FOREWORD INTRODUCTION

Methyl Acrylonitrile

CAS N°:126-98-7

SIDS Initial Assessment Report

For

SIAM 14

26-28 March 2002, Paris, France

1. Chemical Name:	Methyl Acrylonitrile
2. CAS Number:	126-98-7
3. Sponsor Country:	Japan National SIDS Contact Point in Sponsor Country: Mr. Yasuhisa Kawamura, Ministry of Foreign Affairs, Japan
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	The original draft documents were prepared by Japanese government.
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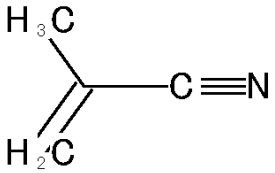
10. Date of last Update:	
11. Comments:	No testing ( ) Testing (x) Vapor pressure, log P_{ow}, Water solubility, Hydrolysis and Photolysis, Biodegradation, Environmental fate, Acute toxicity to fish, daphnia and algae, Chronic toxicity to daphnia, Acute toxicity, Combined repeated and reproductive/developmental toxicity, Ames test and Chromosomal aberration test

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	126-98-7
Chemical Name	Methyl Acrylonitrile
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Methylacrylonitrile was readily absorbed through the gastrointestinal tract. It distributed to all tissues, but the potential for bioaccumulation was minimal. The main excretion route was expired air as carbon dioxide, which was saturable with increased dose. Metabolism and excretion of this chemical depend on the dosing vehicle and the species/strain.

There are definite species differences in the acute toxicity. The oral LD_{50} was 64~240 mg/kg b.w. for rats, 17 mg/kg b.w. for mice, 16 mg/kg b.w. for rabbits and 3.8~4.9 mg/kg b.w. for gerbils. Clinical signs were decrease in locomotor activity, adoption of a prone and/or lateral position, and hyperpnea. Inhalation LC_{50} of rats was also obviously higher than that of mice and rabbits although all these were reported in 1968. Clinical signs by inhalation were unconsciousness and tonic-clonic convulsions. This chemical is mildly irritating to skin and eyes in rabbits**.** In a human voluntary study, this chemical was also slightly irritating to respiratory tracts and eyes (even at 2 ppm (6 mg/m^3) for 10 minutes). There is no available data on skin sensitization.

Six oral and four inhalation repeated dose toxicity studies including two oral carcinogenic studies are available. Anemia and histopathological changes in olfactory epithelium and bone marrow were observed in rat oral studies. In addition, rats and mice at the higher doses showed clinical signs such as lethargy, tremors and convulsions. In NTP 13-week studies, various effects including death were observed at 42.9 mg/kg b.w./day and more in rats, and at 8.6 mg/kg b.w./day in mice, showing significant species differences of the repeated dose toxicity. From a 2-year carcinogenicity study [NTP], the NOAEL for oral repeated dose toxicity was considered to be 7.14 mg/kg b.w./day for rats and 4.29 mg/kg b.w./day for mice. For inhalation exposure (90 days), the NOAEL was reported as 19.3 ppm (57.9 mg/m^3) for rats and 8.8 ppm (26.4 mg/m^3) for dogs although the data quality was not sufficient.

This chemical was not mutagenic with and without an exogenous metabolic activation system in a bacterial test [OECD TG 471], while the cytogenetic effect was judged to be positive because of increases in mammalian cultured cells with structural chromosomal aberrations and polyploidy with an exogenous metabolic activation [OECD TG 473]. However, micronucleus tests by intraperitoneal injection to rats and mice or by gavage to mice showed negative results [NTP]. Therefore, a weight of evidence suggests that methylacrylonitrile may not be genotoxic *in vivo*.

In 2-year gavage studies [NTP], this chemical did not cause any neoplastic changes in rats (up to 21.4 mg/kg b.w./day) and mice (up to 4.29 mg/kg b.w./day). Therefore, methylacrylonitrile was considered not to be carcinogenic in rodents.

In an OECD combined study, there were no effects of this chemical on reproductive/developmental parameters even at the highest dose of 30 mg/kg b.w. In a two-generation study in rats, methylacrylonitrile did not affect the reproductive performance of both sexes, but induced a decrease of epididymal sperm density in the second

generation at 20 mg/kg b.w. At higher doses in rats (40 to 100 mg/kg b.w.), prolonged estrous cycles were observed in an oral 13-week study and the pregnancy was not kept in an oral developmental study. In another developmental study in rats, there were no effects on fetal development up to 50 mg/kg b.w. by oral administration. Based on these results, the oral NOAEL for reproductive/developmental toxicity in rats was considered to be 7 mg/kg b.w./day. On the other hand, there was a decrease in the male/female ratio of fetuses/litter at a dose of 5 mg/kg b.w. in rabbits and a decreased body weight of fetuses was observed at 100 ppm by inhalation, probably due to maternal toxicity. The NOAEL for developmental toxicity was 3 mg/kg b.w. in rabbits by oral administration, and 50 ppm in rats by inhalation. This chemical is not a teratogen.

Environment

Methyl Acrylonitrile is readily biodegradable and its bioaccumulation potential seems to be low based on its Log P_{ow} (0.68). In the air, this chemical is expected to be photodegraded ($T_{1/2}$=about 46 hours). Hydrolysis is not expected to occur. A generic level III fugacity model shows that if methylacrylonitrile is released to one of the compartments of air, water and soil, it is unlikely to distribute into other compartments.

Regarding the acute aquatic toxicity of this substance, the algal ErC50 of 25.3 and EbC50 of 15.1 mg/L are the lowest values among available data on species from three trophic levels.

Chronic toxicity NOEC values of 10 (growth rate) and 1.0 (biomass) mg/L for algae are reported. The NOEC for daphnids is 2.20 mg/L for reproduction.

Exposure

Methylacrylonitrile is a colorless liquid with acrid odor, which is soluble in water (29 g/L at 25 °C). Its vapour pressure is 8.5 x 10^3 Pa at 20° C. The production volume of methyl acrylonitrile in Japan was about 20,000 tonnes in 1998.

This chemical is used as an intermediate in the preparation of methacryllic derivatives, and polymers. Exposure to this chemical via inhalation and dermal routes may be possible during handling of quality control samples, and tank lorry filling. Estimated exposure concentration for these operations is 10-50 ppm by EASE model, and $EHE_{inh+der}$ was 1.3 mg/kg·bw/day at the production site. A TLV (TWA) of 1 ppm has been adopted in several countries.

NATURE OF FURTHER WORK RECOMMENDED

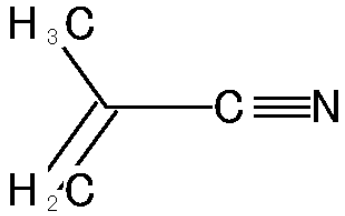
This chemical is currently not a candidate for further work unless there is significant exposure.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 126-98-7
IUPAC Name: Methyl Acrylonitrile
Molecular Formula: C_4H_5N
Structural Formula:



Synonyms: 2-Methyl-2-propenenitrile
Isopropene
Cyanide
Isopropenylcarbonitrile
Alpha-Methylacrylonitrile
2-Methylpropenenitrile
2-Cyanopropene
MAN

1.2 Purity/Impurities/Additives

Substance type: organic

Physical status: liquid

Purity: ≥ 99.97 % w/w

1.3 Physico-Chemical properties

Methyl Acrylonitrile is a colorless liquid with acrid odor, which is soluble in water (29 g/L at 25 °C). Other physical-chemical properties are shown in Table 1.

Table 1: Summary of physico-chemical properties

	Protocol	Results
Melting Point	Unknown	- 35 °C
Boiling Point	Unknown	90 – 92 °C
Density	Unknown	0.800 g/cm^3 at 20 °C
Vapor Pressure	Unknown	8.5 x 10^3 Pa at 20 °C
Partition Coefficient (Log P_{ow})	Calculation	0.68
Water Solubility	OECD TG 105	29 g/L at 25°C

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The production volume of Methyl Acrylonitrile in Japan was about 20,000 tonnes in 1998. This substance was not imported into Japan in 1998.

This chemical is used as an intermediate in preparation of acids, amides, amines, esters, nitriles, homopolymers and copolymers.

2.2 Environmental Exposure and Fate

Methyl Acrylonitrile is readily biodegradable (OECD TG301C: 83 % by BOD after 28 days) and its bioaccumulation potential seems to be low based on its Log P_{ow} (0.68; calculated). If released to the atmosphere, Methyl Acrylonitrile reacts with photochemically-produced hydroxyl radicals or ozone. Based on an atmospheric concentration of 5 x 10^5 OH/cm^3, its atmospheric half-life time is calculated to be about 46 hours. Hydrolysis is not expected to occur (OECD TG117: stable at pH 4, 7 and 9 at 50 °C for five days).

The potential environmental distribution of Methyl Acrylonitrile obtained from a generic level III fugacity model under three emission scenarios is shown in Table 2. The results show that if Methyl Acrylonitrile is released to one of the compartments of air, water and soil, it is unlikely to distribute into other compartments.

Table 2: Environmental distribution of Methyl Acrylonitrile using a generic level III fugacity model under three emission scenarios

Compartment	Release: 100 % to air	Release: 100 % to water	Release: 100 % to soil
Air	90.3 %	8.4 %	8.4 %
Water	9.2 %	91.3 %	10.5 %
Soil	0.5 %	0.0 %	81.0 %
Sediment	0.0 %	0.3 %	0.0 %

2.3 Human Exposure

2.3.1 Occupational Exposure

Major routes of occupational exposure are inhalation of vapor and dermal contact of liquid. Exposure to this chemical is possible through handling quality control samples and tank lorry filling. In quality control sample handling, 50 ml of liquid sample are taken in a cap-seal bottle placed in the sampling hopper with local exhaust ventilation, and analyzed by a gas chromatograph in the fume hood. The sampling operation takes 2 minutes. Estimated exposure concentration for this operation is 10-50 ppm, derived with the EASE model assuming non-dispersive use, medium volatility, and local exhaust ventilation. During lorry filling, vent air from the lorry is transferred to the storage tank by return pipe and the liquid transfer tube is purged with nitrogen before decoupling, to minimize vapor release and liquid spill. The lorry filling operation takes 1 hour but the duration of exposure is less than 5 minutes. The estimated exposure concentration for this operation is 10-50 ppm, assuming medium volatility.

The estimated dermal exposure for these operations is 0-0.1 mg/cm^2/day using the EASE model and assuming non-dispersive use, direct handling, incidental contact. The EHE_{inh} for a worker who does sampling and packing operation is 0.11 mg/kg·bw/day. The EHE_{der} for the same work without protective equipment is 1.2 mg/kg·bw/day. Workers wear safety goggles and protective gloves in these operations. ACGIH recommends a threshold limit value (TWA) for this chemical of 1 ppm (3 mg/m^3) with skin notation.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

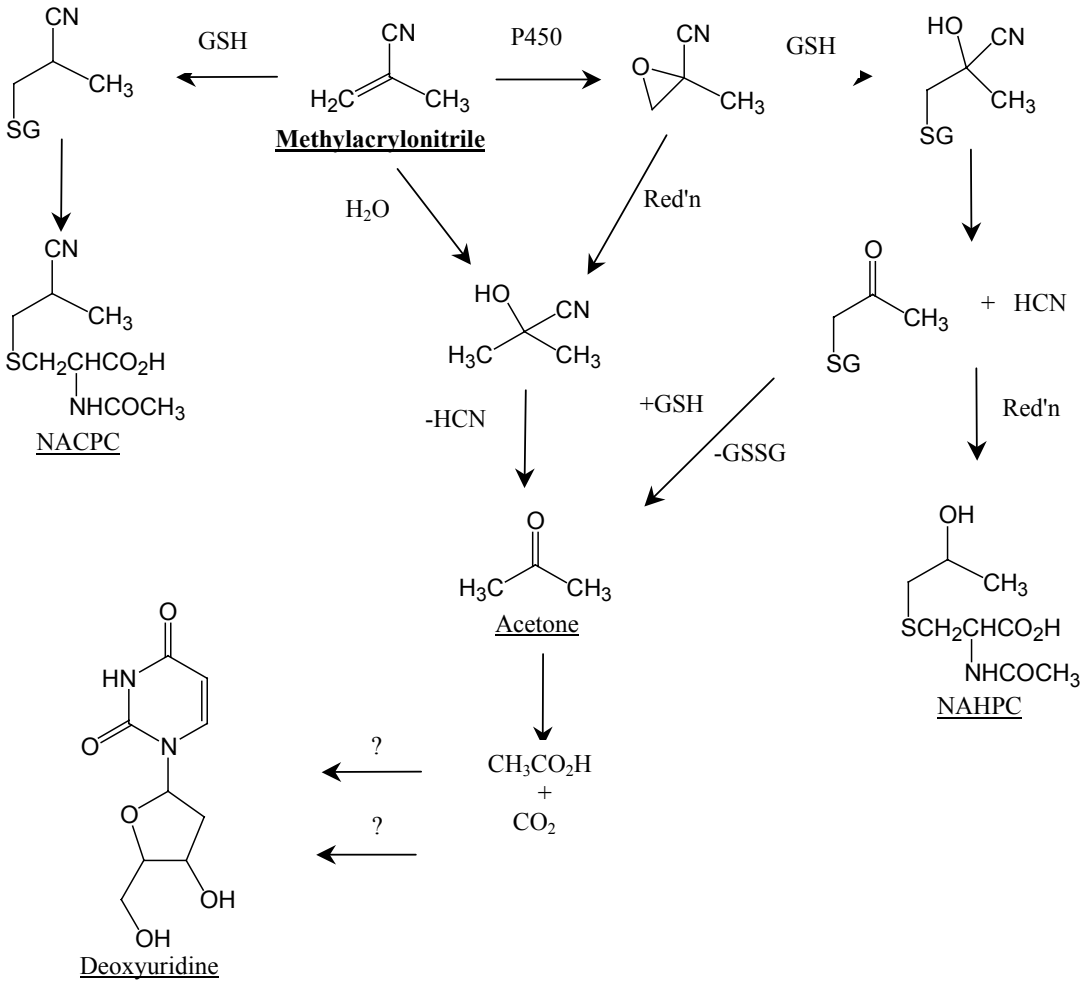
[2-^{14}C]-Methylacrylonitrile orally administered to male F344 rats at 1.15 and 11.5 mg/kg b.w. was excreted mostly in expired air as carbon dioxide (60 % to 70 % of the dose) within 72 hr, while at 115 mg/kg b.w. the exhaled compounds were only 25 % as carbon dioxide, and 35 % as unchanged form and 10 % as acetone [Ghanayem et al.: 1992]. This result suggests that the elimination or metabolism is saturated at dose above 11.5 mg/kg b.w. Urinary excretion accounted for 20-30 % of the dose in all treated groups. Major urinary metabolites were deoxyuridine, N-acetyl-S-(2-hydroxypropyl)-L-cysteine (NAHCP) and N-acetyl-S-(2-cyanopropyl)-L-cysteine (NACPC) [Ghanayem et al.: 1994]. The radioactivity was particularly high in the liver, kidney, urinary bladder, intestine, adrenal gland, and thymus. The radioactivity that remained in tissues 72 hr after dosing was less than 3 % of the dose, suggesting that the potential for methylacrylonitrile bioaccumulation is minimal. Cavazos et al. (1989) reported that the red blood cells retained significant amounts of radioactivity (more than 50 % in red blood cells was detected as covalently bound to hemoglobin and membrane proteins) for more than five days after oral administration of 100 mg [2-^{14}C]-methyl-[2,3-^{14}C]-acrylonitrile/kg b.w. to SD rats.

