day
3.43	0	0	at 21th day
6.17	0	0	at 21th day
11.1	2	20	at 17th day
20.0	10	100	at 5th day

(2) mean days required to first brood production during exposure to 2,4-diamino-6-phenyl-1,3,5-triazine:

Nominal concentration (mg/L)	Mean (day)
control	8.0
1.91	8.0
3.43	8.0
6.17	8.4
11.1	9.0
20.0	-

(3) mean cumulative number of juveniles produced per adult during exposure:

Nominal concentration (mg/L)	Mean (day)
control	148
1.91	136
3.43	101
6.17	76
11.1	48
20.0	0

RESULTS: TEST WITH REFERENCE SUBSTANCE
- results: K2Cr2O7 pure grade :48 hr EiC50 = 0.135 mg/L (immobility data)

Test condition : TEST ORGANISMS
- source/supplier: Sheffield University (United Kingdom)
- age: juveniles less than 24 hr old
- feeding in culture: Chlorella vulgaris, 0.1-0.2 mgC/day/individual
- pretreatment: 2-4 weeks
- feeding during test: Chlorella vulgaris, 0.1-0.2 mgC/day/individual

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- vehicle, solvent: no solvent was used

REFERENCE SUBSTANCE: K2Cr2O7

DILUTION WATER
- source: dechlorinated tap water
- alkalinity: 33.0 mg/L
- hardness: 42.4-49.6 mg/L (as CaCO3)
- chlorinity: less than 0.02 mg/L (as Cl)

TEST SYSTEM
- concentrations: 0, 1.91, 3.43, 6.17, 11.1, 20.0 mg/L
- renewal of test solution: 3 times a week
- exposure vessel type: size; 80 ml test solution in a 100 ml beaker
- number of replicates, individuals per replicate: 10, 10
- test temperature: 20.0-20.5°C
- dissolved oxygen: 8.5-8.8 mg/L
- pH: 7.4-7.8
- intensity of irradiation: room light (less than 1200 lux)
- photoperiod: 16 hr-8 hr light-dark cycle

DURATION OF THE TEST: 21 day
TEST PARAMETER:
number of juveniles produced per adult during exposure
number of dead parental *Daphnia magna* per day during exposure
SAMPLING: 6 times during test
MONITORING OF TEST SUBSTANCE CONCENTRATION: measured by HPLC

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
12.02.2001 (12)

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

Remark : Stubenfliege (Musca domestica):
LC100 = 0.25% (entspricht ca. 2500 mg/L)
Konzentration, die die Verpuppung vollstaendig hemmt;
Verabreichung im Fliegenfutter bzw. Zucker
Source : SKW Trostberg AG Trostberg
05.08.1993 (3)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Species : Rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 5
Vehicle : CMC
Value : = male, 933 mg/kg bw; female, 1231 mg/kg bw
Method : OECD Guide-line 401 "Acute Oral Toxicity"
Year : 1997
GLP : Yes
Test substance : Other TS: NIPPON SHOKUBAI CO.,LTD., purity: 98%
Remark : Deaths occurred in both sexes of the 1000 and 2000 mg/kg groups from 2 days to 6 days. Treatment-related clinical signs were noted as follows: hypoactivity, staggering gait, bradypnea, a prone position, lacrimation, salivation, a lateral position, soiled perinaris, soiled perioculus, deep yellow urine and soiled lower abdomen. Decrease of body weight and/or depression of body weight gain were observed in all treated groups. In the dead animals, a) thickening of the mucosa in the forestomach at a female of 2000 mg/kg, b) retention of dark green urine in the urinary bladder at 3 males of 1000 mg/kg and 2 males and 3 females of 2000 mg/kg, c) atrophy of the spleen at a male and female of 1000 mg/kg and 2 males and a female of 2000 mg/kg, d) white coloration of the thymus at a male of 1000 mg/kg and a male and female of 2000 mg/kg, and e) atrophy in the thymus at a male of 2000 mgkg were noted at necropsy. Histopathological examination showed edema of the submucosal tissue in the forestomach and atrophy in the thymus and the spleen. There were no histopathological abnomalities in the urinary bladder. In the surviving animals, white spots of the mucosa in the forestomach were noted at necropsy at a female of 2000 mg/kg and histopathological examination showed hyperplasia of squamous epithelial cells.
Result : MORTALITY:
- number of deaths at each dose:

Concentration w/v% *	mg BG /kg bw	Number of animals per sex	Number of deaths male	Number of deaths female
2.5	250	5	0	0
5.0	500	5	0	0
10.0	1000	5	3	1
20.0	2000	5	3	4

BG: benzoguanamine (2,4-diamino-6-phenyl-1,3,5-triazine)
* at 10 ml/kg bw

Source MHW Japan
Test condition : TEST ORGANISMS:
- source: Japan Chales Liver Co.
- age: 5 weeks old for the males and females
- weight at study initiation: 165.7-183.0 g for males and 126.4-136.6 g for females
- number of animals/group: 5 per male and female/dose
ADMINISTRATION:
- doses: 0, 250, 500, 1000, 2000 mg/kg
- volume administered or concentration: 10 ml/kg
- post dose obsevation period: 15 days
Conclusion : The lowest LD_{50} value by oral exposure routes in rats was 933 mg/kg (male) and 1231 mg/kg (female). The major toxicity was edema in the forestomach.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
13.02.2001 (28)

Type : LD50
Species : Rat
Strain : Wistar
Sex : male/female
Number of animals : 5
Vehicle :
Value : = 1470 mg/kg bw
Method : other: not specified
Year : 1972
GLP : No
Test substance : as prescribed by 1.1-1.4
Remark : In all dose groups, the affected animals became sluggish and gradually lost consciousness. Some animals showed these symptoms for these days. Deaths occured only during the first these days. After that period, all surviving animals recovered rather quickly and at the end of the 14-day period, they looked quite healthy. No abnormalities were seen in the survivors at necropsy.
Result : MORTALITY:
- number of deaths at each dose:

ml Suspension /kg bw	mg BG /kg bw	Number of animals per sex	Number of deaths male	Number of deaths female
6	1200	5	1	1
7	1400	5	3	3
8	1600	5	1	3
9	1800	5	4	5

BG: benzoguanamine (2,4-diamino-6-phenyl-1,3,5-triazine)

Source : SKW Trostberg AG Trostberg
Test condition : ADMINISTRATION:
- form: A suspension of 20% (w/v) 2,4-diamino-6-phenyl-1,3,5-triazine in a 0.5% aqueous solution of carboxy methyl cellulose was administered via stomach tube.

30.01.2001 (4)

Type : LD50
Species : other: redwing black bird
Strain :
Sex :
Number of animals :
Vehicle :
Value : = 100 mg/kg bw
Source : DIALOG FILE: DOSE (2000)
12.02.2001 (45)

Type : LD50
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Value : = 1050 mg/kg bw
Source : DIALOG FILE: DOSE (2000)
12.02.2001 (54)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 5
Vehicle : other: clean dry filtered compressed air
Exposure time : 4 hr
Post obs. period : 14 day
Value : = 2.932 mg/L
Method : OECD Guide-line 403 "Acute Inhalation Toxicity"
Year : 1989
GLP : yes
Test substance : as prescribed by 1.1-1.4
Result : STATITICAL RESULT:
- death: Deaths occurred in male and female groups at levels of 2.489 mg/L and above. Overall there was a dose-related relationship between mortality and chamber concentration. all deaths occurred on days one and two of the study.
- body weight gain: Body weght losses occurred in the first week of the study in exposed groups, with a degree of recovery in the second week.

TOXIC EFFECTS:
- clinical chemistry: Marked clinical signs without any specific signs of local lung toxicity were first observed on the day of exposure. The signs included lethargy, ataxia and prostation sometimes accompanied by panting.
- histopathology: There was no treatment-related effect on lung weight in survivors, and only occational increases in lung weight in decedents.
- necroscopy: Animals surviving to termination were unremarkable macrocopically. The only changes in decedents were non-specific pulmonary changes.