In an intravenous study at 29, 58 or 116 mg/kg b.w. in male F344 rats, the terminal half-life of 39 min shows that 99 % of the dose is eliminated in less than 5 hr [Demby et al.: 1993]. Clearance at 29 mg/kg b.w. is higher than at the two higher doses. At 58 mg/kg b.w., approximately 36 % of the dose was exhaled as unchanged methylacrylonitrile, 26 % as carbon dioxide and 17 % as acetone, and 16 % was excreted into the urine. In another study [Ahmed et al.: 1996], after intravenous administration of [2-^{14}C]-methylacrylonitrile (14.5 mg/kg b.w.) to male Fischer 344 rats, the respiratory tissues contained high levels of radioactivity at an early period (5 min), while the gastrointestinal mucosa, adrenal cortex, liver, and kidney contained high levels of radioactivity at later periods (8, 24, and 48 hr).

As for the metabolism of methylacrylonitrile, many reports enabled us to propose an overall metabolism scheme (Scheme 1) [Ghanayem et al.: 1994]. A major metabolic pathway of methylacrylonitrile is epoxidation to 1-cyano-1-methyoxirane in a reaction catalyzed by the cytochrome P450 enzymes. 1-Cyano-1-methyloxirane interacts with GSH, resulting in the formation of 1-(S-glutathionyl)-2-propanone (SGTP), which was identified in the bile of male F344 rats administered methylacrylonitrile by gavage [Ghanayem & Burka: 1996]. In a NTP 13-week study [NTP: 2000], dose-related increase in blood cyanide and serum thiocyanate concentrations occurred in rats orally administered methylacrylonitrile at up to 85.7 mg/kg b.w./day. Metabolism of 1-cyano-1-methyloxirane is considered the main pathway leading to release of cyanide, which is converted to thiocyanate.

Metabolism and excretion of methylacrylonitrile is reported to be dosing vehicle and species/strain dependent. In an oral study, rats receiving 115 mg/kg b.w. of methylacrylonitrile in water survived to 72 hr after dosing, while all rats receiving methylacrylonitrile in safflower oil at the same dose

died within 24 hr [Ghanayem et al.: 1992]. Monitoring the fate of methylacrylonitrile in these rats before death showed decreased elimination of unchanged methylacrylonitrile and increased metabolism to acetone and/or decreased degradation of acetone to carbon dioxide. Administration of methylacrylonitrile to SD rats in water or oil caused minimal change in the disposition and showed no lethal effect compared with that caused in F344 rats. Male F344 rats and male B6C3F1 mice orally administered with 11.5 mg/kg b.w. of methylacrylonitrile excreted 7 and 49 %, respectively, of the dose as NAHCP [Ghanayem et al: 1994]. More carbon dioxide and deoxyuridine was eliminated in rats than in mice. These data, in addition to earlier reports showing that a greater portion of the methylacrylonitrile dose was converted to cyanide in mice and gerbils than in rats [Farooqui et al.: 1992], support the hypothesis that mice metabolize methylacrylonitrile via the epoxide intermediate to a greater extent than rats.



Scheme 1: A proposed scheme of methylacrylonitrile metabolism in rats (Ghanayem et al.: 1994)
GSH: Glutathione, P450: cytochrome P450, GSSG: glutathione disulfide
?: Acetone may be incorporated in the biosynthesis of a deoxyuridine that derive deoxyuridine, but the pathway is unsubstantiated.

3.1.2 Acute Toxicity

Studies in Animals

The acute toxicity is significantly different among species and the values in rats are especially higher than that in other species as shown in Table 3. Oral LD_{50} was 64~240 mg/kg b.w. for rats, 17 mg/kg b.w. for mice, 16 mg/kg b.w. for rabbits and 3.8~4.9 mg/kg b.w. for gerbils. In acute inhalation toxicity studies, LC_{50} of rats via inhalation was also obviously different from that of mice and rabbits and common clinical signs were unconsciousness and tonic-clonic convulsions. However, all information on the acute inhalation toxicity were reported in 1968. Dermal LD_{50} study was 2,080 mg/kg for rats and 256 mg/kg for rabbits. In rabbits, gasping and convulsion were observed at 0.25 ml/kg b.w. (195 mg/kg b.w.) or more. The study by MHLW (2001) was identified as a key study because it was the latest study and well conducted.

The study by MHLW (2001) was conducted according to OECD TG 401 under GLP. SD rats were given methylacrylonitrile by gavage at doses of 50, 60, 70, 85 and 100 mg/kg b.w. for males, and 60, 70, 85, 100 and 120 mg/kg b.w. for females. Fatality occurred in both sexes of all treated groups. Clinical signs such as decrease in locomotor activity, adoption of a prone and/or lateral position, and hyperpnea were found in all treated groups. At autopsy, bright orange discoloration in the lung and dilatation of the right atrium in the heart were observed in dead males and females. The LD_{50} values were 64 mg/kg b.w. for males and 73 mg/kg b.w. for females.

Table 3: Acute toxicity of methylacrylonitrile in experimental animals

Route	Species	Type	Value	Reference
Oral	Rat	LD_{50}	64 mg/kg b.w. for males 73 mg/kg b.w. for females	MHLW, Japan: 2001
	Rat	LD_{50}	240 mg/kg b.w. for males	Pozzani et al.: 1968
	Rat	LD_{50}	120 mg/kg b.w.	Kurzaliev: 1985
	Mouse	LD_{50}	17 mg/kg b.w. for males	Tanii & Hashimoto: 1984
	Gerbil	LD_{50}	3.8 mg/kg b.w. for males 4.9 mg/kg b.w. for females	Farooqui et al.: 1991, 1992
	Rabbit	LD_{50}	16 mg/kg b.w.	Kurzaliev: 1985
Inhalation	Rat	LC_{50}	328 ppm/4 hr for males	Pozzani et al.: 1968
	Rat	LC_{50}	328 ppm/4 hr for males	Pozzani et al.: 1968
	Rat	LC_{50}	700 ppm/4 hr for females	Pozzani et al.: 1968
	Rat	LC_{50}	496 ppm/4 hr for females	Pozzani et al.: 1968
	Rat	LC_{100}	85,500 ppm/3.75 min for females	Pozzani et al.: 1968
	Mouse	LC_{50}	36 ppm/4 hr for males	Pozzani et al.: 1968
	Rabbit	LC_{50}	37 ppm/4 hr for males	Pozzani et al.: 1968
	Guinea pig	LC_{50}	88 ppm/4 hr for males	Pozzani et al.: 1968
	Dog	Other*	52.5 ppm/7 hr for female	Pozzani et al.: 1968
	Dog	Other**	106.1 ppm/7 hr for female	Pozzani et al.: 1968
	Dog	Other***	106.1 ppm/3 hours for female	Pozzani et al.: 1968
Dermal	Rat	LD_{50}	2,080 mg/kg b.w.	Kurzaliev: 1985
	Rabbit	LD_{50}	256 mg/kg b.w. (0.32 mL/kg b.w.)/24 hours for males	Pozzani et al.: 1968

*One dog exposed to methylacrylonitrile died overnight.
**One dog exposed to methylacrylonitrile died within 7 hr.
***One dog exposed to methylacrylonitrile died within 3 hr

Studies in Humans

There is no available information on human toxicity.

Conclusion

There are definite species differences in the acute toxicity. The acute toxicity in rats is especially lower than that in other species. The oral LD_{50} was 64~240 mg/kg b.w. for rats, 17 mg/kg b.w. for mice, 16 mg/kg b.w. for rabbits and 3.8~4.9 mg/kg b.w. for gerbils. Inhalation LC_{50} of rats was also obviously higher than that of mice and rabbits although all these were reported in 1968.

3.1.3 Irritation

Studies in Animals

Mild irritation to skin in rabbits at 500 mg /24 hr was reported [Marhold et al.: 1986].

Mild irritation to eyes in rabbits at 500 mg /24 hr was reported [Marhold et al.: 1986].

Studies in Humans

Only one report is available on irritation of the chemical to humans [Pozzani, et al.: 1968]. In the 1st study, groups of eight to nine subjects were exposed to methylacrylonitrile vapor at 0, 2, 7, 14, 24 ppm twice for 1 min with 45 min or longer intervals. Only in the 24 ppm group, nose (6 %), throat (17 %), or eye irritation (22 %) was experienced. In the 2nd study, exposure of 9 subjects to 2 ppm or 7 subjects to 14 ppm vapor for 10 min caused nose, throat and eye irritation only in one to two subjects.

Conclusion

Methylacrylonitrile was mildly irritating to skin and eyes in rabbits. This chemical is slightly irritating to respiratory tracts and eyes in humans (even at 2 ppm (6 mg/m^3) for 10 minutes). There is no available data on skin sensitization.

3.1.4 Sensitisation

There is no data available on skin sensitization.

3.1.5 Repeated Dose Toxicity

Six oral and four inhalation studies including two oral carcinogenic studies were reported as shown in Table 4.

Studies in Animals

Inhalation

Inhalation studies using rats and dogs demonstrated death without any clinical signs in rats, and some central nervous effects including histopathological changes in the brain but no deaths in dogs [Pozzani et al.: 1968]. The NOAELs for repeated dose toxicity by inhalation in rats and dogs were reported as 19.3 ppm and 8.8 ppm, respectively. However, the validity of these studies are not sufficient because the hematological and blood chemical examination were not conducted in the rat study and the measurement of organ weights other than liver and kidneys were not conducted in both studies.

Oral

In 13-week studies by NTP (2000), effects such as death, anemia, and olfactory epithelium metaplasia and necrosis were observed at 60 mg/kg b.w. (42.9 mg/kg b.w./day) and more in rats, and death at 12 mg/kg b.w. (8.6 mg/kg b.w./day) in mice. However, for clinical signs (lethargy, lacrimation, tremors, convulsions, ataxia, and abnormal breathing) observed with dose-dependency, no information on the incidence was reported at each dose. Therefore, a NOAEL for these studies could not be established. The study by MHLW (2001) and the carcinogenicity studies by NTP (draft, 2001) were identified as key studies because they were well conducted under GLP.

According to an OECD combined repeated dose and reproductive/developmental toxicity screening test [TG 422], SD rats (12 animals/sex/dose) received gavage doses of 0 (vehicle: olive oil), 7.5, 15, 30 mg/kg b.w./day [MHLW, Japan: 2001]. Males were dosed for 46 days and females were dosed from 14 days before mating to day 4 of lactation throughout the mating and pregnancy period.

No abnormalities were detected for males and females in cage side observations. No significant changes of body weight and food consumption for males and females, and urinalysis findings for

males were detected. Hematological examination showed decreases in erythrocyte counts and hemoglobin concentrations in males at 30 mg/kg b.w. Blood chemical examination showed a decrease in potassium in males at doses of 15 and 30 mg/kg b.w., an increase in creatinine in males at 30 mg/kg b.w., and increases in total bilirubin and glucose in females at 30 mg/kg b.w. On histopathological examination, extramedullary hematopoiesis in the spleen was observed in 3 or 7 of 12 females at 15 or 30 mg/kg b.w., respectively, but the incidence was statistically significant only at 30 mg/kg b.w. The changes observed at 15 mg/kg b.w. were not considered to be adverse effects. Therefore, based on anemia at 30 mg/kg b.w. in males, the NOAEL for repeated dose toxicity was considered to be 15 mg/kg b.w./day.

In a 2-year carcinogenicity study [NTP, draft: 2001], methylacrylonitrile was administered by gavage to F344 rats at 0 (vehicle control: deionized water), 3, 10 and 30 mg/kg b.w. and to B6C3F1 mice at 0, 1.5, 3 and 6 mg/kg b.w. (once a day, 5 days/week). Hematological and blood biochemical examination was not conducted. In the SIDS Dossier, this study was placed in section 5.7 CARCINOGENICITY.

In rats, survival rates of all dosed groups were similar to that of the vehicle control. Both sexes at 30 mg/kg b.w. showed lower body weights than in the control. The incidences of olfactory epithelial atrophy and metaplasia of the nose were significantly greater at 30 mg/kg b.w. for both sexes than those in the control. The incidence of bone marrow hyperplasia, mostly composed of mixed myeloid and erythroid cells, was increased in females at 30 mg/kg b.w.. The incidence of diffuse cytoplasmic vacuolization, consistent with glycogen infiltration in the liver, significantly increased in males at 30 mg/kg b.w. and in all dosed groups of females. The severities were generally slightly greater than those in the vehicle controls. It was suggested that this liver change represents an adaptive response to the extensive hepatic metabolism of this compound in this species. Therefore, the NOAEL was considered to be 10 mg/kg b.w. (7.14 mg/kg b.w./day) for both sexes, based on histopathological changes in olfactory epithelium and bone marrow.

In mice, there were no changes in survival and mean body weight, and no dose-related histopathological changes in all dosed groups. Therefore, the NOAEL was considered to be 6 mg/kg b.w. (4.29 mg/kg b.w./day).

Table 4: Repeated dose toxicity of methylacrylonitrile in experimental animals.

Route	Species (strains)	Duration	NOAEL	Toxic effects	Reference
Oral	Rat (SD)	At least 39 days	15 mg/kg b.w./day	Anemia	MHLW, Japan: 2001
	Rat (F344/N)	13 weeks (5 days/week)	Not established (no information on the incidence of clinical signs)	Death, clinical signs, anemia, olfactory epithelium metaplasia and necrosis	NTP: 2000
	Rat (F344/N)	2 years (5 days/week)	10 mg/kg b.w. (7.14 mg/kg b.w./day)	Decrease in body weight, olfactory epithelium metaplasia and atrophy, bone marrow hyperplasia	NTP, draft: 2001
	Mouse	13 weeks (5 days/week)	Not established (no information on the incidence of clinical signs)	Death, clinical signs	NTP: 2000
	Mouse	2 years (5 days/week)	6 mg/kg b.w. (4.29 mg/kg b.w./day)	No toxic effects	NTP, draft: 2001
Inhalation	Rat*	9 days (7 hr/day, 5 days/week)	Not established (no information on histopathological findings)	Death	Pozzani, et al.: 1968
	Rat	91 days (7 hr/day, 5days/week)	19.3 ppm for males 109.3 ppm for females	Death	Pozzani, et al.: 1968
	Dog* (female)	8 days (7 hr/day, 5 days/week)	< 20 ppm for females	Vomit, body weight loss	Pozzani, et al.: 1968
	Dog (male)	90 days (7 hr/day, 5 days/week)	8.8 ppm for males	Clinical signs, histological change in brain	Pozzani, et al.: 1968

*preliminary study

Studies in Humans

There is no available toxicity information on humans.