Sex	Concentration mg/L	mortality on day 1	2	3-15	Mortality ratio days 1-15
Male	control				0 / 5
	0.687				0 / 5
	1.400				0 / 5
	2.489		1		1 / 5
	3.365		3		3 / 5
Female	control				0 / 5
	0.687				0 / 5
	1.400				0 / 5
	2.489	1	2		3 / 5
	3.365	3			3 / 5

Source : SKW Trostberg AG Trostberg
Test condition : EXPOSURE
- dose: 0.687, 1.400, 2.489, 3.365 mg/L

NOMINAL CONCENTRATION
- concentration: 2.726, 6.464, 13.947, 20.167 mg/L

Test substance : ADMINISTRATION:
- type of exposure: head only
- particle size: a mean mass median aerodynamic diameter; 5.97 to 11.33 um

Conclusion : The LC_{50} value by inhalation exposure was 2.932 mg/L (4 hr, rat).
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
30.01.2001 (14)

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Species : mouse
Strain :
Sex :
Number of animals :
Vehicle :
Route of admin. : i.p.
Exposure time :
Value : = 100 mg/kg bw
Method :
Year :
GLP :
Test substance : as prescribed by 1.1-1.4
Source : SKW Trostberg AG Trostberg
Reliability : (4) not assignable
14.01.2001 (1)

Type : LD50
Species : mouse
Strain :
Sex :
Number of animals :
Vehicle :
Route of admin. : i.p.
Exposure time :
Value : = 545 mg/kg bw
Method :
Year : 1973
GLP : no
Test substance : as prescribed by 1.1-1.4
Source : SKW Trostberg AG Trostberg
Reliability : (4) not assignable
14.01.2001 (55)

Type : LD50
Species : mouse
Strain :
Sex :
Number of animals :
Vehicle :
Route of admin. : i.p.
Exposure time :
Value : = 320 mg/kg bw
Source : DIALOG FILE:DOSE(2000)
12.02.2001 (8)

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration :
Exposure : semi-occlusive
Exposure time : 4 hr
Number of animals : 3

PDII : 0
Result : Not irritating, Primary irritating index = 0
EC classification :
Method : OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year : 1988
GLP : yes
Test substance : as prescribed by 1.1-1.4
Remark : Applikationsmenge: 500 mg; 4 hr Einwirkzeit, semi-okklusiv
Result : EFFECTS: No signs of irritation and systematic toxicity were observed in any of the treated rabbits.
Source : SKW Trostberg AG Trostberg
Test condition : TEST ANIMALS:
- strain: albino rabbits
- sex: female
- source: New Zealand white
ADMINISTRATION/EXPOSURE
- vehicle: moistened wit Milli-RO water
Reliability : (1) valid without restriction
30.01.2001 (40)

5.2.2 EYE IRRITATION

Species : other: Rabbit (n = 3)
Concentration :
Dose : 94 mg
Exposure Time :
Comment :
Number of animals : 3
Result : Mildly irritating, Draize score = 4 (1 hr)
EC classification :
Method : Directive 84/449/EEC, B.5 "Acute Toxicity (eye irritation)"
Year : 1988
GLP : Yes
Result :

Interpretation of the irritation

Animal No	Body wt (g)	Observation	1 hr	1 day	2 day	3 day
1	3,520	Cornea	0	0	0	0
		Iris	0	0	0	0
		Conjunctive	2	2	2	0
		Subtotal	2	2	2	0
2	3,503	Cornea	0	0	0	0
		Iris	0	0	0	0
		Conjunctive	6	2	2	0
		Subtotal	6	2	2	0
3	3,470	Cornea	0	0	0	0
		Iris	0	0	0	0
		Conjunctive	4	2	2	0
		Subtotal	4	2	2	0
		Total	12	6	4	0
		Mean total	4.0	2.0	1.3	0.0

Test substance : as prescribed by 1.1-1.4
Remark : In all three animals only the conjugativae was affected. All effects were reversible within 72 hr (3 day). No effects on the cornea or iris were observed in the treated animals. Treatment of the eyes with fluorescein 24 hr after instillation of the test substance did not reveal any corneal epithelial damage. No signs of systemic toxicity were observed.
Source : SKW Trostberg AG Trostberg

Conclusion : The test substance should be classified as mildly irritating following the scheme of Kay and Calandra. According to the EEC criteria for classification and labelling, the test substance need not to be labelled as an eye irritant.
Reliability : (1) valid without restriction
30.01.2001 (39)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type : OECD TG 408
Species : rat
Sex : both
Strain : Sprague-Dawley
Route of admin. : oral (dietary)
Exposure period : 90 day
Frequency of treatment : daily
Post obs. Period : none
Doses : dietary concentration 0, 25, 250, and 2000 ppm (equivalent to mean achieved dosages of 0, 1.9, 19.0, and 173.0 mg/kg/day)
Control group : yes
NOAEL : = 19 mg/kg bw
Method : OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year : 1993
GLP : Yes
Test substance : as prescribed by 1.1-1.4
Result : SUMMARY
- At the low dose level, no treatment related effects were observed. And at middle dose level, no ill-effects were shown.
Treatment related changes were only observed in the high dose group. However, the minimal effects seen at 250 ppm were considered unlikely to be indicative of any damage to the health of the animals and a "No Observable Adverse Effect Level" (NOAEL) has been achieved at 250 ppm (equivalent to 19 mg/kg/day).
ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX
- Clinically obsevations
Clinically observable signs of toxicity were detected for high dose animals of
either sex from the end of the first week of treatment. Signs of toxicity included hunched posture and pilo-erection together with extremely isolated incidents of lethargy.
– number of deaths at each dose: no deaths during the study
TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- body weight gain: High dose animals of either sex showed a substantially lower gain in body-weight than controls during the treatment period.
- food consumption: The food intake of high dose animals was lower than that of controls during the treatment period, although females appeared less adversely affected than males.
- ophthalmoscopic examination: No treatment-related ocular were detected.
- blood chemistry: High dose animals of either sex showed a slight but statistically significant increase in plasm alanine aminotransferase and bilirubin levels compared with controls. Plasma sodium concentration was also reduced in high dose males although this was considered to be of dubious toxicological significance in the absense of a concombinant effect on plasma chloride.
Middle and low dose animals showed no treatment-ralated changes.

- hematology: No toxicologically significant change were detected.
- organ weights: High dose females showed a statistically significant increase in liver weight, relative to body weight, compared with controls. Absolute liver weights were also increased for these animals although statistical significance was not achieved. A possible treatment-related increase in relative liver and adrenal weight was also identified for high dose males.
Intemediate and low dose animals showed not reatment-related organ weight changes.
- gross pathology:
- necroscopy: several high dose animals of either sex showed pale adrenals and/or a darkened liver at terminal kill whilst two of the females also had pale kidneys.
- histopathology: Treatment-related morphological changes were observed in the liver,spleen, kidneys, pancreas and adrenal glands. High dose animals showed centrilobular hepatocyte enlargement, an increased severity of splenic extramedullary hemopoiesis, hypertrophy and vacuolation of adrenal zona glomerulosa cells, and degeneration of pancreatic exocrine cells together with associated inflammatory cell infiltrates. An increased severity and/or incidence of hemosiderin pigmnent accumulation was also observed in both the kidneys and the spleen of high dose animals of either sex. At the middle dose level, the sole treatment-related change was confined to males and identified as an increase in the severity of hemosiderin pigment accumulation in the spleen.
- histopathological findings
summary incidence of spleen

Animals	Findings	Dose group (mg/kg/day)			
		control	1.9	19	173
Male	Extramedullary haemopoiesis				
	(minimal)	6	8	5	2
	(slight)	4	2	5	5
	(moderate)	0	0	0	3
	Pigment deposition				
	(minimal)	1	1	0	0
	(slight)	9	6	4	0
	(moderate)	0	3	6	10
	(marked)	0	0	0	0
Female	Extramedullary hemopoiesis				
	(minimal)	9	8	8	1
	(slight)	1	2	2	8
	(moderate)	0	0	0	1
	Pigment deposition				
	(minimal)	0	2	0	0
	(slight)	5	3	5	0
	(moderate)	5	3	5	1
	(marked)	0	2	0	9

No treatment-related morphological changes were observed either for middle dose females or for low dose animals of either sex.
No toxicologically significant macroscopic abnomalities were detected at the remaining dose levels.

Remark : In the 90-day feeding study of rats at 0, 1.9, 19.0, and 173.0 mg/kg/day [OECD TG 408], the body weight gain was decreased in the high dose group. In the histopathological examination, centrilobular hepatocyte enlargement, an increased severity of extramedullary hemopoiesis in the spleen and hemosiderin pigment accumulation in the kidneys and the spleen, hypertrophy and vacuolation of adrenal zona glomerulosa cells, and degeneration of pancreatic exocrine cells together with associated inflammatory cell infiltrates were observed in the high dose group. At the

mid dose, the severity of hemosiderin pigment accumulation in the spleen was also increased moderately in males. This change in the spleen was considered not to be adverse effect because no other changes were observed at this dose level. Therefore, the NOAEL in this study was considered to be 19 mg/kg/day.

Source : SKW Trostberg AG Trostberg
Test condition : TEST ORGANISMS
- age: 5-6 weeks old
- weight at study initiation: 185-238 g for males; 145-192 g for females
- number of animals: 10 per sex per dose group

ADMINISTRATION / EXPOSURE
- type of exposure: dietary
- post exposure period: none
- vehicle: basal laboratory diet
- doses:

Group no.	Number of animals male/famale	Dietary concentration ppm	Mean achieved dose mg/kg/day
1	10/10	0 (control)	0.0
2	10/10	25	1.9
3	10/10	250	19
4	10/10	2000	173.0

CLINICAL OBSERVATIONS AND FREQUENCY:
- clinical signs: once daily
- body weight: weekly intervals
- food consumption: weekly intervals
- water consumption: daily
- ophthalmoscopic examination: before administrtion and control diet and before termination of treatment
- hematology: at the end of study
- biochemistry: at the end of study

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
28.04.2001 (41)

Type : OECD combined study TG 422, combined repeat dose and reproductive/developmental toxicity screening test
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : oral (gavage)
Exposure period : males; 49 days, females; from 14 days before mating to day 3 of lactation (39-54 days)
Frequency of treatment : one administration/day
Post obs. period : none
Doses : 0, 4, 20, 100 mg/kg/day
NOAEL : = 20 mg/kg/day
Control group : yes, concurrent vehicle
Method : OECD combined repeat dose and reproductive/developmental toxicity screening test
Year : 1997
GLP : yes
Test substance : other TS: NIPPON SHOKUBAI CO., LTD., purity 98%

Result : NOAEL: 20 mg/kg/day in both sexes
STATISTICAL RESULTS:
- death: Deaths occured to one male and one female receiving 100 mg/kg.
- body weight gain: Depression of body weight and decrease of food consumption were observed in both sexes of the 20 mg/kg or more groups.

- Body weight changes for male rat

Dose level			Day					
mg/kg/day	Unit		1	11	22	29	39	49
0	Weight	g	391	427	455	477	502	534
	Ratio*	%	(100)	(100)	(100)	(100)	(100)	(100)
4	Weight	g	384	420	455	477	505	526
	Ratio*	%	(98)	(98)	(100)	(100)	(101)	(99)
20	Weight	g	384	406	438	455	473	491
	Ratio*	%	(98)	(95)	(96)	(96)	(94)	(92)
100	Weight	g	384	384	406	420	434	434
	Ratio*	%	(98)	(90)	(89)	(88)	(87)	(81)

:* Ratio = Weight(n)/Weight(0)x100; the toxicological meaning are less profound when weight change ratio (Ratio) during treatment period compared by (control dose level = 100%) are not less than 90%.

- hematology: Hematological examination showed decreases in the erythrocyte counts and hematocrit values, and increase in the reticulocyte counts in males of the 100 mg/kg group.
- blood chemistry: Blood chemical examination showed increases in albumine, A/G ratio, GOT, GPT, total bilirubin, total cholesterol and phospholipids, and decrease in triglycerides in males of the 100 mg/kg group. Absolute and relative liver weights were increased in males of the 100 mg/kg group.
- histopathology: Histopathological examination revealed centrilobular hypertrophy of the hepatocytes in both sexes given 100 mg/kg. Histopathological examination of dead animals revealed cellular infiltration of neutrophils and granulation in the ileum, atrophy and hemorrhage in the thymus, necrosis of the zona fasciculata to zona reticularis in the adrenals, erosion in the glandular stomach, and edema in the lung and atrophy in the spleen.

Source : MHW Japan

Conclusion : In the OECD combined repeat dose and reproductive/ developmental toxicity screening test by gavage [OECD TG 422], this substance was given at 0, 4, 20 and 100 mg/kg/day to rats for at least 39 days. One male and female rats died, and the body weight gain was decreased in the 100 mg/kg group. Hematological and blood chemical examination showed decreases in the erythrocyte counts and hematocrit values with increased reticulocyte counts, and increases of GOT, GPT and total bilirubin with centrilobular hypertrophy of hepatocyte in the 100 mg/kg group. The severity of these changes, however, were toxicologically not significant or adaptive change, except increase in reticulocyte count whose significance was equivocal.
The NOAEL in this study was considered as 20 mg/kg/day.

Test condition : TEST ORGANISMS
- age: 8 weeks
- weight at study initiation: 347-432 g for males; 220-255 g for females
- number of animals: 12 per sex per dose group
ADMINISTRATION / EXPOSURE
- duration of exposure:
male; 14 days premating, 35 days including 14 days for mating
female; 14 days premating, 22 days of gestation after impregnation 4 days of lactation
- type of exposure: oral feed by tube to stomach
- vehicle: carboxy methyl cellulose - sodium solution
- concentration in vehicle: 0.5w/v %

- total volume applied: 2.5 ml/kg of 0.16%, 0.8%, 4w/v%
- doses: 0, 4, 20, 100 mg/kg b.w.
CLINICAL OBSERVATIONS AND FREQUENCY:
- clinical signs: more than twice a day
- mortality: more than twice a day
- body weight and food consumption
male; twice a week during administration
female; twice a week till end of mating, 0, 4th, 7th, 10th, 14th, 17th during impregnation, 0, 4th during lactation
- water consumption: none
- hematology, boichemistry and urinalysis: for only male at time of necropsy
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- macroscopic: thymus, spleen, liver, adrenal, kidney, testes
Preliminary examination: at 300 mg/kg/day group, death occurs within 14 days

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.02.2001 (29)

Type
Species : hen
Sex : no data
Strain : no data
Route of admin. : oral feed
Exposure period : 6 day
Frequency of treatment : taeglich
Post obs. period : Keine
Doses : 3 % im Futter
Control group :
Method :
Year : 1975
GLP : No
Test substance : as prescribed by 1.1-1.4
Remark : Bei den untersuchten Tieren handelte es sich um Kueken.
Result : Mortalitaet: 4/5 Tieren
Gewichtsverlust, Appetitlosigkeit und Magengeschwuere wurden beobachtet.
Source : SKW Trostberg AG Trostberg
30.01.2001 (22)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Salmonella typhimurium (TA100, TA98, TA1535, TA1537); Escherichia coli (WP2uvrA)
Concentration : -S9: 0, 156, 313, 625, 1250, 2500, 5000 ug/plate;
+S9: 0, 156, 313, 625, 1250, 2500, 5000 ug/plate
Cycotoxic conc. : Toxicity was not observed up to 5000ug/plate in five strains with or without S9mix.
Metabolic activation : with and without
Result : negative
Method : other: OECD Test Guidelines 471 and 472 "Genetic Toxicology (Salmonella typhimurium and Escherichia coli)
Year : 1997
GLP : Yes
Test substance : other TS: NIPPON SHOKUBAI CO., LTD., purity: 98%
Result : GENOTOXIC EFFECTS:
- with metabolic activation:

Salmonella typhimurium TA100, TA1535, TA98, TA537; negative
Escherichia coli WP2 uvrA; negative
- without metabolic activation:
Salmonella typhimurium TA100,TA1535,TA98,TA537; negative
Escherichia coli WP2 uvrA; negative
PRECIPITATION CONCENTRATION:
At the dose level more than 2500 ug/plate, visible precipitation was shown at the end of exposure period.

Source : MHW Japan
Test condition : SYSTEM OF TESTING
- metabolic activation system: S9 from rat liver,induced with phenobarbital and 5,6-benzoflavone
ADMINISTRATION:
- number of replicates: 2
- plates per test: 3
- application: pre-incubation
- positive control groups and treatment:
-S9mix; 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98, WP2), sodium azide (TA1535) and 9-aminoacridine hydrochloride (TA1537)
+S9mix; 2-aminoanthracene (five strains)
- solvent: DMSO
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.02.2001 (26)

Type : Other: Genmutation an Prokaryonten (Ames-Test)
System of testing : Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration : experiment 1; 8, 40, 200, 1000, 5000 ug/plate
experiment 2; 1000, 2000, 3000, 4000, 5000 ug/plate
Cycotoxic conc. : no signs of toxicity were observed up to concentrarions 5000 ug/plate in the presence and absence of metabolic activation (S9mix)
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year : 1988
GLP : yes
Test substance : as prescribed by 1.1-1.4
Result : GENOTOXIC EFFECTS:
- with metabolic activation: negative
- without metabolic activation: negative
FREQUENCY OF EFFECTS:
PRECIPITATION CONCENTRATION: Precipitation of test substance were observed during treatment at 4000 and 5000 ug/plate.
Source : SKW Trostberg AG Trostberg
Test condition : SYSTEM OF TESTING:
- metabolic activation sysytem: mammalian liver post-mitochondorial fraction (S-9) prepared from male Winstar rats.
ADMINISTRATION:
- application: vehicle: sterile analytical grade anhydrous dimethyl sulphoxide (DMSO)
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
04.05.2001 (25)

Type : Chromosomal aberration test
System of testing : CHL/IU cell
Concentration :
Cycotoxic conc. :
Metabolic activation : with and without
Result : positive