Conclusion

In oral repeated dose studies in rats, anemia and histopathological changes in olfactory epithelium and bone marrow were observed. In addition, rats and mice at the higher doses showed clinical signs such as lethargy, tremors and convulsions. In a 2-year carcinogenicity study, the NOAEL for repeated dose toxicity via oral administration was considered to be 7.14 mg/kg b.w./day for rats and 4.29 mg/kg b.w./day for mice. For inhalation exposure (90 days), the NOAEL was reported as 19.3 ppm (57.9 mg/m^3) for rats and 8.8 ppm (26.4 mg/m^3) for dogs although the data quality was not sufficient.

3.1.6 Mutagenicity

Table 5: Summary of genotoxicity assay

Type of test	Test system	Doses	Result	Reference
Bacterial test				
Ames test *(reverse mutation)*	*S. typhimurium* (TA98, TA100, TA1535, TA1537) *E. coli* (WP2 *uvr* A)	Up to 5,000 ug/plate	Negative (+ & - MA*)	MHLW, Japan: 2001
Ames test *(reverse mutation)*	*S. typhimurium* (TA97, TA98, TA100, TA1535, TA1537)	Up to 10,000 ug/plate	Negative (+ & - MA)	Zeiger et al.: 1987, NTP: 2000
Ames test *(reverse mutation)*	*S. typhimurium* (TA98, TA100)	Up to concentrations which exhibit toxic effects	Negative (+ & - MA)	Knaap et al.: 1985
Fluctuation test	*Klebsiella pneumoniae*	Up to concentrations which exhibit toxic effects	Positive (- MA)	Knaap et al.: 1985
Non-bacterial in vitro test				
Gene mutation test	L5178Y mouse lymphoma cells	Up to concentrations which exhibit toxic effects	Negative (+ & - MA)	Knaap et al.: 1985
Chromosomal aberration test	CHL cells	Up to 0.67 mg/mL	Positive (+ MA) Negative (- MA)	MHLW, Japan: 2001
Unscheduled DNA synthesis assay	HepG2 cells	Up to 40 nm/plate	Inconclusive (- MA)	Vasanthakumari et al.: 1997
In vivo test				
Micronucleus assay	Rat (male)	Up to 200 mg/kg b.w. (i.p.)	Negative	NTP: 2000
Micronucleus assay	Mouse (male)	Up to 25 mg/kg b.w. (i.p.)	Negative	NTP: 2000
Micronucleus assay	Mouse (both sexes)	Up to 8.57 mg/kg b.w /day (by gavage for 13 weeks)	Negative	NTP, draft: 2001

In vitro Studies

Bacterial tests

Methylacrylonitrile had been investigated in three Ames tests, all of which showed negative results. A fluctuation test using Klebsiella pneumoniae showed positive result, but it was reported only as a brief abstract and there were no information on chemical concentrations and frequency of fluctuations. The Ames test by MHLW (2001) was identified as a key study because it was well conducted and reported under GLP.

A reverse gene mutation assay was conducted according to OECD TG 471 & Japanese Guideline for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan) [MHLW, Japan: 2001]. This chemical was not mutagenic in Salmonella typhimurium TA100, TA1535, TA98, TA1537 and Escherichia coli WP2 urv A at concentrations of up to 5,000 ug/plate, with or without an exogenous metabolic activation.

Non-bacterial tests

A gene mutation test, a chromosomal aberration test and an unscheduled DNA synthesis (UDS) assay were reported. The gene mutation test at the HPRT- and TK-loci in L5178Y mouse lymphoma cells showed negative results [Knaap et al.: 1985], but it was reported only as a brief abstract. Positive results were given in an UDS assay in HepG2 cells but it did not show dose-dependency and there were insufficient data on cytotoxicity [Vasanthakumari: 1997]. The Chromosomal aberration test [MHLW, Japan: 2001] was identified as a key study because all experimental conditions and reporting were sufficient.

The chromosomal aberration test was conducted with cultured Chinese hamster lung (CHL/IU) cells according to OECD TG 473 under GLP [MHLW, Japan: 2001]. Cells with structural chromosomal aberrations increased dose-dependently after short-term treatment at 0.068, 0.14 and 0.27 mg/mL with an exogenous metabolic activation (frequency: 7.5, 15.0, 62.0 %, respectively). A significant increase in incidence of polyploidy was observed after short-term treatment at 0.068 and 0.14 mg/mL (frequency: 3.13 and 1.88 %, respectively) with an exogenous metabolic activation but did not show dose-dependency, which may be due to a division delay because cell number and mitotic index decreased. Cytotoxicity was observed after short-term treatment at the highest concentration of 0.54 mg/mL with an exogenous metabolic activation.

In vivo Studies

Three micronucleus tests in rats and mice were reported. Results of bone marrow micronucleus tests by intraperitoneal injection to male rats and male mice were negative, but no sufficient information was given on the toxicity induced by the injection [NTP: 2000]. In another micronucleus study, at the end of the above-mentioned 13-week study in mice, peripheral blood samples were obtained and there were also no evidence of methylacrylonitrile-induced genetic damage [NTP, draft: 2001]. This test was identified as a key study because it was well conducted and reported.

In a micronucleus test using male and female B6C3F1 mice, methylacrylonitrile was administered by gavage for 13 weeks (5 days/week) at 0, 0.75, 1.5, 3, 6, or 12 mg/kg b.w. [NTP, draft: 2001]. After that, peripheral blood samples were obtained. As a result, no increase in the frequency of micronucleated polychromatic erythrocytes was observed in all dosed groups. Death occurred at 12 mg/kg b.w.

Conclusion

This chemical was not mutagenic with and without an exogenous metabolic activation system in bacterial test, while the cytogenetic effect was judged to be positive because of increases of cells with structural chromosomal aberrations and polyploidy with an exogenous metabolic activation in mammalian cultured cells. However, micronucleus tests by intraperitoneal injection to rats and mice or by gavage to mice showed negative results. Therefore, a weight of evidence suggests that this chemical is not genotoxic in vivo.

3.1.7 Carcinogenicity

In vivo Studies in Animals

Oral

Two oral carcinogenicity studies in rats and mice were reported [NTP, draft: 2001]. Both were identified as key studies because they were well conducted and reported under GLP.

Methylacrylonitrile was administered by gavage to F344 rats at 0 (vehicle control: deionized water), 3, 10 and 30 mg/kg b.w. and to B6C3F1 mice at 0, 1.5, 3 and 6 mg/kg b.w. for 2 years (once a day, 5 days/week) [NTP, draft: 2001]. No changes in the incidences of neoplasms were attributed to exposure to methylacrylonitrile in rats and mice. Other information is mentioned in section e) Repeated dose toxicity.

Studies in Humans

There is no carcinogenic information on humans.

Conclusion

In 2-year oral studies, methylacrylonitrile did not cause any neoplastic changes in rats (up to 21.4 mg/kg b.w./day) and mice (up to 4.29 mg/kg b.w./day). Therefore, this chemical was considered not to be carcinogenic in rodents.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

Two studies were conducted on reproductive toxicity. One is an OECD combined repeated dose and reproductive/developmental toxicity screening test (OECD TG 422) [MHLW, Japan: 2001]. Another study was conducted according to a Reproductive Assessment by Continuous Breeding protocol (RABC) in the National Toxicology Program [NTIS: 1997]. Both were identified as key studies because these studies were conducted according to the current test guideline or protocol under GLP. On the other hand, in the above-mentioned 13-week study [NTP: 2000], longer estrous cycle was observed in female rats orally administered at 42.9 or 85.7 mg/kg b.w./day but not at 21.4 mg/kg b.w./day. In addition, in one developmental toxicity study, the NOAEL for reproductive toxicity was not established because most of the pregnant rats did not deliver at 50 or 100 mg/kg b.w. by oral administration for the first or second week of gestation. These rats showed severe clinical signs such as ataxia and convulsion, decreased body weight gain, and increased incidence of edema and release of fluids in the reproductive tract [Farooqui & Villarreal: 1992].

In the MHLW study (2001), methylacrylonitrile was administered to SD rats by gavage at doses of 0 (vehicle: olive oil), 7.5, 15 and 30 mg/kg b.w./day for 46 days from 14 days prior to mating in males and for 39-51 days from 14 days prior to mating to day 4 of lactation throughout mating and pregnancy in females [MHLW, Japan: 2001].

No effects were observed on reproductive performance such as mating, fertility, delivery and lactation in both sexes of all treated groups. There were also no effects on estrous cycles during the pre-mating period. The NOAEL for reproductive toxicity is considered to be 30 mg/kg b.w./day for both sexes.

In the RACB study [NTIS: 1997], methylacrylonitrile was administered by gavage to SD rats at 2, 7, and 20 mg/kg b.w. for two generations. In the first generation, after 1-week exposure, rats (F0)

were housed as breeding pairs for about 15 weeks. Generally, four to five litters are delivered per pair during this cohabitation period and the pups are removed and humanely killed. After the cohabitation period, the pair was separated for 6 weeks, during which the female delivered and nursed to weaning any last litter that she may have conceived just prior to the end of the cohabitation period. In the second generation, exposure to methylacrylonitrile started at weaning at the same exposure level as that given to their parents. When they were approximately 80 days of age, they were cohabited within the treated groups for a week. The female carried and delivered the litter, and the pups were killed.

Methylacrylonitrile did not affect the reproductive performance of F0 or F1 rats. The percent of normal sperm was decreased slightly (by ~1%) in the 2 and 20 mg/kg b.w. of F0 males while no differences were seen in F0 epididymal sperm density. In the F1 generation, epididymal sperm density was decreased by 19 % at 20 mg/kg b.w. but epididymal sperm morphology was unchanged. F0 and F1 sperm motion parameters and testicular spermatid head counts were unchanged. The change in epididymal sperm abnormalities in F0 rats was within the historical control range in this laboratory. Therefore, NOAELs for reproductive toxicity were considered 7 mg/kg b.w./day, based on low sperm density in epididymis in second generation.

Developmental Toxicity

Seven studies were available for developmental toxicity of methylacrylonitrile, as shown in Table 6. Farooqui & Villarreal (1992) conducted a developmental study, in which methylacrylonitrile in safflower oil was administered by gavage to rats for the first week of gestation at 50 mg/kg b.w. or the second week at 50 or 100 mg/kg b.w. Due to severe maternal toxicity (most of rats could not keep pregnancy), effects on fetal development could not be examined. These maternal effects were not observed even at 50 mg/kg b.w. in rats in another developmental study by George et al. (1996). The reason for these different results was attributed to safflower oil which was used as vehicle in the study by Farooqui & Villarreal (1992), compared with distilled water in the study by George et al. (1996). In the above-mentioned OECD combined study (TG 422) [MHLW, Japan: 2001], no effect was detected on viability, general appearance or autopsy findings of offspring. On the other hand, in the RABC study [NTIS: 1997], since epididymal sperm density was decreased by 19 % at 20 mg/kg b.w. in the second generation, the NOAEL for developmental toxicity was established at 7 mg/kg b.w. In addition to the latter two studies, oral studies in rats and rabbits by George et al. (1996) and inhalation study in rats by Saillenfait et al. (1993) were identified as key studies because they were well conducted and reported.

George et al. (1996) conducted an oral developmental toxicity study under GLP. Methylacrylonitrile in distilled water was administered by gavage to SD rats at 5, 25 or 50 mg/kg b.w. from days 6 to 15 of gestation, and to New Zealand white rabbits at 1, 3 or 5 mg/kg b.w. from days 6 to 19 of gestation.

No treatment-related effects on maternal mortality, clinical signs or body weight were observed in all treated rats. Since there was also no effect on the number of live fetuses, fetal body weight per litter or morphological development, the NOAEL was considered to be 50 mg/kg b.w./day.

In the rabbit study, no dose-related effects on maternal mortality, clinical signs or body weight were observed. Although there was no effect on live litter size or fetal body weight per litter, male/female ratio of fetuses per litter was significantly dropped at 5 mg/kg b.w. (40 %) compared to the control (61 %). The prevalence of external, visceral, or skeletal malformations or variations was not affected. Therefore, the NOAEL was considered to be 3 mg/kg b.w., based on a decreased ratio of male/female per litter.

In the inhalation study, SD rats were exposed to 6, 12, 25, 50, 100 ppm of methylacrylonitrile from days 6 to 20 of gestation (6 hr/day) [Saillenfait et al.: 1993].

No maternal deaths were observed. The maternal body weight gain between days 6 and 21 of gestation in the 100 ppm group significantly decreased by about 25 %, compared to that in the control group. No effects of the test chemical on the number of live fetuses, male/female ratio of fetuses, general appearance or autopsy findings of fetuses were observed. Male and female fetal body weights were significantly decreased at 100 ppm, which was considered to be due to the decrease in maternal body weight gain. The NOAEL for developmental toxicity was 50 ppm, based on low fetal body weights.

Table 6: Developmental toxicity of methylacrylonitrile in experimental animals.

Route	Species	Exposure period	NOAEL	Toxic effects	Reference
Oral (gavage)	Rat (SD)	Days 6 to 15 of gestation	50 mg/kg b.w.	No adverse effects	George et al.: 1996
	Rat (SD)	For the first week of gestation	Not established	Not examined due to maternal toxicity	Farooqui & Villarreal: 1992
	Rat (SD)	For the second week of gestation	Not established	Not examined due to maternal toxicity	Farooqui & Villarreal: 1992
	Rat (SD)	Reproductive test	30 mg/kg b.w.	No adverse effects	MHLW, Japan: 2001
	Rat (SD)	Reproductive test	7 mg/kg b.w.	Decrease in epididymal sperm density in the second generation	NTIS: 1997
	Rabbit (NZW*)	Days 6 to 19 of gestation	3 mg/kg b.w.	Decrease in male/female ratio of fetuses/litter	George et al.: 1996
Inhalation	Rat (SD)	Days 6 to 20 of gestation (6 hr/day)	50 ppm	Decrease in fetal body weight	Saillenfait, et al.: 1993

*NZW: New Zealand White rabbit

Studies in Humans

There is no available information on humans.

Conclusion

In an OECD combined study, there were no effects of this chemical on reproductive/developmental parameters even at the highest dose of 30 mg/kg b.w.. In a two-generation study in rats, this chemical did not affect the reproductive performance of both sexes, but induced a decrease of epididymal sperm density in the second generation at 20 mg/kg b.w. At the higher doses in rats (40 to 100 mg/kg b.w.), prolonged estrous cycles were observed in an oral 13-week study and the pregnancy was not kept in an oral developmental study. In another developmental study in rats, there were no effects on fetal development up to 50 mg/kg b.w. by oral administration. Based on these information, the oral NOAEL for reproductive/developmental toxicity in rats was considered to be 7 mg/kg b.w./day. On the other hand, there was a decrease in the male/female ratio of fetuses/litter at a dose of 5 mg/kg b.w. in rabbits and a decreased body weight of fetuses was observed at 100 ppm (300 mg/m^3) by inhalation, probably due to maternal toxicity. The NOAEL for developmental toxicity was 3 mg/kg b.w. in rabbits by oral administration, and 50 ppm (150 mg/m^3) in rats by inhalation. This chemical is not a teratogen.