Method : OECD Guide-line 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"
Year : 1997
GLP : yes
Test substance : other TS: NIPPON SHOKUBAI CO.,LTD. Osaka
Result : GENOTOXIC EFFECTS:
- with metabolic activation:
clastogenicity; positive: polyploidy; negative
- without metabolic activation:
clastogenicity; positive: polyploidy; positive
FREQUENCY OF EFFECTS:
PRECIPITATION CONCENTRATION: At the concentration with the mark P, visible precipitation was shown at the end of exposure period.
-S9mix (24 and 48 hr continuous treatment); 0, 100, 200, 400P, 800P ug/ml
-S9mix (short-term treatment); 0, 1250P, 2500P, 5000P ug/ml
+S9mix (short-term treatment); 0, 19.5, 39.1, 78.1, 156P ug/ml
-S9mix (24 hr continuous treatment, additional test); 0, 300, 400P, 500P, 600P, 700P, 800P, 900P ug/ml
+S9mix (short-term treatment, additional test); 0, 60, 80, 100P, 120P, 140P, 160P ug/ml
-S9mix (48 hr continuous treatment, confirmative test); 0, 200, 400P, 800P, 1600P ug/ml
MITOTIC INDEX:
CYTOTOXIC CONCENTRATION: lowest concentration producing cytogenetic effects *in vitro*;
- with metabolic activation (short-term tratment):
78.1 ug/ml (abstructural abnormality)
- without metabolic activation (48 hr continuous treatment-24 hr recovery time): 800 ug/ml (polyploidy)
TEST-SPECIFIC CONFOUNDING FACTORS:
STATISTICAL RESULTS: Structural chromosomal aberrations were induced under the following conditions: 48 hr continuous treatment (0.2, 0.4, and 0.8 mg/ml, 11.0, 35.5 and 29.1%); short-term treatment with an S9mix (0.0781 mg/ml, 41.5%). An additional test was conducted with short-term treatment with an S9mix and 24 hr continuous treatment, because structural chromosomal aberrations were induced at only one dosage and the frequency of structural aberrations was from 5% to less than 10%. As a result, structural chromosomal aberrations were induced dose-dependently.
There were many metaphase that showed c-mitosis at the dosage of 0.8 mg/ml for 48 hr continuously treatment, and some spreads showed polyploidy. Therefore a confirmative examination was conducted. Chromosome preparations were made after 24 hr recovery subsequent to 48 hr exposure. As a result, polyploidy was induced dose-dependently (0.8 and 1.6 mg/ml, 11.5 and 14.5%). Data was summarized in Appendix 8.
Appendix : 8. Chromosamal aberration test on CHL cells *in vitro*
Source : MHW Japan
Test condition : SYSTEM OF TESTING
- deficiences/proficiences:
- methabolic activation system: S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone
- no. of metaphases analyzed:
ADMINISTRATION:
- dosing:
-S9mix (24 and 48 hr continuous treatment); 0, 100, 200, 400, 800 ug/ml
-S9mix (short-term treatment); 0, 1250, 2500, 5000 ug/ml
+S9mix (short-term treatment); 0, 19.5, 39.1, 78.1, 156 ug/ml
-S9mix (24 hr continuous treatment, additional test); 0, 300, 400, 500, 600, 700, 800, 900 ug/ml
+S9mix (short-term treatment, additional test); 0, 60, 80, 100, 120, 140,

160 ug/ml
-S9mix (48 hr continuous treatment, confirmativ test); 0, 200, 400, 800, 1600 ug/ml
- plates/test: 2
- application:
- positive control groups:
-S9mix (24 and 48 hr continuous treatment); Mitomycin C
-S9mix (short-termtratment); cyclophosphamide
+S9mix (short-termtratment); cyclophosphamide
- solvent: DMSO

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
30.04.2001 (27)

Type : Chromosomal aberration test
System of testing : Human lymphocytes
Concentration : 78.125, 156.25, 312.5, 625, 1250 ug/ml and additionally 2500 ug/ml for the 30 hr cell harvest without metabolic activation
Cycotoxic conc. :
Metabolic activation : with and without
Result : negative (with metabolic activation)
negative within the solubility limit (without metabolic activity)
positive above solubility limit (without metabolic activity)
Method : other: OECD Guid-line 473 and Directive. 84/449, B.10 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"
Year : 1994
GLP : yes
Test substance : as prescribed by 1.1-1.4
Remark : All negative (solvent) controls gave frequncies of cells with aberrations within the range expected for normal Human lymphocytes. All the positive control treatments gave statistically significant increases in the frequncy of cells with aberrations indicating the satisfactory perfomance of the test and of the activity of the metabolising system.
Result : PRECIPITATION CONCENTRATION: A precipitate of test substance was observed at and above a final concentration of 625 ug/ml after addition of the test material solution to the culuture media.
TEST-SPECIFIC CONFOUNDING FACTORS:
STATISTICAL RESULTS: Test substance did not induce chromosomal aberrations at doses within the solibility limit of the test substance. It produced a statistically significant but quite modest increase in the frequency of cells with chromosomal aberrations only at dose levels exceeding the solubility limit in the absense of a liver enzym metabolizing sysytem. Data was summarized in Appendix 8.
Appendix : 8. Chromosamal aberration test on Human lyphocytes *in vitro*
Source : SKW Trostberg AG Trostberg
Test condition : SYSTEM OF TESTING
- species/cell type: Human lymphocytes
- metabolic activation system: S9mix prepared from the livers of male Sprague-Dawley rats, after induction with Aroclor 1254.
ADMINISTRATION:
- pre-incubation time:
with metabolic activation: 4 hr exposure and with cell harvest after 20 and 30 hr.
without matabolic acvation: continuous exposure with cell harvest after 20 and 30 hr.
- positive control groups:
-S9mix; 500 ug/ml ethyl methanesulphonate
+S9mix; 25 ug/ml cyclophosphamide
- solvent: DMSO
DESCRIPTION OF FOLLOW UP REPEAT STUDY:
CRITERIA FOR EVALUATING RESULTS:

Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
04.05.2001		(42)

Type	:	Mammalian cell gene mutation assay
System of testing	:	Mouse lymphoma cells, L5178
Concentration	:	up to 2500 ug/ml
Cycotoxic conc.	:	no signs of toxicity were observed up to concentrarions 2500 ug/ml in the presence and absence of metabolic activation (S9mix)
Metabolic activation	:	with and without
Result	:	negative within the solubility limit (with metabolic activity) positive above the solubility limit (with metabolic activity) negative (without metabolic activity)
Method	:	OECD Guide-line 476 "Genetic Toxicology: In vitro Mammalian Cell Gene Mutation Tests"
Year	:	1994
GLP	:	yes
Test substance	:	as prescribed by 1.1-1.4
Result	:	PRECIPITATION CONCENTRATION: at and above 625 ug/ml STATISTICAL RESULTS: This substance produced no statistically significant increase in the frequncy of mutant colonies, at dose levels at which this substance was soluble, in the presence or absence of metabolic activation, in both the first and second experiment. At 625 ug/ml for the first experiment and 1250 ug/ml for the second expriment, a small but significant increase in the frequncy of mutant colonies was observed only in the presence of metabolic activation. The induced colonies were small ones, suggesting a clastogenic potential of the test material. However, the increase in the frequency of mutant colonies observed at doses above the solubility limit was not considered to be of toxicological significance. In conclusion, benzoguanamine (2,4-diamino-6-phenyl-1,3,5-triazine) was not genotoxic at doses within the solubility limit. Data was summarized in Appendix 8.
Appendix	:	8. Chromosamal aberration test on Mouse lymphoma cells (L5178) *in vitro*
Source	:	SKW Trostberg AG Trostberg
Test condition	:	SYSTEM OF TESTING - species/cell type: the L5178 TK +/- Mouse lymphoma cell line - metabolic activation system: S9mix prepared from the livers of males Sprague-Dawley rats after induction with Aroclor1254 ADMINISTRATION: - dosing: experiment 1: 0, 78.1, 156.25, 312.5, 625, 1250 ug/ml experiment 2: 0, 156.25, 312.5, 625, 1250, 2500 ug/ml - number of replicates: 2 - positive and negative control groups and treatment: negative control: DMSO positive control: -S9mix; ethylmethanesulphnate +S9mix; cyclophosphamide
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
04.05.2001		(43)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	NMRI
Route of admin.	:	oral (gavage)
Exposure period	:	24 hr, 48 hr

Doses : male mice; 75, 150, 300 mg/kg b.w.
female mice; 50, 100, 200 mg/kg b.w.
Result : negative
Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 2000
GLP : Yes
Test substance : As prescribed by 1.1-1.4
Result : STATISTICAL RESULTS:
- The highest dose (300 mg/kg for males and 200 mg/kg b.w. for females) was estimated by five pre-experiments to the suitable since higher concentrations were lethal. After treatment with the test item the number of NCEs was not substantially increased as compared to the mean value of NCEs of the vehicle control thus indicating that this substance at the indicated concentrations had no cytotoxic effectiveness in the bone marrow.
There was no biologically and statistically relevant enhancement in the frequency of the detected micronuclei after administration of the test item at any dose level or sampling time as compared to vehicle controle. 40 mg/kg b.w. cyclophosphamide administered orally was used as positive control which showed a substantial increase of induced micronucleus frequency.