3.1.9 Other human health related information

Neurotoxicity

One study was available regarding neurotoxicity of methylacrylonitrile. Male SD rats were orally administrated methylacrylonitrile at 50, 70 or 90 mg/kg b.w. for 12 weeks (5 days/week) [Gagnaire et al.: 1998]. Two and eight rats died in the low and high dose groups, respectively. The body weight was significantly decreased at 70 and 90 mg/kg b.w. However, no abnormal behaviors or no significant changes in motor and sensory conduction velocities and amplitudes of the sensory and motor potentials of the tail nerve were seen.

Mutation test in insect

There were two sex-linked recessive lethal mutation assays using Drosophila melanogaster. Sex-linked recessive lethal mutations were not induced in germ cells of male Drosophila melanogaster fed methylacrylonitrile (approximately 6,000 ppm in feed) during the larval stage (Zimmering et al.: 1989, NTP: 2000). Another sex-linked recessive lethal assay in Drosophila melanogaster also showed the same results (injection; up to concentrations which exhibit toxic effects) [Knaap et al: 1985].

Conclusion

Sex-linked recessive lethal assays in Drosophila melanogaster indicated negative result.

3.2 Initial Assessment for Human Health

Methylacrylonitrile was readily absorbed through the gastrointestinal tract. It distributed to all tissues, but the potential for the bioaccumulation was minimal. The main excretion route was expired air as carbon dioxide, which was saturable with increased dose. Metabolism and excretion of this chemical depend on the dosing vehicle and the species/strain.

There are definite species differences in the acute toxicity. The oral LD_{50} was 64~240 mg/kg b.w. for rats, 17 mg/kg b.w. for mice, 16 mg/kg b.w. for rabbits and 3.8~4.9 mg/kg b.w. for gerbils. Clinical signs were decrease in locomotor activity, adoption of a prone and/or lateral position, and hyperpnea. Inhalation LC_{50} of rats was also obviously higher than that of mice and rabbits although all these were reported in 1968. Clinical signs by inhalation were unconsciousness and tonic-clonic convulsions.

The acute toxicity profile of this chemical in all species was very much simular to cyanide-related central nervous system poisoning. Farooqui et al. (1992) also reported that a greater portion of the methylacrylonitrile dose was converted to cyanide in mice and gerbils than in rats. Significant differences in metablism of the methylacrylonitrile epoxide intermediate, which is likely to be responsible for the release of cyanide from methylacrylonitrile, may explain the species differences in acute toxicity of this chemical. Since there were no information on both the lethality and metablism of this chemical in humans, it is impossible to speculate which is the most appropriate animal model for the acute toxicity in humans. However, workers could easily avoid the lethality risk through the atmosphere because this chemical is irritanting to respiratory tracts and eyes as reported in human volantary studies [Pozzani, et al.: 1968].

This chemical was mildly irritating to skin and eyes in rabbits. In human voluntary study, this chemical was also slightly irritating to respiratory tracts and eyes (even at 2 ppm (6 mg/m^3) for 10 minutes). There is no available data on skin sensitization.

Six oral and four inhalation repeated dose toxicity studies including two oral carcinogenicity studies are available. Anemia and histopathological changes in olfactory epithelium and bone marrow

were observed in rat oral studies. In addition, rats and mice at the higher doses showed clinical signs such as lethargy, tremors and convulsions. In NTP 13-week studies, various effects including death were observed at 42.9 mg/kg b.w./day and more in rats, and at 8.6 mg/kg b.w./day in mice, showing significant species differences of the repeated dose toxicity. From a 2-year carcinogenicity study [NTP], the NOAEL for oral repeated dose toxicity was considered to be 7.14 mg/kg b.w./day for rats and 4.29 mg/kg b.w./day for mice. For inhalation exposure (90 days), the NOAEL was reported as 19.3 ppm (57.9 mg/m^3) for rats and 8.8 ppm (26.4 mg/m^3) for dogs although the data quality was not sufficient.

This chemical was not mutagenic with and without an exogenous metabolic activation system in bacterial tests [OECD TG 471], while the cytogenetic effect was judged to be positive because of increases in mammalian cultured cells with structural chromosomal aberrations and polyploidy with an exogenous metabolic activation [OECD TG 473]. However, micronucleus tests by intraperitoneal injection to rats and mice or by gavage to mice showed negative results [NTP]. Therefore, a weight of evidence suggests that this chemical is not genotoxic *in vivo*.

In 2-year gavage studies [NTP], this chemical did not cause any neoplastic changes in rats (up to 21.4 mg/kg b.w./day) and mice (up to 4.29 mg/kg b.w./day). Therefore, this chemical was considered not to be carcinogenic in rodents.

In an OECD combined study [TG 422], there were no effects of this chemical on reproductive/developmental parameters even at the highest dose of 30 mg/kg b.w.. In a two-generation study [NTP, RACB] in rats, this chemical did not affect the reproductive performance of both sexes, but induced a decrease of epididymal sperm density in the second generation at 20 mg/kg b.w. At higher doses in rats (40 to 100 mg/kg b.w.), prolonged estrous cycles were observed in an oral 13-week study [NTP] and the pregnancy was not kept in an oral developmental study. In another developmental study in rats, there were no effects on fetal development up to 50 mg/kg b.w. by oral administration. Based on these information, the oral NOAEL for reproductive/developmental toxicity in rats was considered to be 7 mg/kg b.w./day. On the other hand, there was a decrease in the male/female ratio of fetuses/litter at dose of 5 mg/kg b.w. in rabbits and a decreased body weight of fetuses was observed at 100 ppm (300 mg/m^3) by inhalation, probably due to maternal toxicity. The NOAEL for developmental toxicity was 3 mg/kg b.w. in rabbits by oral administration, and 50 ppm (150 mg/m^3) in rats by inhalation. This chemical is not a teratogen.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Methyl Acrylonitrile has been tested in a limited number of aquatic species. Results are summarized in Table 7. Regarding acute toxicity, for algae (*Selenastrum capricornutum*), a ErC50 of 25.3 mg/L(OECD TG 201, based on growth rate during 24-72 h) and a 72 h EbC50 of 15.1 mg/L (OECD TG 201) was determined. For daphnids (Daphnia magna) a 24 h EC50 of 440 and a 48 h EC50 of 200 mg/L (OECD TG 202 part 1) was determined. For fish (*Oryzias latipes*) a 96 h LC50 of >100 mg/L (OECD TG 203) was reported, however the test for fish was conducted as a limit test in which one concentration of 100 mg/L and a control was examined (MOE, Japan, 2001). The lowest acute toxicity of this substance was reported from the algal inhibition test (72 h EbC50 of 15.1 mg/L). A LC50 of 29.8 mg (21 d, OECD TG 211, parental mortality) was determined in a prolonged exposure test of this chemical to daphnids.

Two chronic toxicity values, for algae (*Selenastrum capricornutum*) and daphnids (*Daphnia magna*) are available. For algae a 72 h NOErC on growth inhibition of 10 mg/L (OECD TG 211,

based on growth rate) and a NOEbC of 1.0 mg/L (biomass method) were reported. For daphnids a 21 d EC50 of 6.33 and NOEC for reproduction of 2.2 mg/L were reported. All the values shown here were obtained from the tests conducted under GLP, and were calculated based on nominal concentration, since measured concentrations were ranged within 20 % difference of nominal ones (MOE, Japan, 2001). No information on the hazard potential of Methyl Acrylonitrile to sediment dwellers such as chironomid larvae are available.

Table 7: Summary of effects of Methyl Acrylonitrile on aquatic organisms

Organisms	Test duration	Result (mg/L)	Reference
Aquatic plants, e.g. algae			
Green alga (*Selenastrum capricornutum*)	72 h (cl,s)	Based on growth rate ErC50(24-48hr) >100(nc) NOECr (24-48hr) = 10(nc) ErC50(24-72hr) = 25.3(nc) NOECr (24-72hr) = 10 (nc) Based on biomass EbC_{50} = 15.1 (nc) LOEbC = 3.2 (nc) NOEbC = 1.0 (nc)	MOE , Japan (2001)
Invertebrates			
Water flea (*Daphnia magna*)	24 h (cl,s) 48 h (cl,s) 48 h (cl,s)	EC_{50} (Imm) = 440 (nc) EC_{50} (Imm) = 200 (nc) EC_0 (Imm) = 180 (nc)	MOE , Japan (2001)
	21 d (cl,ss)	LC_{50} = 29.8 (nc) EC_{50} (Rep) = 6.33 (nc) LOEC (Rep) = 4.60(nc) NOEC (Rep) = 2.20(nc)	MOE , Japan (2001)
Fish			
Medaka (*Oryzias latipes*)	96 h (cl,ss)	LC_{50} > 100 (nc) LC_0 = 100 (nc)	MOE , Japan (2001)

cl = closed system, s = static, ss = semi-static, nc = nominal, Bms = biomass, Imm = immobilization, Rep = reproduction

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

Methyl Acrylonitrile is readily biodegradable and its bioaccumulation potential seems to be low based on its Log P_{ow} (0.68). In the air, this chemical is expected to be photodegraded ($T_{1/2}$=about 46 hours). Hydrolysis is not expected to occur. A generic level III fugacity model shows that if Methyl Acrylonitrile is released to one of the compartments of air, water and soil, it is unlikely to distribute into other compartments.

Regarding the acute aquatic toxicity of this substance, the algal ErC50 of 25.3 mg/L and EbC50 of 15.1 mg/L are the lowest values among available data on species from three trophic levels.

Chronic toxicity NOEC values of 10 (growth rate) and 1.0 (biomass) mg/L for algae are reported. The NOEC for daphnids is 2.20 mg/L for reproduction.

The predicted no effect concentration (PNEC) of 0.01 mg/L for the aquatic organisms is calculated from the 72 h NOEbC for *Selenastrum capricornutum* using an assessment factor of 100, because two chronic data (*Daphnia* and *Selenastrum*) are available.

5 RECOMMENDATIONS

This chemical is not a candidate for further work unless there is significant exposure.

6 REFERENCES

Ahmed, A.E. et al. (1996) *Fundam. Appl. Toxicol.*, 33, 49-59.

Cavazos, R.Jr. et al. (1989) *J. Appl. Toxicol*., 9, 53-57.

Demby, K.B. et al. (1993) *Toxicol. Appl. Pharmacol.*, 119, 115-121.

Farooqui, M.Y. & Villarreal, M.I. (1992) *Bull. Environ. Contam. Toxicol.*, 48, 696-700.

Farooqui, M.Y. et al. (1991) *Toxicology*, 65, 239-250.

Farooqui, M.Y. et al. (1992) *Drug Metab. Disposit.*, 20, 156-160.

Gagnaire, F. et al. (1998) *J. Appl. Toxicol.*, 18, 25-31.

George, J.D. et al. (1996) *Fundam. Appl. Toxicol.*, 34, 249-259.

Ghanayem, B.I. & Burka, L.T. (1996) *Drug Metab. Disposit.*, 24, 390-394.

Ghanayem, B.I. et al. (1992) *Drug Metab. Disposit.*, 20, 643-652.

Ghanayem, B.I. et al. (1994) *J. Pharmacol. Exp. Ther.,* 269, 581-588.

Knaap, A.G.A. et al. (1985) *Mutat. Res.*, 147(5), 303.

Kurzaliev, S.A. (1985) *Gig. Tr. Prof. Zabol.* 5, 37-40.

Marhold, J. (1986) "Prehled Prumyslove Toxikologie; Organicke Latky," Prague, Czechoslovakia, Avicenum.

MHLW (Ministry of Health, Labour and Welfare; former MHW), Japan (2001) *Toxicity Testing Reports of Environmental Chemicals,* 8, 629-659.

MOE (Ministry of the Environment), Japan (2001).

NTIS Technical Report (1997) NTIS/PB97-176390 (NTP/RACB-94-019).

NTP (2000) NTP toxicity studies, 47.

NTP (2001) NTP technical reports, 497 (Draft).

Pozzani, U.C. et al. (1968) *Am. Ind. Hyg. Ass. J*., 29, 202-210.

Saillenfait, A.M. et al. (1993) *Fundam. Appl. Toxicol.,* 20, 365-375.

Tanii, H. & Hashimoto, K. (1984) *Arch. Toxicol.,* 55, 47-54.

Vasanthakumari, V et al. (1997) *Bull. Environ. Contam. Toxicol.*, 59, 274-278.

Zeiger, E. et al. (1987) *Environ. Mutagen.*, 9 (Suppl. 9), 1-110.

Zimmering, S. et al. (1989) *Environ. Mol. Mutagen.*, 14, 245-251.

SIDS DOSSIER

Methylacrylonitrile

CAS No. 126-98-7

Existing Chemical	:	ID: 126-98-7
CAS No.	:	126-98-7
EINECS Name	:	methacrylonitrile
EINECS No.	:	204-817-5
Molecular Weight	:	67.09
Common name	:	2-methyl-2-propenenitrile
Molecular Formula	:	C4H5N

Producer Related Part

Sponcer country	:	Japan
Creation date	:	07.10.2001
Printing date	:	22.01.2002
Revision date	:	
Date of last Update	:	22.01.2002
Number of Pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organic
Physical status : liquid
Purity : % w/w
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

2-Cyanopropene
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

2-Cyanopropene-1
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

2-Methyl-2-propenenitrile
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

2-Methylpropenenitrile
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

alpha-Methylacrylonitrile
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

Isopropene Cyanide
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

Isopropenylcarbonitrile
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

Methacrylonitrile
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

Methacrylonitrile
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
11.01.2002

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : TLV (US)
Limit value : 1 ppm
Remark : skin
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
22.01.2002 (2)

Type of limit : other: NIOSH REL (US)
Limit value : 1 ppm
Remark : 10 hour TWA
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
21.01.2002 (9)

Type of limit : other: OEL (Australia)
Limit value : 1 ppm
Remark : Skin
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
21.01.2002 (34)

Type of limit : other: OEL (Belgium)
Limit value : 1 ppm
Remark : Skin
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo

Reliability : (1) valid without restriction
21.01.2002 (34)

Type of limit : other: OEL (Denmark)
Limit value : 1 ppm
Remark : Skin
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
21.01.2002 (34)

Type of limit : other: OEL (Finland)
Limit value : 1 ppm
Remark : Skin
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
21.01.2002 (34)

Type of limit : other: OEL (France)
Limit value : 1 ppm
Remark : Skin
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
21.01.2002 (34)

Type of limit : other: OEL (Norway)
Limit value : 1 ppm
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
21.01.2002 (34)

Type of limit : other: OEL (Switzerland)
Limit value : 1 ppm
Remark : Skin
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
21.01.2002 (34)

Type of limit : other: OEL (The Netherlands)
Limit value : 1 ppm
Remark : Skin
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
21.01.2002 (34)

Type of limit : other: OEL (UK)
Limit value : 1 ppm
Remark : Skin
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Reliability : (1) valid without restriction
21.01.2002 (34)

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

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	= -35 ° C
Decomposition	:	no at ° C
Sublimation	:	
Method	:	other: Unknown
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion	:	Melting point is -35 C.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

11.01.2002 (40)

2.2 BOILING POINT

Value	:	= 90 - 92 ° C at
Decomposition	:	no
Method	:	other: Unknown
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion	:	Boiling point is 90-92 C.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

11.01.2002 (40)

2.3 DENSITY

Type	:	density
Value	:	= .8 g/cm3 at 20° C
Method	:	other: Unknown
Year	:	
GLP	:	no data
Test substance	:	no data
Source	:	Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion	:	Density is 0.800 g/cm3 at 20 C.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

11.01.2002 (44)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= 85 hPa at 20° C
Decomposition	:	no
Method		other (measured): Unknown
Year	:	
GLP	:	no data

Test substance : no data
Decomposition : no
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion Vapor pressure is 85 hPa at 20 C.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
11.01.2002 (40)

2.5 PARTITION COEFFICIENT

Log pow : = .68 at ° C
Method other (calculated)
Year :
GLP : no
Test substance :
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion : Log Pow is 0.68
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
11.01.2002 (14)

2.6.1 WATER SOLUBILITY

Value : = 29 g/l at 25 ° C
Qualitative : very soluble (> 10000 mg/L)
Pka : at 25 ° C
PH : at and ° C
Method : OECD Guide-line 105 "Water Solubility"
Year : 2000
GLP : yes
Test substance : other TS: Wako Pure Chemcial Industires Ltd. Purity: 99.97%
Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion : Water solubility is 29 g/L at 25 C.
Reliability : (1) valid without restriction
Well conducted study, carried out by Chemicals Evaluation and Research Institute, Japan.
Flag : Critical study for SIDS endpoint
11.01.2002

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	500000 molecule/cm3
Rate constant	:	= .00000000000836 cm3/(molecule*sec)
Degradation	:	= 50 % after 46 hour(s)
Deg. Product	:	
Method	:	other (calculated): Calculation by AOP Win (Syracuse research Corporation)
Year	:	2002
GLP	:	no
Test substance	:	no data
Source	:	Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion	:	The half-life time of this substance by the reaction with OH radicals in air is 46 hours.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

11.01.2002

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	at degree C
t1/2 pH9	:	at degree C
Deg. Product	:	no
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	2000
GLP	:	yes
Test substance	:	other TS: Wako Pure Chemcial Industries Ltd. Purity: 99.97%
Source	:	Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion	:	This chemical is stable at pH 4, 7 and 9 at 50 C for five days.
Reliability	:	(1) valid without restriction Well conducted study, carried out by Chemicals Evaluation and Research Institute, Japan.
Flag	:	Critical study for SIDS endpoint

11.01.2002

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	

Air (level I) :
Water (level I) :
Soil (level I) :
Biota (level II / III) :
Soil (level II / III) :
Method :
Year : 2002
Method : Parameters used in the calculation are as follows;
Molecular weight: 67.09
Melting point: -35 C
Vapor puressure: 94.9 hPa
Water solubility: 29 g/L
Log Pow: 0.68
Half-life time in air: 46 hours
Half-life time in waer: 360 hours
Half-life time in soil: 360 hours
Half-life time in sediment: 1080 hours
Result : Estimated Distribution under three emission scenarios

Compartment	Release 100% to Air	Release 100% to Water	Release 100% to Soil
Air	90.3 %	8.4 %	8.4 %
Water	9.2 %	91.3 %	10.5 %
Soil	0.5 %	0.0 %	81.0 %
Sediment	0.0 %	0.3 %	0.0 %

Source : Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion : If this chemical is released to one of the comparmtnes of air, water and soil, it is unlikely to be distributed into other compartments.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
11.01.2002

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge
Concentration : 300mg/l related to Test substance related to
Contact time : 28 day
Degradation : = 83 % after 28 day
Result : readily biodegradable
Control substance : Aniline
Kinetic : **%**
%
Deg. Product : no
Method : OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year : 1999

GLP	:	yes
Test substance	:	other TS: Wako Pure Chemical Industries Ltd. Purity 99.97%
Result	:	Biodegradability of test substance 83 % by BOD after 28 days 98 % by TOC after 28 days 100 % by GC after 28 days
Source	:	Chemicals Evaluation and Research Institute (CERI) Tokyo
Conclusion	:	This chemical is readily biodegradable.
Reliability	:	(1) valid without restriction Well conducted study, carried out by Chemicals Evaluation and Research Institute, Japan.
Flag	:	Critical study for SIDS endpoint

11.01.2002

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : semistatic
Species : Oryzias latipes
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : yes
LC50 : > 100
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1999
GLP : yes
Test substance : other TS: Wako Pure Chemical Industries, Ltd., Purity 100 %, Lot No.ACP7397
Method : -Test Organisms:
a) Size (length and weight): 2.18 cm (1.90 - 2.49 cm) in length; 0.20 g (0.09 - 0.33 g) in weight
b) Age: Not described
c) Supplier/Source: Test organisms were reproducted and prepared by the testing body.
d) Any pretreatment: Acclimated for 7 days before testing , any group showing > 5 % mortality was not used for testing. Not fed for 24 hours before the test started.

-Test Conditions:
a) Dilution Water Source: Dechlorinated tap water
b) Dilution Water Chemistry: Total hardness 30.3 mg/L Alkalinity 24.7 mg/L EC 94 micro S/cm, BOD less than 0.5 mg/L, COD less than 0.5 mg/L
c) Nominal Concentrations: Control and 100mg/L
d) Vehicle/Solvent and Concentrations: Not used
e) Stock Solutions Preparations and Stability: 300 mg-test substance was added in 3 L-dilution water.
f) Number of Replicates: 1
g) Fish per Replicates: 10
h) Renewal Rate of Test Water: Every 48 hours
i) Water Temperature: 23.9 - 24.2 ºC
j) Light Condition: 16:8 hours, light-darkness cycle (room light) l) Feeding: No

- Analytical Procedure: Test concentrations were mesured by High-Performance Liquid Chromatography.

-Statistical Method:
a) Data Analysis: Not described
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Geometric Mean

Result : - Measured Concentrations: The tested concentrations were measured at 0 hour and 48 hours later (before exchange of test solution).

Nominal concentration mg/L	Measured concentration, mg/L (percent of Nominal) 0 Hour (new)	48 Hours (old)	Mean* measured concentration mg/L
Control	<0.04	<0.04	-
100	87.9(88)	82.9(83)	0.83(85)

*: Geometric Mean- Water chemistry in test (pH and DO): pH 7.4 - 8.2, DO 5.9 - 8.4 mg/L

-Effect Data(mortality): 96hr LC50 > 100 mg/L

- Cumulative Mortality: No death occurred to the tested fish during the test period.

Nominal Concentration mg/L	Mean* Measured Concentration mg/L	Cumulative Mortality (Percent Mortality) 24hr	48hr	72hr	96hr
Control	-	0 (0)	0 (0)	0 (0)	0 (0)
100	85.4	0 (0)	0 (0)	0 (0)	0(0)

*Geometric Mean

-Other Effect:No toxicological symptom was observed during the test period.

Nominal Concentration mg/L	Mean* Measured Concentration mg/L	Symptoms (Symptom-number of fish) 24hr	48hr	72hr	96hr
Control	-	N**	N	N	N
100	85.4	N	N	N	N

*Geometric Mean
**N: No toxicological symptom was observed

- Calculation of toxic values: Based on the nominal concentrations, because the tested concentration at 48 hours was showed as 85 % of nominal concentration

Source : MOE, Japan (2001), Ministry of the Environment, Japan.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.01.2002 (33)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : yes
NOEC : = 180
EC50 : = 200
Method : OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year : 1999
GLP : yes
Test substance : other TS: Wako Pure Chemical Industries, Ltd., Purity 100 %, Lot No.ACP7397
Method : - Test Organisms:
a) Age: < 24 hours old
b) Supplier/Source: National Institute for Environmental Studies (JAPAN)

- Test Conditions:
a) Dilution Water Source: Elendt M4 (OECD Guide-line 211)

b) Dilution Water Chemistry (pH, EC, Total hardness ,Alkalinity, etc.): Not described, reconsititution water was used.
c) Exposure Vessel Type: Closed system, 100 mL test solution in a 200 mL Glass Beaker with glass cap
d) Nominal Concentrations: control, 100, 180, 320, 560 and 1,000 mg/L.
e) Vehicle/Solvent and Concentrations: Not used
f) Stock Solutions Preparations and Stability: 1,000 mg/L stock solution was prepared, in the following way: 2000 mg-test substance was added in 2 L-dilution water.
g) Number of Replicates: 4
h) Individuals per Replicates: 5
i) Renewal Rate of Test Water: None
j) Water Temperature: 20.3 - 20.7 ºC
k) Light Condition: 16:8 hours, light-darkness cycle (room light)
l) Feeding: No

- Analytical Procedure: Test concentrations were mesured by High Performance Liquid Chromatography.

- Statistical Method:
a) Data Analysis: Binomial Method for EC50 value
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Geometric Mean

Result : - Measured Concentrations : The tested concentrations were measured at 0 hour and 48 hours later. The tested concentration at 48 hours later was showed as 80-83 % of nominal concentration.

Nominal concentration	Measured concentration (mg/L) (Percent of nominal)		Geometric Mean During 48 hours (mg/L)
mg/L	0 Hour	48 Hours	
Control	<0.05(--)	<0.05(--)	--
100	86.1(86)	83.1(83)	84.6
180	159(88)	150(83)	154
320	270(84)	265(83)	267
560	473(84)	450(80)	461
1000	845(85)	810(81)	827

- Water chemistry in test (pH and DO): pH 8.2 - 8.6, DO 8.2 mg/L

-Effect Data(immobilization):48hr EC50 = 200 (170 based on measured concentration)mg/L (95% C. I.: 180 – 320, 154-267)48hr NOEC = 180(154)mg/L

- Cumulative number of Immobilized Parental Daphnia:

Measured concentration	Cumulative number of Immobilized Parental Daphnia (percent immobility)	
mg/L	24 hour	48 hour
Control	0(0)	0(0)
100	0(0)	0(0)
180	0(0)	0(0)
320	0(0)	20(100)
560	20(100)	20(100)

1000	20(100)	20(100)

Calculation of toxic values: Based on the nominal concentrations, because the tested concentration at 48 hours was showed as 80-83 % of nominal concentration.

Source : MOE, Japan (2001), Ministry of the Environment, Japan.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.01.2002 (33)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Selenastrum capricornutum (Algae)
Endpoint : biomass
Exposure period : 72 hour(s)
Unit : mg/l
Analytical monitoring : yes
NOErC : = 10
ErC50 : = 25.3
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1999
GLP : yes
Test substance : other TS: Wako Pure Chemical Industries, Ltd., Purity 100 %, Lot No.ACP7397
Method : - Test Organisms:
a) Method of Cultivation: Not described
b) Stain Number: ATCC22662
c) Supplier/Source: American Type Culture Collection

- Test Conditions:
a) Medium: OECD medium
b) Exposure Vessel Type: 100 mL Medium in a 500 mL Erlenmeyer Flask with glass cap
c) Nominal Concentrations: Control, 1.0, 3.2, 10, 32 and 100mg/L.
d) Vehicle/Solvent and Concentrations: Not used.
e) Stock Solutions Preparations and Stability: 10,000 mg/L stock solution was prepared.
f) Number of Replicates: 3
g) Initial Cell Number: 10,000 cells/mL
h) Water Temperature: 22.7 - 23.5 ºC
i) Light Condition: 4,000 - 5,000 lux, continues
j)Shaking: 100 rpm- Analytical Procedure: Test concentrations were mesured by High-Performance Liquid Chromatography.

- Statistical Method:
a) Data Analysis: Not described
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Not described

Remark : NOEC was determined based on growth inhibition.
Result : - Measured Concentrations : The tested concentrations were measured at 0 hour and 72 hours later. The tested concentration at 72 hours later was showed as 90 - 96 % of nominal concentration.

Nominal concentration	Measured concentration, mg/L	Percent of nominal

mg/L	0 Hour	72 Hours	0 Hour	72 Hours
Control	<0.04	<0.04	--	--
1.0	0.94	0.90	94	90
3.2	3.04	2.95	95	92
10	9.52	9.54	95	95
32	30.3	25.8	95	90
100	99.3	96.4	99	96

- Water chemistry in test (pH and DO): pH 8.7 - 10.2

-Effect Data:area method
EbC50(0-72hr) = 15.1 mg/L (95% C. I.: 12.1 - 18.8)
NOECb(0-72hr) = 1.0 mg/Lrate method
-Effect Data:rate method
ErC50(24-48hr) >100 mg/L
NOECr (24-48hr) = 10 mg/L
ErC50(24-72hr) = 25.3 mg/L (95% C. I.: 23.6 - 27.0)
NOECr (24-72hr) = 10 mg/L

- Percent Growth Inhibition of Selenastrum capricornutum

Nominal		Area under the growth curves	
Concentration		Area	Inhibition (%)*1
mg/L	No.	A (0-72hr)	IA (0-72hr)
Control	1	846	
	2	906	
	3	879	
	Average	877.0	-
	SD	30.0	
1.0	1	903	
	2	909	
	3	936	
	Average	916.0	-4.45
	SD	17.6	
3.2	1	678	
	2	735	
	3	651	
	Average	688.0	21.55**
	SD	42.9	
10	1	603	
	2	618	
	3	648	
	Average	623.0	28.96**
	SD	22.9	
32	1	114	
	2	180	
	3	153	
	Average	149.0	83.01**
	SD	33.2	
100	1	90	
	2	117	
	3	96	
	Average	101.0	88.48**
	SD	14.2	

Nominal Concentration mg/L	No.	Growth rate Rate u(24-48hr)	Inhibition(%)*1 Im(24-48hr)	Rate u(24-72hr)	Inhibition(%)*1 Im(24-72hr)
Control	1	0.0649		0.0545	
	2	0.0613		0.0523	
	3	0.0578		0.0497	
	Average	0.0613	-	0.0521	-
	SD	0.0036		0.0024	
1.0	1	0.0551		0.0491	
	2	0.0558		0.0491	
	3	0.0559		0.0477	
	Average	0.0556	9.40	0.0486	6.71
	SD	0.0004		0.0008	
3.2	1	0.0569		0.0493	
	2	0.0539		0.0472	
	3	0.0538		0.0522	
	Average	0.0548	10.58	0.0496	4.91
	SD	0.0018		0.0025	
10	1	0.0505		0.0506	
	2	0.0622		0.0553	
	3	0.0631		0.0487	
	Average	0.0586	4.47	0.0496	1.14
	SD	0.0070		0.0034	
32	1	0.0480		0.0060	
	2	0.0458		0.0144	
	3	0.0333		0.0077	
	Average	0.0424	30.94**	0.0094	82.04**
	SD	0.0079		0.0034	
100	1	0.0289		0.0028	
	2	0.0437		-0.0070	
	3	0.0318		0.0028	
	Average	0.0348	43.28**	-0.0005	100.92**
	SD	0.0079		0.0057	

*1: Values are the percent inhibitaition relative to the controlSD: Stadard deviation
**: Significant difference p<0.01- Growth Curves: Log phase during the test period

Source : MOE, Japan (2001), Ministry of the Environment, Japan.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.01.2002 (33)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species : Daphnia magna (Crustacea)
Endpoint : reproduction rate
Exposure period : 21 day