- micronucleus test results

(A) Male animals

Test group	Dose mg/kg b.w.	Sampling time (hr)	Sampling micronuclei (%)	NCEs per 2000 PCEs
vehicle	0	24	0.02	1566
BG	75	24	0.08	1562
BG	150	24	0.09	1814
BG	300	24	0.02	1582
CP	40	24	1.11	2033
vehicle	0	48	0.01	1694
BG	75	48	0.02	1639
BG	150	48	0.08	1795
BG	300	48	0.07	1755
vehicle	0	72	0.03	1610
BG	75	72	0.04	1417
BG	150	72	0.03	1549
BG	300	72	0.02	1645

(B) Female animals

Test group	Dose mg/kg b.w.	Sampling time (hr)	Sampling micronuclei (%)	NCEs per 2000 PCEs
vehicle	0	24	0.03	1652
BG	50	24	0.03	1563
BG	100	24	0.09	1463
BG	200	24	0.04	1889
CP	40	24	0.98	1755
vehicle	0	48	0.01	2113
BG	50	48	0.04	1727
BG	100	48	0.01	1628
BG	200	48	0.02	1945
vehicle	0	72	0.02	1577
BG	50	72	0.02	1408

BG	100	72	0.04	1638
BG	200	72	0.01	1492

BG = benzoguanamine (2,4-diamino-6-phenyl-1,3,5-triazine)
CP = cyclo phosphamide

Source : SKW "P-SDS"
Conclusion : This substance was not mutagenic in bacteria [OECD TG 471 & 472]. It induced chromosomal aberration in CHL/IU cells with and without an exogenous metabolic activation system even under the soluble concentrations. It also gave a positive response in the human lymphocytes tested [OECD TG 473] and the mouse lymphoma TK assay [OECD TG 476] but only under the insoluble dose levels. The cytogenetic effect observed in *in vitro* assays however, could not be reproduced in the micronucleus tests *in vivo* [OECD TG 474].
Based on the weight of evidence, it could be concluded that this substance was not genotoxic *in vivo*.
Test condition : TEST ORGANISMS:
- age: 8-12 weeks
- weight at study initiation: males mean value ; 34.3 g
female mean value; 28.2 g
- no. of animals per dose: 5 per sex and dose
ADMINISTRATION:
- vehicle: corn oil
- sampling times and number of samples: 24 hr, 48 hr, 72 hr
- control groups and treatment:
positive control; cyclophosphamide, 40 mg/kg b.w.
dissolved in deionised water, 10 ml/kg b.w.
vehicle control; 10ml/kg b.w.
EXAMINATIONS:
- criteria for evaluating results: NCEs and 2000PCEs
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
03.05.2001 (36)

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral (gavage)
Exposure period : 24 hr, 48 hr
Doses : 0, 125, 250, 500 mg/kg b.w
Result : inconclusive
Method : other: Directive 92/69/EEC, B.12 "Genetic Toxicology: Micronucleus Test"
Year : 1996
GLP : Yes
Test substance : as prescribed by 1.1-1.4

Result : EFFECT ON MITOTIC INDEX OR PCEs/NCEs RATIO:
- No significant change in the PCEs/NCEs ratio was observed after dosing with the test material.
STATISTICAL RESULTS:
- As shown Table 1, there was evidence of a small, dose related and statistically significant increase in the incidence of micronucleated polychromatic erythrocytes in animals dosed with the test material in the 48 hr groups when compared to the concurrent vehicle control group. Whilst the response observed in the 48 hr at 250 and 500 mg/kg groups was not sufficiently pronounced to give a clear positive result it was outside the current histrical control range and thus precludes a negative result. No significant change in the PCEs/NCEs ratio was observed after dosing with the test material. However, the presence of clinical signs was taken to confirm that systematic absorption had been achieved.
- Clincal signs were observed in animals dosed with this substance at and above 125 mg/kg ,and induced as follows:
hunched posture, lethargy, splayed gait, decreased respiratory rate, laboured respiration, ataxia, loss of righting reflex and ptosis.

Table 1. Micronucleus study – summary of group mean data

Treatment group			Number of PCEs with micronuclei per 1000 PCEs		PCEs/NCEs ratio	
	mg/kg	hr	group mean	SD	group mean	SD
vehicle control		48	0.8 (0.10-1.90)	0.6	1.45 (0.88-2.20)	0.36
vehicle control		24	1.2 (0.20-2.00)	1.4	1.45 (0.71-2.54)	0.46
positive control		24	21.8***	7.5	1.68	0.62
BG	500	48	2.4*	2.1	1.51	0.44
BG	250	48	2.1*	1.6	1.51	0.32
BG	125	48	1.4	2.0	1.62	0.42
BG	500	24	1.9	1.9	1.65	0.42
BG	250	24	1.3	0.9	2.19	0.86
BG	125	24	0.5	0.7	1.76	0.64

PCEs = polychromatic erythrocytes
NCEs = normochromatic erythrocytes
SD = standard deviation
*** = $p < 0.001$
* = $p < 0.05$
vehicle control = Arachis oil
positive control = Cyclophosphamide 50 mg/kg
( ) = historical data
BG = benzoguanamine (2,4-diamino-6-phenyl-1,3,5-triazine)

- As shown Table 2, a further evaluation of the replicate slides of each animal was performed by an independent laboratory in an attempt to resolve the equivocal nature of the response. The data from this evaluation show no significant increase in frequency of micronucleated polychromatic erythrocytes in any of the animal groups exposed to this substance.
However, the criteria used by the independent laboratory for the classification of micronuclei resulted in lower frequncies of micronuclei in the vehicle and positive controle groups compared to the in-house data. The reductions were negative that two data in the ten data of the positive animals (cyclophosphamide, 50 mg/kg, 24 hr, mean 16.4/2000 scored) had micronucleus scores (5.0/2000 and 8.0/2000 scored) that were negative as compared to the SafePharm Laboratories limited historical negative control value, even when large samples of PCEs (4000) were scored for micronuclei.

Table 2. Micronucleus study – summary of group mean data
(A further evaluation of the replica slides by RCC)

Treatment group		Number of PCEs with micronuclei per 1000 PCEs		PCEs/NCEs ratio	
mg/kg	hr	group mean	SD	group mean	SD
vehicle control	48	0.7	0.8	1.22	0.11
vehicle control	24	1.6	1.3	1.13	0.06
positive control	24	16.4***	6.3	1.18	0.12
BG 500	48	0.8	1.2	1.18	0.08
BG 250	48	1.5	1.4	1.17	0.07
BG 125	48	0.6	0.7	1.18	0.08
BG 500	24	1.4	1.3	1.20	0.09
BG 250	24	0.7	1.1	1.20	0.15
BG 125	24	0.6	1.0	1.15	0.10

PCEs = polychromatic erythrocytes
NCEs = normochromatic erythrocytes
vehicle control = Arachis oil
positive control = cyclophosphamide 50 mg/kg
SD = standard deviation
*** = $p < 0.001$
BG = benzoguanamine (2,4-diamino-6-phenyl-1,3,5-triazine)

Source : SKW "P-SDS"

Test condition : TEST ORGANISMS:
- age: 5-7 weeks old
- weight at study initiation: 24-30 g for males and 20-26 g for females
- no. of animals per dose: 5 per sex per dose group

ADMINISTRATION:
- vehicle: Arachis oil
- sampling times and number of samples: 24 hr, 48 hr
- control groups and treatment:
  negative control; vehicle, 10 ml/kg, 24 hr and 48 hr
  positive control; cyclophosphamide, 50 mg/kg, 24 hr

EXAMINATIONS:
- clinical observations: The presence of clinical signs was taken to confirm that systematic absorption had been achieved.

Remark : In this test, the test result was inconclusive from following two reasons.
As first reason, there were small deviations in the value of PCEs with micronuclei/1000PCEs = 2.1, 2.4 at the 48 hr in the 500, 250 mg/kg groups respectively.
As second reason, the mean value of positive control had two low scores which were very lower than SafePfarm's historical control values conducted by the further evaluation of the replica slides.
The above test result was inadequate as advised by the Scientific Committee on Food (SCF) of the European Commission (EC); SCF/CS/PM (GEN) 3334 final, adopted at the 118th SCF meeting on September 23 1999.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

30.06.2001 (44)

5.7 CARCINOGENITY

Type

Species : rat

Sex : male

Strain : other: Charles-River

Route of admin. : oral feed

Exposure period : 18 month
Frequency of treatment : Taeglich
Post. obs. period : 4, 6 month
Doses : 500, 1000 ppm (37.5, 75 mg/kg/day)
Result : not tumorigenicity
Control group : yes
Method :
Year : 1973
GLP : no
Test substance : Aldrich, melting point: 226-228°C
Result : MORTALITY AND TIME TO DEATH: The survival curve was not affected although there was a dose-related inhibition of growth.
BODY WEIGHT GAIN: decreased proportionally by the dose volume
At the high dose level, it decreased c.a. 20% of controled case.
OPHTALMOSCOPIC EXAMINATION: The incidence of tumors was no greater than in controls. 4 tumors (a squamous papilloma of the stomach, a renal cell caricinoma, a liposacroma of the kidney and one adrenal pheochromo-cytoma) were seen which had not been observed in the simultaneous control. One of these occured earlier (15 months) than any tumors observed in the controle and two other tumors (fibrosacroma and pituitary adenoma) were noted at 13 months. These events, however, have no significant frequency.
Source : SKW Trostberg AG Trostberg
Test condition : TEST ORGANISMS
- number of animals: 25
ADMINISTRATION/EXPOSURE
- type of exposure: dietary in animal feed
- doses:

Group no.	Animals	Number of animals	Dose level mg/kg food	mg/kg b.w.
1a	male rats	25	Control	control
1b	male rats	25	500	37.5
1c	male rats	25	1000	75.0

CLINICAL OBSERVATION AND FREQUENCY
- food comsumption: 75 mg food/kg b.w./day
Reliability : (2) valid with restriction
Flag : Critical study for SIDS endpoint
03.05.2001 (2) (58)

Type
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral feed
Exposure period : 18 month
Frequency of treatment : daily
Post. obs. period : 4, 6 month
Doses : 2000, 4000 ppm (300, 600 mg/kg/day)
Result : no tumorigenicity
Control group : yes
Method :
Year : 1973
GLP : no
Test substance : Aldrich, melting point; 226-228°C

Result : OPHTALMOSCOPIC EXAMINATION: This test substance had no significant effects on survival and weight gain and did not cause a significant number of tumors not observed in control mice or significantly earlier tumors than those occuring spontanously.

- tumor found data in male and female mice

Dose	High dose (4000 mg/kg)		Low dose (2000 mg/kg)		Control (pooled)	
Sex	male	female	male	female	m	f
Initial No	25	25	25	25	150	
Early death	9	4	11	4	51	48
Mice with tumor	9	9	3	8	53	76
Mice with Multiple tumors	3	5	1	3	14	21
Tumor found	12	15	4	11	72	99
Lung					24	32
Adenoma	7	3	2	2		
Liver						
Hepatoma	2	1			7	1
Hemangioma				1		
Spleen and uterus						
Hemangiosarcoma				1		
Stomach						
Squamous papilloma		3				
Adenocarcinoma	1*	1	1	1		
kidny and ovary						
Hemangiosarcoma		1				
Breast (mammary for female)						7
Adenocarcinoma		1**				
Adenoacanthoma		1				
Uterus						
Adenocarcinoma		1***				
Leiomyoma		1		1		
Hemangioma		1		2		
Adrenal						
Cortical adenoma	1			1		
Lymphosarcoma	1					
Lymphosarcoma of thymus		1				
Lymphocytic leukemia			1	2	17	32
Vascular tumor					5	9
Others in Control					19	18

* metastatic to liver and bowel
** metastatic to lung
*** metastatic to lymph node

This substance had no significant effects on survival and body weight gain, and did not cause a significant number of tumors including mammary tumors and bladder tumors.

Source : SKW Trostberg AG Trostberg

Test condition : TEST ORGANISMS
- number of animals: 25
ADMINISTRATION/EXPOSURE
- type of exposure: dietary in animal feed
- doses:

Group no.	Animals	Number of animals	Dose level mg/kg food	mg/kg b.w.
2a	male mice	25	control	control
2b	male mice	25	2000	300
2c	male mice	25	4000	600
3a	female mice	25	control	control

	3b	female mice	25	2000	300
	3c	female mice	25	4000	600

CLINICAL OBSERVATION AND FREQUENCY
- food comsumption: 150 mg food/kg b.w./day

Conclusion : Two dietary studies using male rats and male/female mice for 18 months showed no tumorigenic activity of this substance. However, these studies were considered to be insufficient for assessment of the carcinogenicity because of insufficient testing protocol compared to current test guidelines.

Reliability : (2) valid with restriction

Flag : Critical study for SIDS endpoint

03.05.2001 (2) (58)

5.8 TOXICITY TO REPRODUCTION

Type : OECD combined study TG 422, combined repeat dose and reproductive/developmental toxicity screening test

Species : rat

Sex : male/female

Strain : Sprague-Dawley

Route of admin. : oral (gavage)

Exposure period : male; 49 days: female; for 14 days before mating to day 3 of lactation

Frequency of treatment : one administration/day

Premating exposure period :

Male : 14 day

Female : 14 day

Duration of test : male: 49 day
female: 39-53 day

Doses : 0, 4, 20, 100 mg/kg/day (vehicle: CMC-Na 0.5 wt% solution)

Control group : yes, concurrent vehicle

NOAEL parental : = 100 mg/kg bw (male), 4 mg/kg/ bw (female)

NOAEL F1 offspring : = 20 mg/kg bw

Method : OECD combined repeat dose and reproductive/developmental toxicity screening test

Year :

GLP : yes

Test substance : other TS: NIPPON SHOKUBAI CO., LTD., purity: 98%

Result : STATISTICAL RESULTS: As for reproductive performance, no effects related to this substance were observed for the estrous cycle, numbers of corpora lutea and implantation, copulation index, conception index, and duration of mating. On examination after delivery, poor collection and heating of new borns were observed with dams of the 100 mg/kg group. Furthermore, the birth index decreased with increase of stillborns at this dose. No effects related to this substance were observed in terms of gestational days, number of litters and live newborns, gestation index and sex ratio. There were no external anomalies of pups. Examination during the lactation period, revealed poor collection, nursing and heating for newborns. A decrease in the viability index on day 4 of lactation was observed for dams of the 20 mg/kg or more group.

Findings of delivery of Fo dams treated orally with the test subsutance

Dose (mg/kg)	0	4	20	100
No. of copulated (male, female)	12	12	12	12
No. of impregnated (female)	11	12	12	11
No. of dams	11	12	12	10

Gestation index	100.00	100.00	100.00	90.90
No. of poor nursing dams				
on day 0	0	0	0	2[1]
day 4	0	0	2[2)]	7[2)]
Mean no. of newborns/litter	15.45	14.45	13.75	15.20
S.D.	3.14	1.66	3.70	2.25
No. of stillborns	0	4*	4	43**
No. of live newborns	170	173	161	109
Mean no. of live newborns/litter	15.45	14.42	13.43	10.90
S.D.	3.14	1.62	3.45	5.07
Birth index	100.00	97.74	97.58	71.71**
Sex ratio of live newborns	0.87	0.90	0.96	0.98
Body weight of live newborns (g)				
male on day 0	6.3	6.8	6.2	5.1**
day 4	9.6	10.6	9.9	6.8**
female on day 0	6.0	6.5	5.8	4.7**
day 4	9.2	10.1	9.3	5.8**
Viability index	99.41	99.42	75.78*	11.93**
No. of external anomalies	0	0	0	0

Gestation index = (Number of dams with live newborns/Number of pregnant females) x 100
Birth index = (Number of live newborns/Number of (stillborns + live newborns)) x 100
Viability index = [number of live newborns on day 4 after birth/number of live newborns] x 100
*: $p < 0.05$, **: $p < 0.01$ (significantly different from control)
1): All newborns were dead and counted as stillborn
2): All newborns were dead before day 4

Remark : Changes of litter sizes:
- Historical control value changes of litter sizes in the same laborotory;
13.67 +/- 3.08 (CAS No 4189-44-0, 1999)
14.25 +/- 1.22 (CAS No 105-45-3, 1998)
14.73 +/- 2.65 (CAS No 11070-44-3, 1997)
13.83 +/- 1.40 (CAS No 98-08-8, 1996)
litter size = No. of live newborn pups/litter

A dose-related decrease of litter sizes (number of live newborn pups/litter) was observed. However, the value at 20 mg/kg group is within the historical control values (13.67 +/- 3.08, 14.25 +/- 1.22, 14.73 +/- 2.65, 13.83 +/- 1.40). Therefore, the decrease tendency in 4 and 20 mg/kg is not considered due to chemical-related effect. The decrease of litter size observed at 100 mg/kg seems to be the chemical-induced effect although it is not statistically significant.

Remark : The lack of maternal nursing activity;
・Study director clearly mentioned in the final report that the lack of nursing activity (collection, lactation and warming of pups) was obviously recognized in 2 of 20 mg/kg and 7 of 100 mg/kg.
・Other pups in 20 mg/kg group had normal body weight at birth and normally grew up to day 4.
Based on these evidence, the lack of nursing activity might be due to maternal toxicity.

Source : MHW Japan (2001)

Remark : In the OECD combined repeat dose and reproductive/ developmental (one generation) toxicity screening test [OECD TG 422], this substance was given for 49 days from 14 days before mating in males and from 14 days before mating to day 3 of lactation in females. At the 100 mg/kg group, one female died in gestation and another female was not impregnated. Birth index was decreased with increase in stillborns at the 100 mg/kg. All pups of two dams at the 20 mg/kg and seven dams at 100 mg/kg died due to the lack of nursing activity, and the viability index on day 4 after birth was consequently decreased in these groups. The body weights of pups were also decreased at birth and day 4 of lactation in the 100 mg/kg group. The decrease of litter size observed at the 100 mg/kg seems to be the chemical-induced effect although it is not statistically significant. No malformations or variations were observed in the pups.