Unit : mg/l
Analytical monitoring : yes
NOEC : = 2.2
LCEC : = 4.6
EC50 : = 6.33
LC50 : = 29.8
Method : other: OECD TG 211 (revised edition of No.202)
Year : 1999
GLP : yes
Test substance : other TS: Wako Pure Chemical Industries, Ltd., Purity 100 %, Lot No.ACP7397
Method : - Test Organisms:
a) Age: < 24 hours old
b) Supplier/Source: National Institute for Environmental Studies (JAPAN)

- Test Conditions:
a) Dilution Water Source: Elendt M4 (OECD Guide-line 211)
b) Dilution Water Chemistry (pH, EC, Total hardness ,Alkalinity, etc.): Not described, reconsititute water was used
c) Exposure Vessel Type: 80 mL test solution in a 200 mL Glass Beaker with glass cap
d) Nominal Concentrations: control, 0.46, 1.0, 2.2, 4.6, 10, 22, 46 and 100 mg/L.
e) Vehicle/Solvent and Concentrations: Not used
f) Stock Solutions Preparations and Stability: 1,000 mg/L stock solution of test substance was prepared.
g) Number of Replicates: 10
h) Individuals per Replicates: 1
i) Renewal Rate of Test Water: 3 times per a week
j) Water Temperature: 20.2 - 20.9 ºC
k) Light Condition: 16:8 hours, light-darkness room light)
l) Feeding: 0.15 - 0.2 mg carbon/day/individual (Chlorella: Green Algae)

- Statistical Method:
a) Data Analysis: Logit Method for LC50, Probit Method for EC50, Dunnett's Multicomparison test for NOEC and LOEC
b) Method of Calculating Mean Measured Concentrations (i.e. arithmetic mean, geometric mean, etc.): Time-weighted Mean

Remark : NOEC was determined based on the cumulative number of juveniles produced per adult alive for 21 days.
Result : - Effect: reproduction- Measured Concentrations (as mg/L):

Nominal Concentration (mg/L)	Measured Concentration (mg/L) (Percent of Nominal)					
	0	3	9	12	19	21
	new	old	new	old	new	old
Control	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
0.46	0.41(89)	0.41(89)	0.46(100)	0.46(100)	0.47(102)	0.46(100)
1.0	0.94(94)	0.92(92)	1.00(100)	0.98(98)	1.01(101	0.99(99)
2.2	2.04(93)	2.02(92)	2.14(97)	2.14(97)	2.18(99)	2.13(97)
4.6	4.40(96)	4.30(93)	4.46(97)	4.43(96)	4.60(100)	4.47(97)
10	8.94(89)	8.85(89)	9.13(91)	8.91(89)	9.25(93)	9.15(92)
22	20.6(94)	19.7(90)	20.7(94)	20.3(92)	21.7(99)	21.5(98)
46	43.0(93)	41.7(91)	43.4(94)	42.5(92)	--	--
100	92.7(93)	89.6(90)	92.8(93)	90.2(90)	--	--

Nominal Concentration (mg/L)	Time-weighted mean during 21 days (mg/L) (percent ofnominal)
Control	--
0.46	0.45(98)
1.0	0.98(98)
2.2	2.11(96)
4.6	4.44(97)
10	9.04(90)
22	20.7(94)
46	41.7(93)
100	91.4(91)

- Water chemistry in test (pH and DO): pH 7.4 - 8.5, DO 6.7 - 8.5 mg/L, Total hardness: 221 - 294 mg/L

-Effect Data(reproduction):21days LC50 = 29.8 mg/L (95% C. I.: 25.0 - 34.5)21days EC50 = 6.33 mg/L (95% C. I.: 3.99 - 15.5)21days NOEC = 2.20 mg/L21days LOEC = 4.60 mg/L

- Cumulative Number of Died Parental Daphnids:

Nominal Concentration (mg/L)	Cumulative Number of Died Parental Daphnids (days) 1	2	3	4	5	6	7	8	9	10
Control	0	0	0	0	0	0	0	0	0	0
0.46	0	0	0	0	0	0	0	0	0	0
1.0	0	0	0	0	0	0	0	0	0	0
2.2	0	0	0	0	0	0	0	0	0	0
4.6	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0

Nominal Concentration (mg/L)	Cumulative Number of Died Parental Daphnids (days) 11	12	13	14	15	16	17	18	19	20	21
Control	0	0	0	0	0	0	0	0	0	0	0
0.46	0	0	0	0	0	0	0	0	0	0	0
1.0	0	0	0	0	0	0	0	0	0	0	0
2.2	0	0	0	0	0	0	1	1	1	1	1
4.6	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	1	1	1	1
46	0	0	0	0	1	3	3	5	10	10	10
100	0	0	0	1	4	8	8	9	10	10	10

- Time (days) of the First Brood Production: Mean; Control(7 days). 0.46 mg/L (7 days), 1.0 mg/L (7 days), 2.2 mg/L (8 days), 4.6 mg/L (8 days), 10 mg/L (8 days), 22 mg/L (9 days), 46 mg/L (--) and 100 mg/L (--)

- Mean Cumulative Number of Offsprings Produced per Adult: 21days;

Control(129.1). 0.46 mg/L (129.8), 1.0 mg/L (127.4), 2.2 mg/L (103.6), 4.6 mg/L (76.5), 10 mg/L (47.5), 22 mg/L (1.6), 46 mg/L (--) and 100 mg/L (--)

- Calculation of toxic values: Based on the nominal concentrations, because the tested concentration at 48 hours later was showed as 89-100 % of nominal concentration.

Source : MOE, Japan (2001), Ministry of the Environment, Japan.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
16.01.2002 (33)

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

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	5
Vehicle	:	other:olive oil
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	2001
GLP	:	yes
Test substance	:	other TS
Remark	:	Doses were 50, 60, 70, 85 and 100 mg/kgbw for males and 60, 70, 85, 100 and 120 mg/kgbw for females.
Result	:	LD50 (95% confidence limits) was 64 (49-76) mg/kg bw for males; 73 (49-87) mg/kgbw for females. Deaths occurred in males and females in each group except for the control. Decrease in locomotor activity, adoption of a prone and/or lateral position, and hyperpnea were found in each group, in males and females, except for the control, within several minutes to 2 hours after administration. Clonic convulsion, salivation, diarrhea, and soiling of perigenital, perianal, and perioral fur were observed. Decrease in body weight was noted in females given 70 and 85 mg/kg on the day after administration. At autopsy, bright orange discoloration in the lung and dilatation of the right atrium in the heart were observed in dead males and females. Mortality: Dose(mg/kg) Male 0 50 60 70 85 100 No.of animals 5 5 5 5 5 5 No.of death 0 1 2 3 4 5 Dose(mg/kg) Female 0 60 70 85 100 120 No.of animals 5 5 5 5 5 5 No. of death 0 2 1 4 4 5
Test substance	:	Purity: 99%
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

26.12.2001 (29)

Type	:	LD50
Species	:	rat
Strain	:	other:Harlan-Wistar
Sex	:	male
Number of animals	:	5
Vehicle	:	water
Method	:	other
Year	:	1968
GLP	:	no
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	Non-fasted animals were administered with 1.0 % (w/v) methylacrylonitrile. There were no data on the doses used and necropsy findings.
Result	:	LD50(range) was 0.24(0.16-0.36)g/kg. Four of the five rats given 0.4 g/kg died on the day of dosing and the remaining animal died overnight. The 0.2 g/kg and 0.1 g/kg dosages each killed one of five rats

overnight. All victims experienced prostration and convulsions within 1.5 hours of dosing. Some survivors had the same symptoms to a lesser degree, but all gained weight normally during the subsequent 14-day observation period.

26.12.2001 (3)

Type : LD50
Species : Rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Value : = 120 mg/kg bw
Method : other
Year : 1985
GLP : no data
Test substance : no data
Remark : Details of the test condition and observed toxic effects were not reported.

26.12.2001 (19)

Type : LD50
Species : Mouse
Strain : other:ddY
Sex : Male
Number of animals : 4/dose level
Vehicle : other:olive oil
Method : other
Year : 1984
GLP : no data
Test substance : no data
Remark : Male mice weighing about 25g were used. The oral LD50 value were measured according to Weil using four animals per dose level and four different doses.
There were no data on the doses used, post observation period, number of deaths, necropsy findings and so on.
Result : LD50(95% confidence limit) was 17(14-21) mg/kg

26.12.2001 (4)

Type : LD50
Species : Gerbil
Strain : other: Mongolian
Sex : no data
Number of animals :
Vehicle : no data
Method : other
Year : 1991
GLP : no data
Test substance : no data
Remark : There were no data on the doses used, number of animals, post observation period, number of deaths at each dose level, necropsy findings and so on.
Result : LD50 was 3.8 (95 % confidence intervals: 2.66-5.24) mg/kg for males and 4.9 (3.18-7.63) mg/kg for females.

26.12.2001 (10) (43)

Type : LD50
Species : Rabbit
Strain : no data
Sex : no data
Number of animals :

Vehicle	:	no data
Value	:	= 16 mg/kg bw
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	no data
Remark	:	Details of the test condition and observed toxic effects were not reported.

15.12.2001 (19)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Species	:	rat
Strain	:	other:Harlan-Wistar
Sex	:	male
Number of animals	:	6/exposure level
Vehicle	:	no data
Exposure time	:	4 hour(s)
Value	:	= 328 ppm
Method	:	other
Year	:	1968
GLP	:	no data
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	Male rats weighing 344-510g were used in the study. Animals were exposed to various concentrations of methylacrylonitrile vapor. The concentrations were varied by a factor of two (no clear information on concentrations used). Observation period after exposure was 14 days. There were no information on number of deaths.
Result	:	LC50(range) was 328(208-516)ppm. The responses were consistently dose-related and followed loss of consciousness, tonic-clonic convulsions and death. Some survivors were unconscious, but none progressed to the convulsive stage, and most gained weight normally during the subsequent 14-day observation period. The lowest concentration of 176 ppm caused loss of consciousness within 180 min., and one death preceeded by convulsions. At autopsy, no gross lesions attributable to exposure were found in any of the victims or survivors.

26.12.2001 (3)

Type	:	LC50
Species	:	rat
Strain	:	other:Harlan-Wistar
Sex	:	male
Number of animals	:	6/exposure level
Vehicle	:	no data
Exposure time	:	4 hour(s)
Method	:	other
Year	:	1968
GLP	:	no data
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	Male rats weighing 123-207g were used in the study. Animals were exposed to various concentrations of methylacrylonitrile vapor. The concentrations were varied by a factor of two (no clear information on concentrations used). Observation period after exposure was 14 days. There were no information on number of deaths.
Result	:	LC50(range) was 328(231-494)ppm. The responses were consistently dose-related and followed loss of consciousness, tonic-clonic convulsions

and death. Some survivors were unconscious, but none progressed to the convulsive stage, and most gained weight normally during the subsequent 14-day observation period. The lowest concentration of 176 ppm caused loss of consciousness within 180 min., but no death. At autopsy, no gross lesions attributable to exposure were found in any of the victims or survivors.

26.12.2001 (3)

Type : LC50
Species : rat
Strain : other: Harlan-Wistar
Sex : female
Number of animals : 6/exposure level
Vehicle : other
Exposure time : 4 hour(s)
Method : other
Year : 1968
GLP : no data
Test substance : Purity: minimum of 99.0 wt.%
Remark : Female rats weighing 213-317g were used in the study.
Animals were exposed to various concentrations of methylacrylonitrile vapor. The concentrations were varied by a factor of two (no clear information on concentrations used).
Observation period after exposure was 14 days.
There were no information on number of deaths.
Result : LC50(range) was 700(213-2327)ppm. The responses were consistently dose-related and followed loss of consciousness, tonic-clonic convulsions and death. Some survivors were unconscious, but none progressed to the convulsive stage, and most gained weight normally during the subsequent 14-day observation period. The lowest concentration of 176 ppm caused loss of consciousness within 180 min., but no death. At autopsy, no gross lesions attributable to exposure were found in any of the victims or survivors.

26.12.2001 (3)

Type : LC50
Species : rat
Strain : other:Harlan-Wistar
Sex : female
Number of animals : 6/exposure level
Vehicle : no data
Exposure time : 4 hour(s)
Method : other
Year : 1968
GLP : no data
Test substance : Purity: minimum of 99.0 wt.%
Remark : Female rats weighing 95-172g were used in the study.
Animals were exposed to various concentrations of methylacrylonitrile vapor. The concentrations were varied by a factor of two (no clear information on concentrations used).
Observation period after exposure was 14 days.
There were no information on number of deaths.
Result : LC50(range) was 496(250-993)ppm. The responses were consistently dose-related and followed loss of consciousness, tonic-clonic convulsions and death. Some survivors were unconscious, but none progressed to the convulsive stage, and most gained weight normally during the subsequent 14-day observation period. The lowest concentration of 176 ppm caused loss of consciousness within 180 min., but no deaths. At autopsy, no gross lesions attributable to exposure were found in any of the victims or survivors.

26.12.2001 (3)

Type	:	LC100
Species	:	rat
Strain	:	other: Harlan Wistar
Sex	:	female
Number of animals	:	6/group
Vehicle	:	
Exposure time	:	See result
Value	:	= 85500 ppm
Method	:	Other
Year	:	1968
GLP	:	no data
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	Animals were exposed to essentially saturated vapor of methylacrylonitrile for 14, 7.5, 3.75, 1.88, 0.93 and 0.47 minutes. Observation period after exposure was 14 days. There were no information on number of deaths and necropsy finding.
Result	:	The exposure to essentially saturated vapor of methylacrylonitrile for 14, 7.5, 3.75, 1.88, 0.93 and 0.47 minutes resulted in respective mortality ratios of 6/6, 6/6, 6/6, 1/6, 0/6 and 0/6. All victims died during the 14-minute exposure, within 1.5 hours after the 7.5 minutes exposure, and within 24 hours following the 3.75 and 1.88 minute exposures. Prostration and loss of consciousness always preceded death, but these symptoms also appeared in most of the survivors exposed for as short a period as 1.88 minutes. The rats exposed for 0.93 minute appeared normal during the inhalation period, but became prostrated approximately 0.5 hours after the exposure, and remained in this condition for 2 hours. The rats exposed for 0.47 minutes appeared normal during and after the inhalation period. Most of the survivors gained weight normally during the subsequent 14-day observation period.

26.12.2001 (3)

Type	:	LC50
Species	:	mouse
Strain	:	other: A/J strain
Sex	:	male
Number of animals	:	6/exposure level
Vehicle	:	no data
Exposure time	:	4 hour(s)
Method	:	other
Year	:	1968
GLP	:	no data
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	Animal weight range was 23-33g. Animals were exposed to various concentrations of methylacrylonitrile vapor. The concentrations were varied by a factor of two (no clear information on concentrations used). Observation period after exposure was 14 days. There were no information on number of deaths.
Result	:	LC50(range) was 36(25-43)ppm. The responses were consistently dose-related and followed loss of consciousness, tonic-clonic convulsions and death. Some survivors were unconscious, but none progressed to the convulsive stage, and most gained weight normally during the subsequent 14-day observation period. The lowest concentration of 19.7 ppm caused no symptoms. At autopsy, no gross lesions attributable to exposure were found in any of the victims or survivors.