Conclusion : The parental NOAEL of reproductive toxicity was considered to be 100 mg/kg/day for males, and 4 mg/kg/day for females, based on the lack of nursing activity. And the NOAEL of developmental toxicity was considered to be 20 mg/kg/day, based on decreases of birth index and body weight of pups.

Test condition : TEST ORGANISMS:
- Rat/Sprague-Dawley IGS, 8 weeks
ADMINISTRATION/EXPOSURE
- type of exposure: oral feed by tube to stomach
- duration of test/exposure:
males; 49 days including 14 pre-mating
females; 14 days pre-mating, 21 days after impregnated, 4 days off-lactation
- vehicle: 0.5% carboxymethyl cellulose sodium salt solution
- concentration in vehicle: 0.16, 0.8, 4w/v%
- total volume applied: 2.5 ml/kg
- doses: 0, 4, 20, 100 mg/kg
MATING PROCEDURES: max 14 days

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

04.03.2001 (29)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.10 OTHER RELEVANT INFORMATION

Remark : 25 mg benzoguanamin/kg Kgw. i.v. verursachten bei maennlichen Kueken (1-7 Tage alte white Leghorn) Sedation und Ataxie.

Source : SKW Trostberg AG Trostberg
EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)

05.08.1993 (35)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

(1) Anonym: Natl. Tech. Inf. Service (AD 277-689) zitiert in RTECS, Registry of Toxic Effects of Chemical Substances 1992

(2) Bio-Research Consultants, Inc. (1973): Carcinogenicity of chemicals present in man's environment, Final report, 31, 271-285 (Weisburger, E.K. et al.)

(3) Borkovec, A.B.et al. (1972): J. Econ. Entomol. 65, 69-73

(4) Central Institute for Nutrition and Food Research, TNO (1972): Determination of the acute oral toxicity of Benzoguanamine in rats, October 9, 1972

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3.3.2 Distribution

The Fugacity Model (Mackay level Ⅲ) treated with 2,4-diamino-6-phenyl-1,3,5-triazine

scenario 1

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	1,000	4.0E-09	4.0E+01	0.0	2.5E-01	4.0E-01
water	0	4.9E-02	9.9E+05	29.3	2.9E+00	9.9E+02
soil	0	1.5E+00	2.4E+06	70.5	6.9E+00	
sediment		5.2E-02	5.2E+03	0.2	5.0E-03	1.0E-01
		totalamount	3.4E+06			

scenario 2

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	0	5.0E-15	5.0E-05	0.0	3.2E-07	5.0E-07
water	1000	5.0E-02	1.0E+06	99.5	2.9E+00	1.0E+03
soil	0	1.9E-06	3.0E+00	0.0	8.6E-06	
sediment		5.3E-02	5.3E+03	0.5	5.1E-03	1.1E-01
		totalamount	1.0E+06			

scenario 3

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	0	1.0E-12	1.0E-02	0.0	6.3E-05	1.0E-04
water	0	4.9E-02	9.9E+05	24.9	2.9E+00	9.9E+02
soil	1000	1.9E+00	3.0E+06	75.0	8.6E+00	
sediment		5.2E-02	5.2E+03	0.1	5.0E-03	1.0E-01
		totalamount	4.0E+06			

scenario 4

	emission rate [kg/h]	conc. [g/m^3]	amount [kg]	percent [%]	transfomation rate [kg/h]	
					reaction	advection
air	600	2.4E-09	2.4E+01	0.0	1.5E-01	2.4E-01
water	300	5.0E-02	9.9E+05	36.4	2.9E+00	9.9E+02
soil	100	1.1E+00	1.7E+06	63.4	5.0E+00	
sediment		5.2E-02	5.2E+03	0.2	5.1E-03	1.0E-01
		totalamount	2.7E+06			

molecular weight		187.2	Measured
melting point [℃]		228	Measured
vapor pressure [Pa]		2.00E-05	Estimated
water solubility [g/m^3]		320	Measured
log Kow		1.38	Estimated
half life [h]	in air	110	Estimated
	in water	240000	Estimated
	in soil	240000	Estimated
	in sediment	720000	Estimated

Temp. [℃]	25

Environmetal parameter

		volume [m^3]	depth [m]	area [m^2]	organic carbon [—]	lipid content [—]	density [kg/m^3]	residence time [h]
bulk air	air	1.0E+13					1.2	100
	particles	2.0E+03						
	total	1.0E+13	1000	1E+10				
bulk water	water	2.0E+10					1000	1000
	particles	1.0E+06			0.04		1500	
	fish	2.0E+05				0.05	1000	
	total	2.0E+10	10	2E+09				
bulk soil	air	3.2E+08					1.2	
	water	4.8E+08					1000	
	solid	8.0E+08			0.04		2400	
	total	1.6E+09	0.2	8E+09				
bulk sediment	water	8.0E+07					1000	
	solid	2.0E+07			0.06		2400	50000
	total	1.0E+08	0.05	2E+09				

Intermedia Transport Parameters [m/h]

air side air-water MTC	5	soil air boundary layer MTC	5
water side air water MTC	0.05	sediment-water MTC	1E-04
rain rate	1E-04	sediment deposition	5E-07
aerosol deposition	6E-10	sediment resuspension	2E-07
soil air phase diffusion MTC	0.02	soil water runoff	5E-05
soil water phase diffusion MTC	1E-05	soil solid runoff	1E-08

5.5 Genetic toxicity *in vitro* (1)

Chromosomal aberration test on CHL cells *in vitro* treated with 2,4-diamino-6-phenyl-1,3,5-triazine (BG)

Experiment no.1 on the test of contiuous treatment

Compd	Dose (ug/ml)	Time of exposure (hr)	No. of cells analised	No. of structural aberrations gap	ctb	cte	csb	cse	oth	Total +gap (%)	Total -gap (%)	Polploid cells (%)	Judge SA	Pol
BG	0	24	200	1	1	0	0	0	0	1.0	0.5	0.0	-	-
BG	100	24	200	1	1	1	0	0	0	1.5	0.5	0.0	-	-
BG	200	24	200	4	0	2	0	0	0	3.0	1.0	0.5	-	-
BG	400P	24	200	4	5	9	0	0	0	9.0	7.0	0.0	+/-	-
BG	800P	24	Toxic											
MMC*	0.05	24	200	7	24	51	0	0	0	35.5	33.5	0.0	+	-
BG	0	48	200	0	0	0	0	0	0	0.0	0.0	0.0	-	-
BG	100	48	200	3	1	1	0	0	0	2.5	1.0	1.0	-	-
BG	200	48	200	3	4	16	0	0	0	11.0	9.5	1.0	+	-
BG	400P	48	200	15	31	45	0	0	0	35.5	33.5	0.0	+	-
BG	800P	48	141	8	15	29	0	0	0	29.1	26.2	0.0	+	-
MMC*	0.025	48	200	7	22	59	0	0	1	37.5	37.0	0.5	+	-

Confirmative examination 1

Compd	Dose (ug/ml)	Time of exposure (hr)	No. of cells analised	No. of structural aberrations gap	(%)	(%)	(%)	SA	(%)	Total +gap (%)	Total -gap (%)	Polploid cells (%)	Judge SA	Pol
BG	0	48(24)	200									0.5		-
BG	200	48(24)	200									0.0		-
BG	400P	48(24)	200									2.5	NE	-
BG	800P	48(24)	200									11.5		+
BG	1600P	48(24)	200									14.5		+

Confirmative examination 2

Compd	Dose (ug/ml)	Time of exposure (hr)	No. of cells analised	No. of structural aberrations gap	(%)	(%)	(%)	SA	(%)	Total +gap (%)	Total -gap (%)	Polploid cells (%)	Judge SA	Pol
BG	0	24	200	0	0	0	0	0	0	0.0	0.0	0.0	-	-
BG	300	24	200	3	2	2	0	0	0	3.0	2.0	0.5	-	-
BG	400P	24	200	0	5	5	0	0	0	5.0	5.0	0.0	+/-	-
BG	500P	24	200	3	7	4	0	0	0	7.0	5.5	0.0	+/-	-
BG	600P	24	200	1	5	5	0	0	0	5.5	5.0	0.0	+/-	-
BG	700P	24	200	4	11	7	0	0	1	10.0	8.0	0.5	+	-
BG	800P	24	200	2	8	12	1	1	0	11.0	10.0	0.0	+	-
BG	900P	24	Toxic											
MMC*	0.05	24	200	5	28	59	0	0	0	39.5	39.5	0.0	+	-

*: positive control MMC = Mitomycin C
ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others
SA: structual aberration Pol: polyploid cell
P: Visible precipitation was shown at the end of exposure period

5.5 Genetic toxicity *in vitro* (2)

Chromosomal aberration test on CHL cells *in vitro* short tearm treated with 2,4-diamino-6-phenyl-1,3,5-triazine (BG)