26.12.2001 (3)

Type	:	LC50
Species	:	guinea pig
Strain	:	no data
Sex	:	male
Number of animals	:	6/exposure level
Vehicle	:	no data
Exposure time	:	4 hour(s)
Method	:	other
Year	:	1968
GLP	:	no data
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	Body weight:585-1035g Animals were exposed to various concentrations of methylacrylonitrile vapor. The concentrations were varied by a factor of two (no clear information on concentrations used). Observation period after exposure was 14 days. There were no information on number of deaths.
Result	:	LC50(range) was 88(62-124)ppm. The responses were consistently dose-related and followed loss of consciousness, tonic-clonic convulsions and death. Some survivors were unconscious, but none progressed to the convulsive stage, and most gained weight normally during the subsequent 14-day observation period. The lowest concentration of 52.5 ppm caused no symptoms. At autopsy, no gross lesions attributable to exposure were found in any of the victims or survivors.

26.12.2001 (3)

Type	:	LC50
Species	:	rabbit
Strain	:	no data
Sex	:	male
Number of animals	:	4/exposure level
Vehicle	:	no data
Exposure time	:	4 hour(s)
Method	:	other
Year	:	1968
GLP	:	no data
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	Body weight range was 2556-4290 g. Animals were exposed to various concentrations of methylacrylonitrile vapor. The concentrations were varied by a factor of two (no clear information on concentrations used). Observation period after exposure was 14 days. There were no information on number of deaths.
Result	:	LC50(range) was 37(23-57)ppm. The responses were consistently dose-related and followed loss of consciousness, tonic-clonic convulsions and death. Some survivors were unconscious, but none progressed to the convulsive stage, and most gained weight normally during the subsequent 14-day observation period. The lowest concentration of 19.7 ppm caused no symptoms. At autopsy, no gross lesions attributable to exposure were found in any of the victims or survivors.

26.12.2001 (3)

Type	:	other
Species	:	dog
Strain	:	other: coker spaniel
Sex	:	female
Number of animals	:	1
Vehicle	:	no data

Exposure time : 7 hour(s)
Method : other
Year : 1968
GLP : no data
Test substance : Purity: minimum of 99.0 wt.%
Remark : Body weight: 8100 g
Result : 52.5 ppm caused vomiting, convulsions, and loss of consciousness within 7 hours. The dog died overnight. At autopsy, no gross lesions attributable to exposure were found.

26.12.2001 (3)

Type : other
Species : dog
Strain : other: Mongrel
Sex : female
Number of animals : 1
Vehicle :
Exposure time : 3 hour(s)
Value : = 106.1 ppm
Method :
Year : 1968
GLP : no data
Test substance : Purity: minimum of 99.0 wt.%
Remark : Body weight; 9540 g
Result : Convulsions were observed, followed by death in three hours. At autopsy, no gross lesions attributable to exposure were found.

26.12.2001 (3)

Type : other
Species : dog
Strain : other: Mongrel
Sex : female
Number of animals : 1
Vehicle :
Exposure time : 7 hour(s)
Value : = 106.1 ppm
Method :
Year : 1968
GLP : no data
Test substance : Purity: minimum of 99.0 wt.%
Remark : Body weight: 6800 g
Result : Vomiting, diarrhea and convulsions were observed, followed by death within seven hours. At autopsy, no gross lesions attributable to exposure were found.

26.12.2001 (3)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Value : = 2080 mg/kg bw
Method : other
Year : 1985
GLP : no data

Test substance	:	no data
Remark	:	Details of the test condition and observed toxic effects were not reported.

18.12.2001 (19)

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	4
Vehicle	:	other: undiluted
Method	:	other
Year	:	1968
GLP	:	no data
Test substance	:	other TS
Remark	:	The rabbits were contact with undiluted test substance for 24 hours. Observation period after exposure was 14 days. There were no information on dose used and necropsy findings.
Result	:	LD50(range) was 0.32 (0.19-0.51) mL/kg (250 mg/kg) All four rabbits administered 0.5 ml/kg (391 mg/kg) methylacrylonitrile died within three hours and 45 minutes, and were gasping or convulsing before death. One of four rabbits administered 0.25 ml/kg (195 mg/kg), gasped, convulsed and died in two hours and 40 minutes. The three survivors had no symptoms and gained weight normally during the subsequent 14-day observation period.
Test substance	:	Purity: minimum of 99.0 wt.%

26.12.2001 (3)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LDLo
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Route of admin.	:	i.p.
Exposure time	:	
Value	:	= 15 mg/kg bw
Method	:	no data
Year	:	1949
GLP	:	no data
Test substance	:	no data

18.12.2001 (26)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	200 mg
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	moderately irritating
EC classification	:	
Method	:	Draize Test
Year	:	1949

GLP : no data
Test substance : no data
18.12.2001 (25)

Species : rabbit
Concentration : 500 mg
Exposure :
Exposure time : 24 hour(s)
Number of animals :
PDII :
Result : moderately irritating
EC classification : irritating
Method : Draize Test
Year : 1986
GLP : no data
Test substance : no data
18.12.2001 (1)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration :
Dose : 500 mg
Exposure Time : 24 hour(s)
Comment :
Number of animals :
Result : moderately irritating
EC classification :
Method : Draize Test
Year : 1986
GLP : no data
Test substance : no data
18.12.2001 (1)

Species : rabbit
Concentration :
Dose : 50 mg
Exposure Time :
Comment :
Number of animals :
Result :
EC classification :
Method : Draize Test
Year :
GLP :
Test substance :
15.12.2001 (25)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species : rat
Sex : male/female
Strain : other:CrjCD(SD)IGS

Route of admin.	:	gavage
Exposure period	:	Males:46 days Females:from 14 days before mating to day 4 of lactation
Frequency of treatment	:	Once a day
Post obs. period	:	None
Doses	:	7.5, 15, 30 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 15 mg/kg bw
Method	:	other:OECD Test guideline 422
Year	:	2001
GLP	:	yes
Test substance	:	
Remark	:	This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study (Test guideline: 422). Test condition: Age at study initiation: 10 week old for both sexes Weight at study initiation: 354-434g for males; 210-259g for females No. of animals per sex per dose: 12 Study design: Vehicle: Olive oil Clinical observation performed and frequency: General condition was observed once a day, body weight and food consumption were determined at days 1(before dosing),2,5,7,10 and 14 of treatment for males and females, thereafter once a week and at autopsy for males, or at days 0,1,3,5,7,10,14,17 and 20 of gestation period and at days 0,1 and 4 of lactation period and at autopsy for females, but food consumption was not determined during mating period for males, and at day 0 of gestation and lactation periods for females. For 6 males per group, urinalysis was carried out at 43-44 days of administration period. For all males and 6 females per group, hematology and biochemistry were carried out at time of necropsy after 47 days for males and at 5 days after delivery for females. Organs examined at necropsy Organ weight: Brain, heart, liver, kidney, spleen, adrenal, thymus, testis and epididymis Microscopic examination: Brain, pituitary, thymus, thyroid, parathyroid, adrenal, spleen, heart, thoracic aort, tongue, esophagus, stomach, liver, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, larynx, trachea, lung, kidney, urinary bladder, testis, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, eye, harderian gland, mammarian gland, skin, sternum, femur, spinal cord, skeletal muscle, mesentery lymph node, mandibular lymph node, submandibular gland, sublingual gland, parotid gland,ischiadic nerve Statistical methods:Dunnett's test for continuous data and Mann-Whitney U test for quantal data
Result	:	Clinical signs: No abnormality was detected for males and females. Body weight: No statistically significant changes for males and females. Food consumption: No dose-dependent changes for males and females. Urinalysis: No statistically significant changes.

Hematology: Males: Decreases in RBC, hematocrit and hemoglobin concentration in 30mg/kg group.

Dose(mg/kg)	0	7.5	15	30
No.of animals	12	12	12	12
RBC Mean	904.7	915.3	910.5	856.7**
SD	39.7	29.8	26.9	38.6
Ht Mean	48.68	48.39	48.01	46.23*
SD	2.65	2.42	2.01	1.61
Hg Mean	16.38	16.22	15.88	15.52**
SD	0.63	0.72	0.52	0.62

Note: RBC, erythrocyte counts(104/micro L)
Ht, hematocrit(%)
Hg, hemoglobin(g/dL)
*, p<0.05
**, p<0.01

Females: No dose-related changes were observed.

Biochem: Males: Decreases in potassium in 15 and 30mg/kg groups, increase in creatinine in 30mg/kg group.

Dose (mg/kg)	0	7.5	15	30
No.of animals	12	12	12	12
K Mean	4.861	4.709	4.522**	4.613*
SD	0.253	0.212	0.178	0.208
Cr Mean	0.458	0.475	0.492	0.513**
SD	0.033	0.068	0.042	0.084

Note: K, Potassium(mEq/L)
Cr, Creatinine(mg/dL)
*, P<0.05
**, p<0.01

Females: Increase in total bilirubin and glucose in 30mg/kg group.

Dose (mg/kg)	0	7.5	15	30
No.of animals	12	12	12	12
TB Mean	0.058	0.055	0.078	0.080*
SD	0.012	0.015	0.019	0.011
GL Mean	126.7	128.3	134.0	148.0*
SD	8.2	14.4	16.4	13.9

Note: TB, Total bilirubin(mg/dL)
GL, Glucose(mg/dL)
*, p<0.05

Necropsy: Males: Dark red patches on the mucosa of the glandular stomach in one out of twelve animals given 30mg/kg.

Females: Dark red patches on the mucosa of the glandular stomach in one out of twelve animals given 7.5 or 15mg/kg and in two out of twelve animals given 30mg/kg.

Organ weight: Males: Increase in a relative liver weight in 30mg/kg group.

Dose(mg/kg)		0	7.5	15	30
No.of animals		12	12	12	12
Absolute Liver(g)	Mean	13.891	13.664	14.575	15.398
	SD	2.222	1.896	2.256	2.655
Relative Liver(%)	Mean	2.698	2.717	2.889	3.063**

	SD	0.199	0.181	0.244	0.230

Note:**, p<0.01

Females: Increase in relative liver weight in 7.5, 15 and 30mg/kg groups and in absolute liver weight in 30mg/kg group, in absolute heart weight in 7.5, 15 and 30mg/kg groups and in relative heart weight in 15 and 30mg/kg groups and in absolute and relative spleen weight in 30mg/kg group.

Dose(mg/kg)		0	7.5	15	30
No.of animals		12	12	12	12
Absolute					
Heart(g)	Mean	0.922	1.005*	0.980*	1.024*
	SD	0.042	0.132	0.051	0.135
Absolute					
Liver(g)	Mean	9.694	10.659	10.478	10.724*
	SD	0.746	1.004	0.929	1.210
Absolute					
Spleen(g)	Mean	0.613	0.625	0.673	0.838**
	SD	0.098	0.110	0.103	0.119
Relative					
Heart(%)	Mean	0.298	0.324	0.319*	0.330*
	SD	0.017	0.040	0.018	0.036
Relative					
Liver(%)	Mean	3.140	3.420**	3.143**	3.465**
	SD	0.213	0.166	0.215	0.206
Relative					
Spleen(%)	Mean	0.196	0.200	0.220	0.274**
	SD	0.024	0.024	0.038	0.038

Note: *,p<0.05
**, p<0.01

Histopathology:
Slight erosion was observed in the glandular stomach in animals showed dark red patches on the mucosa at necropsy. The incidence was as follows. However, the incidence was not statistically significant.

Dose(mg/kg)	0	7.5	15	30
No.of animals	12	12	12	12
Male	0	0	0	1
Female	0	1	1	2

Values are number of animals with findings
*, p<0.05

Extramedullary hematopoiesis in the spleen was observed in 3 females given 15mg/kg, and 7 females given 30mg/kg.

Histopathological findings: Spleen, slight extramedullary hematopoiesis

Dose(mg/kg)	0	7.5	15	30
No.of animals	12	12	12	12
	1	0	3	7*

Note:
Values are number of animals with findings
*, p<0.05

Test substance : Purity: 99%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
11.01.2002 (30)

Species	:	rat
Sex	:	male/female
Strain	:	other:F344/N
Route of admin.	:	gavage
Exposure period	:	13 weeks
Frequency of treatment	:	once a day, five days per week
Post obs. period	:	none
Doses	:	7.5, 15, 30, 60, 120mg/kg
Control group	:	yes, concurrent vehicle
Method	:	other (calculated)
Year	:	1992
GLP	:	yes
Test substance	:	
Remark	:	Dose formulations were prepared by mixing methylacrylonitrile with deionized, purified water to give the required concentrations. Dosing volumes were 5mL/kg body weight. Animals were 7 to 8 weeks old when the study began. Groups of 20 male and 20 female rats were administered methylacrylonitrile by gavage. Ten animals from each group were preselected for interim evaluation; those animals were dosed 5 days per week for 32 days and then killed and examined. The remaining 10 male and 10 female rats were administered methylacrylonitrile 5 days per week for 13 weeks. Animals were observed twice daily. Clinical findings and individual body weight were recorded weekly and at necropsy. Hematology and clinical chemistry evaluations were performed on the 32-day interim evaluation rats and on core study rats at the end of the 13-week study. The 32-day interim evaluation rats were also evaluated for hematology and clinical chemistry after 4 days of dosing. At the end of the core study, sperm motility(sperm count and motility) and vaginal cytology evaluations(relative number of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrus cycle stage) were performed on male rats in the 0, 15, 30, and 60 mg/kg groups, female rats in the 0, 30, 60, and 120 mg/kg groups. Complete necropsies were performed on all animals. The heart, right kidney, liver, lung, stomach, right testis, and thymus of all animals were weighed. Complete histopathologic examinations were performed on all animals that died before scheduled evaluations, all vehicle control animals, male rats in the 60 mg/kg group, female rats in the 120 mg/kg group. The nasal cavity of rats was identified as a target organ and examined in all lower dose groups. The following tissues were evaluated: adrenal gland, brain (three section), esophagus, eyes (if grossly abnormal), femur with marrow, gross lesions and tissue masses, heart, intestines (large: cecum, colon, rectum; small: duodenum, jejunum, ileum), kidney, larynx, liver, lung with mainstem bronchi, lymph nodes (mandibular and mesenteric), mamary gland with adjacent skin, nasal cavity and turbinates (three sections), ovary, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland, prostate gland, salivary gland, spinal cord/sciatic nerve, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thigh muscle (if neurologic signs were present), thymus, thyroid gland, trachea, urinary bladder, uterus and

vagina (females in vaginal cytology studies only).
Statistical method: The Fisher exact test was used for analysis of lesion incidences. Organ and body weight data were analyzed with the parametric multiple comparison procedures of Williams and Dunnett. Clinical chemistry, hematology, spermatid, and spermatozoal data, were analyzed with the nonparametric multiple comparison method of Shirley and Dunn. Average severity values were analyzed for significance using the Mann-Whitney U test.