Experiment no.2 on the test of short-term treatment

-S9

Compd	Dose (ug/ml)	Time of exposure (hr)	No. of cells analised	No. of structural aberrations gap	(%)	(%)	(%)	SA	(%)	Total +gap (%)	Total -gap (%)	Polploid cells (%)	Judge SA	Pol
BG	0	6-(18)	200	0	0	1	0	0	0	0.5	0.5	0.0	-	-
BG	1250P	6-(18)	200	4	2	1	0	0	0	3.5	1.5	0.0	-	-
BG	2500P	6-(18)	200	2	3	2	0	0	0	3.5	2.5	1.0	-	-
BG	5000P	6-(18)	200	3	2	0	0	0	0	2.5	1.0	0.0	-	-
CP*	12.5	6-(18)	200	0	2	0	0	0	0	1.0	1.0	0.0	-	-

+S9

Compd	Dose (ug/ml)	Time of exposure (hr)	No. of cells analised	No. of structural aberrations gap	(%)	(%)	(%)	SA	(%)	Total +gap (%)	Total -gap (%)	Polploid cells (%)	Judge SA	Pol
BG	0	6-(18)	200	0	0	0	0	0	0	0.0	0.0	0.0	-	-
BG	19.5	6-(18)	200	1	1	0	0	0	0	1.0	0.0	0.0	-	-
BG	39.1	6-(18)	200	0	0	3	0	0	0	1.5	1.5	0.0	-	-
BG	78.1	6-(18)	200	8	31	57	0	0	0	41.5	40.0	1.0	+	-
BG	156P	6-(18)	Toxic											
CP*	12.5	6-(18)	200	4	49	142	1	0	0	76.0	75.5	0.0	+	-

Confirmative examination +S9

Compd	Dose (ug/ml)	Time of exposure (hr)	No. of cells analised	No. of structural aberrations gap	(%)	(%)	(%)	SA	(%)	Total +gap (%)	Total -gap (%)	Polploid cells (%)	Judge SA	Pol
BG	0	6-(18)	200	0	0	2	0	0	0	1.0	1.0	0.5	-	-
BG	60.0	6-(18)	200	0	0	2	0	0	0	1.0	1.0	0.5	-	-
BG	80.0	6-(18)	200	1	1	10	0	0	0	5.0	5.0	0.5	+/-	-
BG	100P	6-(18)	200	1	14	34	0	0	1	20.0	20.0	0.5	+	-
BG	120P	6-(18)	200	9	29	57	0	0	1	31.5	30.5	0.0	+	-
BG	140P	6-(18)	200	5	18	47	0	0	0	25.5	25.0	0.0	+	-
BG	160P	6-(18)	Toxic											
CP*	12.5	6-(18)	200	3	24	94	0	0	0	50.0	49.5	0.0	+	-

*: positive control CP = Cyclophosphamide

ctb: Chromatid break cte: Chromatid exchange csb: Chromosome break cse: Chromosome exchange oth: others
SA: structual aberration Pol: polyploid cell

P: Visible precipitation was shown at the end of exposure period

5.5 Genetoxicity *in vitro* (3)

Chromosomal aberration test on Human lymphocytes *in vitro* treated with 2,4-diamino-6-phenyl-1,3,5-triazine

				aberration(%) per 100cells								
Harvest hr	S9	Dose ug/ml	Total gaps	Chromatid		Chromosome		Others	Total aberration		Aberrant cells	
				break	exchange	break	exchange	x	+gaps	-gaps	+gaps	-gaps
20	-S9	negative control	0.5	0	0	0	0	0	0.5	0	0.5	0
		78.125	0	0	0	1.5	0	0	1.5	1.5	1	1
		156.25	0	1	0	0	0	0	1	1	1	1
		312.5	0.5	0.5	0	0.5	0	0	1.5	1	1.5	1
		625P	4.5	3.5	0.5	0.5	0	0	9	4.5	7.5***	4.5**
		1250P	1	1.5	0	1	0	0	3.5	2.5	3	2
		positive control (EMS 500)	19.3	22	7.3	4	0	0.7	52.7	33.3	38	26.7
20	+S9	negative control	1	0	0	0	0	0	1	0	1	0
		78.125	0.5	0.5	0	0	0	0	1	0.5	1	0.5
		156.25	0	0	0	0	0	0	0	0	0	0
		312.5	1	0	0	1.5	0	0	2.5	1.5	2	1
		625P	0	0.5	0	0.5	0	0	1	1	1	1
		1250P	1	3	0	0	0	0	4	3	3.5	2.5*
		positive control (CP 25)	28.5	19	8	3	0	0	58.5	30	31.0***	19.5***
30	-S9	negative control	0.5	0	0	0	0	0	0.5	0	0.5	0
		78.125	1.5	0	0	0	0	0	1.5	0	1.5	0
		156.25	0	0	0	0.5	0	0	0.5	0.5	0.5	0.5
		312.5	0	0	0	0	0	0	0	0	0	0
		625P	9	3.5	1	1	0	0	14.5	5.5	13.5***	5.0***
		1250P	8.5	2	1	1	0	0	12.5	4	8.0***	3.0*
		2500P	13.5	7.5	1	1.5	0	0	23.5	10	17.5***	7.5***
		positive control (EMS 500)	30	42	26	4	0	0.7	106	76	59.0***	50***
30	+S9	negative control	0	0	0	2	0	0	2	2	1	1
		78.125	0.5	0.5	0	0	0	0	1	0.5	1	0.5
		156.25	0.5	0.5	0	0	0	0	1	0.5	1	0.5
		312.5	1	0	1	0	0	0	2	1	1	0.5
		625P	0	0	0	0	0	0	0	0	0	0
		1250P	4	2	0	2	0	0	8	4	7.0*	3
		positive control (CP 25)	3	19	8	2	0.5	0.5	32.5	29.5	16.0***	15.5***

P: precipitate observed during exposure period
X: > 10 aberrations per cell (not induced in total aberrations)
* p <0.05
** p <0.01
*** p <0.001
EMS: ethly methanesulphonate
CP: cyclophosphamide

5.5 Genetoxicity *in vitro* (4)

Mammalian cell gene mutation test on Mouse lymphoma cells (L5178) *in vitro* treated with 2,4-diamino-6-phenyl-1,3,5-triazine

Experiment no.1 on the test of genotoxicity

-S9			+S9		
Treatment ug/ml	RS %	MF/SV x10E-6	Treatment ug/ml	RS %	MF/SV x10E-6
0	100.00	66.88	0	100.00	52.48
78.1	87.96	40.99	78.1	92.82	53.10
156.25	97.87	86.56	156.25	100.36	116.76
312.5	95.79	69.74	312.5	96.17	138.08
625P	98.57	80.63	625P	87.71	155.68*
1250P	93.10	91.26	1250P	70.25	129.81
EMS 1000	58.32	973.81	Cp 7.5	27.76	1179.54
	Linear trend	NS		Linear trend	**

Experiment no.2 on the test of genotoxicity

-S9			+S9		
Treatment ug/ml	RS %	MF/SV x10E-6	Treatment ug/ml	RS %	MF/SV x10E-6
0	100.00	96.51	0	100.00	90.23
156.25	114.67	137.08	156.25	118.96	93.22
312.5	112.95	69.13	312.5	118.96	152.31
625P	103.33	94.85	625P	125.34	141.97
1250P	116.43	104.08	1250P	105.89	198.63*
2500P	104.86	107.49	2500P	116.36	155.90
Ems 1000	68.80	1139.62	Cp 7.5	78.56	717.52
	Linear trend	NS		Linear trend	*

P: precipitate observed during exposure period
* $p < 0.05$
** $p < 0.01$
EMS: ethly methanesulphonate
CP: cyclophosphamide
RS: rerative survival
MF/SVx10E-6: mutation frequency per 10xE6 cells per survivor
NS: not significant

% small colonies on experiment no.2 with metabolic activation

			Total colonies		Large colonies		Small colonies		small
dose ug/ml	P.E.	% control	MF/SV x10E-6	IMF/SV x10E-6	MF/SV x10E-6	IMF/SV x10E-6	MF/SV x10E-6	IMF/SV x10E-6	colonies %
0	57.7	100	90.23	-	58.3	-	29.8	-	34
156.25	59.0	102	93.22	2.99	54.7	-3.6	36.1	6.3	40
312.5	59.9	104	152.31	62.08	56.2	-2.1	89.5	59.7	61
625P	65.3	113	141.97	51.74	53.7	-4.6	82.0	52.2	60
1250P	52.3	90	198.63	108.40*	75.1	16.8	113.6	83.8	60
2500P	51.5	89	155.90	65.67	73.5	15.2	76.2	46.4	51
Cp 7.5	40.7	70	717.52	627.29	92.9	34.6	566.6	536.8	84

Linear trend: slope = 3.36x10E-08; variance = 2.45x10E-16; b/sb = 4.592*
P.E.: plating efficiency
IMF/SV: induced MF/SV