Result : Among groups for the 32-interim evaluation, 9 of 10 males in the 120 mg/kg group died during the first week of the study; all female rats survived. Male rats in the 60 mg/kg group had a significantly lower final mean body weight and mean body weight gain than those of the controls

Survival and body weight at the 32-day interim evaluation rats:

Male Dose (mg/kg)	Survival	Final body weight(g)	Gain(g)
0	10/10	Mean 251	91
		SE 4	4
7.5	10/10	Mean 253	90
		SE 3	2
15	10/10	Mean 254	91
		SE 3	2
30	10/10	Mean 247	84
		SE 3	2
60	10/10	Mean 232**	73**
		SE 2	2
120	1/10	Mean 225	56
Female			
0	10/10	Mean 154	32
		SE 1	1
7.5	10/10	Mean 158	35
		SE 3	1
15	10/10	Mean 154	31
		SE 2	2
30	10/10	Mean 155	33
		SE 2	2
60	10/10	Mean 150	25*
		SE 2	1
120	10/10	Mean 153	28*
		SE 2	2

Note: Survival:No. of animals surviving on day 32/No.initially in group
*, p<0.05; **, p<0.01

Clinical findings of toxicity at the 32-day interim evaluation were dose dependent and included lethargy, lacrimation, tremors, convulsions, ataxia, and abnormal breathing. These effects were observed within minutes of dosing and disappeared within several hours after dosing. No information were reported on the incidence of clinical signs at each dose.

Among groups scheduled for evaluation at the end of the 13-week study, all males and one female in the 120 mg/kg groups and 2 of 10 male rats in the 60 mg/kg group died during the first week of the study. Male rat and females in the 120 mg/kg group had significantly lower final mean body weights and mean body weight gains than those of the

controls
Survival and body weight at the 13-week evaluation rats:

Male Dose (mg/kg)	Survival		Final body weight(g)	Gain(g)
0	10/10	Mean	326	205
		SE	4	3
7.5	10/10	Mean	320	198
		SE	2	2
15	10/10	Mean	318	202
		SE	3	2
30	10/10	Mean	321	202
		SE	7	7
60	8/10	Mean	295**	175**
		SE	6	5
120	0/10			
Female				
0	10/10	Mean	185	77
		SE	2	2
7.5	10/10	Mean	185	79
		SE	4	3
15	10/10	Mean	186	80
		SE	3	3
30	10/10	Mean	191	81
		SE	3	2
60	10/10	Mean	178	73
		SE	2	2
120	9/10	Mean	171**	62**
		SE	3	2

Note: Survival:No. of animals surviving at 13 weeks/ No.initially in group
*, $p<0.05$; **, $p<0.01$

Clinical findings of toxicity in the 13-week study were dose dependent and included lethargy, lacrimation, tremors, convulsions, ataxia, and abnormal breathing. These effects were observed within minutes of dosing and disappeared within several hours after dosing. No information were reported on the incidence of clinical signs at each dose.

Hematology: On day 32, a minimal anemia, evidenced by decreased hemoglobin cxoncentrations in males given 60 or 120 mg/kg, and decresed hematocrit values, hemoglobin concentrations and erythrocytes counts in females given 30 mg/kg or greater, was observed. By week 13, the anemia had ameliorated and was evidenced only by minimal decreases in hemoglobin concentration in males in the 60 mg/kg group and females in the 120 mg/kg group.

Dose-related, significant increase in blood cyanide and serum thiocyanate concentrations occurred in males and females at
all time points. On day 4, dose-related decreases in bile salt concentrations occurred in males and females. On days 4 and 32, serum alanine aminotransferase actvities were significantly decreased in males in the 60 mg/kg group and in all dosed groups of females. At week 13, there was evidence of increased hepatocellular leakge and/or altered function in dosed males, as demonstrated by increased serum sorbitol dehydrogenase and alanine aminotransferase activities and bile salt concentrations. Also at 13 weeks, minimal increases in urea nitrogen concentrations occurred

in all dosed groups of males and all but the 7.5 mg/kg group of females.
Urea nitrogen concentrations were also increased on days 4 and 32 in males given 15, 30, or 60 mg/kg and on day 32 in females given 60 or 120 mg/kg.

Clinical pathological data:
Hematology

Male Dose(mg/kg)		0	7.5	15	30	60	120
No.of animals							
Day 4		10	10	10	10	10	1
Day 32		10	10	10	10	9	1
Week 13		10	10	10	9a	8	0
Hemoglobin(g/dL)							
Day 32	Mean	16.4	16.1	16.2	16.1	15.7**	14.6
	SE	0.2	0.1	0.2	0.1	0.1	
Week 13	Mean	16.0	15.7	16.1	15.7	15.4*	
	SE	0.1	0.2	0.2	0.2	0.1	

Note: a: 9 out of 10 animals in the 30 mg/kg group were examined in hematology

Female							
No.of animals							
Day 4		10	10	10	10	10	10
Day 32		10	10	10	10	10	10
Week 13		10	10	10	10	10	9
Hematocrit(%)							
Day 32	Mean	48.1	47.2	47.3	46.8*	45.3**	43.8**
	SE	0.4	0.3	0.3	0.2	0.3	0.3
Hemoglobin(g/dL)							
Day 32	Mean	16.1	15.8*	15.8	15.7**	15.4**	14.7**
	SE	0.1	0.1	0.1	0.1	0.1	0.1
Week 13	Mean	15.2	15.3	15.5	15.4	15.3	14.6*
	SE	0.2	0.1	0.1	0.2	0.2	0.2
Erythrocytes(10exp6/microL)							
Day 32	Mean	7.98	7.84	7.87	7.76**	7.54**	7.31**
	SE	0.06	0.05	0.05	0.05	0.04	0.05

Clinical chemistry

Male Dose(mg/kg)		0	7.5	15	30	60	120
No.of animals							
Day 4		10	10	10	10	10	1
Day 32		10	10	10	10	10	1
Week13		10	10	10	10	8	0
Cyanide(umol/L)							
Day 4	Mean	0.18	0.45	0.27*	0.88**	9.13**	16.20
	SE	0.07	0.19	0.05	0.15	1.04	
Day 32	Mean	0.15	0.29*	0.39**	1.45**	3.92**	3.90
	SE	0.02	0.05	0.06	0.20	0.46	
Week 13	Mean	0.37	0.62**	1.03**	1.70**	1.82**	
	SE	0.05	0.08	0.07	0.13	0.17	
Thiocyanate(ug/L)							
Day 4	Mean	130.0	356.3**	454.0**	700.5**	739.6**	941.0
	SE	3.6	6.4	17.8	14.8	20.4	
Day 32	Mean	229.7	395.1**	556.8**	688.7**	832.3**	951.0
	SE	12.6	8.2	5.4	12.2	18.1	
Week 13	Mean	158.4	429.6**	596.4**	735.1**	790.1**	
	SE	6.3	8.7	16.2	23.7	9.2	
Urea nitrogen(mg/dL)							
Day 4	Mean	19.2	20.2	22.9**	21.8**	24.8**	23.0
	SE	0.4	0.7(9)	0.5	0.4	0.4	

Day 32 Mean 21.5 22.3 23.4* 22.1 25.0** 27.0
SE 0.5 0.3 0.6 0.4 0.6
Week 13 Mean 21.1 23.5** 24.8** 25.1** 24.0**
SE 0.5 0.4 0.5 0.5 0.3
Alanine aminotransferase(IU/L)
Day 4 Mean 41 40 42 37 26** 32
SE 1 2(9) 2 1 1
Day 32 Mean 62 58 75 51 42** 39
SE 4 5 9 4 3
Week 13 Mean 57 90** 90* 123** 66
SE 2 9 12 21 5
Sorbitol dehydrogenase(IU/L)
Day 4 Mean 21 22 25* 24* 29* 31
SE 1 1 1 1 1
Day 32 Mean 27 26 38 28 26 35
SE 2 2 5 2 2
Week 13 Mean 19 33** 37** 52** 26**
SE 2 3 4 7 2
Bile salts(umol/L)
Day 4 Mean 25.4 23.4 22.2 17.8* 14.2** 13.5
SE 2.9 1.7 3.3 1.3 0.9
Day 32 Mean 22.4 28.6 26.4 18.0 21.3 33.5
SE 1.7 1.9 2.3 1.4 2.6
Week 13 Mean 18.9 25.6 22.7 33.5** 26.9
SE 2.7(5) 3.3(8) 1.3(8) 2.9(8) 4.4(6)

Female

Dose(mg/kg) 0 7.5 15 30 60 120
No.of animals
Day 4 10 10 10 10 10 10
Day 32 10 10 10 10 10 10
Week13 10 10 10 10 10 9
Cyanide(umol/L)
Day 4 Mean 0.34 0.39 0.44 0.95** 2.10** 2.43**
SE 0.03 0.03 0.03 0.08 0.08 0.13
Day 32 Mean 0.16 0.26 0.49** 1.17** 2.77** 2.35**
SE 0.02 0.05 0.06 0.07 0.38 0.27
Week13 Mean 0.11 0.18* 0.24** 0.77** 1.61** 1.58**
SE 0.02 0.01 0.02 0.14 0.07 0.10
Thiocyanate(ug/L)
Day 4 Mean 97.7 368.6** 510.1** 734.4** 740.4** 925.6**
SE 3.6 12.4 17.2 15.7 12.4 22.0
Day 32 Mean 193.3 413.0** 604.7** 791.4** 840.3** 883.4**
SE 2.9 7.1 13.3 25.1 22.7 12.2
Week13 Mean 128.8 488.0** 625.1** 751.2** 904.3** 861.1**
SE 4.1 10.1 13.9 19.7 40.7 32.7
Urea nitrogen(mg/dL)
Day 4 Mean 20.7 21.2 21.0 21.0 22.5 22.1
SE 0.7 0.5 0.6 0.6 0.5 0.4
Day 32 Mean 19.1 20.3 20.2 20.7 22.0** 21.5**
SE 0.6 0.5 0.7 0.4 0.4 1.0
Week13 Mean 21.2 22.7 24.1** 24.5** 24.0** 25.6**
SE 0.9 0.6 0.4 0.7 0.3 0.9
Alanine aminotransferase(IU/L)
Day 4 Mean 38 34* 30** 30** 24** 19**
SE 2 1 1 1 1 1
Day 32 Mean 58 47 43* 37** 29** 31**
SE 5 3 5 3 2 1
Week13 Mean 52 84 78 56 45 35**
SE 2 12 10 9 4 1
Sorbitol dehydrogenase(IU/L)

Day 4	Mean	20	18	19	20	23	21
	SE	1	1	1	1	1	1
Day 32	Mean	26	26	23	24	22	18**
	SE	2	2	3	1	2	1
Week13	Mean	23	34	30	28	25	22
	SE	2	5	3	3	2	1
Bile salts(umol/L)							
Day 4	Mean	35.3	32.5	29.6	23.9*	18.7**	15.0**
	SE	4.6	2.5	2.4	1.5	1.9	1.3
Day 32	Mean	29.2	33.0	31.4	32.3	28.8	32.9
	SE	2.7	3.6	5.5	2.8	3.1	2.7
Week13	Mean	39.2	36.8	46.9	34.1	32.3	31.2
	SE	4.8	3.4	3.3	2.5	2.2	4.1

Note: (n) is no. of animals examined.
*, p<0.05; **, p<0.01

Pathological findings
At the 32-day interim evaluation, absolute right kidney and thymus weights were less than those of the control, and relative heart, stomach, and right testis weights in the 60 mg/kg group of males were greater than those of the control. Absolute and relative liver weights in the 120 mg/kg group, absolute and relative stomach weights in the 60 and 120 mg/kg groups of females were greater than those of the control. Absolute and relative thymus weights in the 120 mg/kg group of females were less than those of control.

Dose(mg/kg)		0	7.5	15	30	60	120
Male							
No.of animals		10	10	10	10	10	1
Absolute right kidney(g)							
	Mean	1.054	1.046	1.062	1.057	0.968**	1.021
	SE	0.018	0.016	0.013	0.017	0.019	
Absolute thymus(g)							
	Mean	0.389	0.371	0.371	0.354	0.327**	0.186
	SE	0.015	0.012	0.012	0.010	0.010	
Relative heart							
	Mean	3.31	3.32	3.22	3.39	3.54**	3.64
	SE	0.04	0.06	0.04	0.06	0.06	
Relative stomach							
	Mean	4.68	4.67	4.75	4.95	5.36**	5.89
	SE	0.10	0.08	0.10	0.09	0.12	
Relative right testis							
	Mean	5.52	5.42	5.42	5.60	5.88**	5.54
	SE	0.06	0.05	0.03(9)	0.08	0.11	
Female							
No.of animals		10	10	10	10	10	9
Absolute liver(g)							
	Mean	5.850	5.932	5.942	6.101	6.089	6.617**
	SE	0.123	0.139	0.137	0.162	0.123	0.177
Relative liver							
	Mean	37.11	36.44	37.42	37.57	37.85	40.74**
	SE	0.71	0.50	1.05	0.57	0.61	1.16
Absolute stomach							
	Mean	0.911	0.940	0.923	0.960	0.995**	1.162**
	SE	0.017	0.024	0.011	0.017	0.025	0.030
Relative stomach							
	Mean	5.78	5.78	5.81	5.93	6.19*	7.15**
	SE	0.09	0.13	0.08	0.14	0.15	0.17

Absolute thymus(g)						
Mean	0.289	0.288	0.274	0.290	0.291	0.227**
SE	0.008	0.007	0.007	0.009	0.009	0.011
Relative thymus						
Mean	1.83	1.77	1.73	1.78	1.81	1.40**
SE	0.05	0.04	0.05	0.04	0.06	0.06

Note: (n) is no. of animals examined.
*, p<0.05; **, p<0.01

At the end of the 13-week study, liver weights of males in the 30 and 60 mg/kg groups were greater than those of the control. Absolute stomach weight of males in the 60 mg/kg group and the relative weights of all dosed groups of males were greater than those of the control. Relative lung weights in the 30 and 60 mg/kg groups of males were greater than those of the control. In female, absolute and relative stomach weights in the 60 and 120 mg/kg of female were greater than those of the control. Absolute thymus weights in the 60 and 120 mg/kg groups, and relative thymus weights in the 120 mg/kg group were less than those of the control. Relative heart, right kidney and liver weights in the 120 mg/kg groups were greater than those of the control.

Dose(mg/kg)	0	7.5	15	30	60	120
Male						
No.of animals	10	10	10	10	8	0
Absolute liver(g)						
Mean	10.936	11.267	11.278	12.525**	11.764**	
SE	0.235	0.205	0.185	0.364	0.549	
Relative liver						
Mean	33.45	35.04	35.28	39.04**	40.09**	
SE	0.60	0.50	0.38	0.87	1.39	
Relative lung						
Mean	4.43	4.54	4.71	4.86*	4.89**	
SE	0.09	0.11	0.13	0.14	0.09	
Absolute stomach(g)						
Mean	1.360	1.445	1.411	1.439	1.595**	
SE	0.038	0.020	0.028	0.020	0.036	
Relative stomach						
Mean	4.16	4.50*	4.41*	4.50**	5.45**	
SE	0.09	0.06	0.07	0.10	0.09	
Female						
No.of animals	10	10	10	10	10	9
Relative heart						
Mean	3.42	3.39	3.35	3.44	3.57	3.83**
SE	0.03	0.11	0.05	0.11	0.06	0.08
Relative rigt kidney						
Mean	3.49	3.49	3.57	3.57	3.61	3.69*
SE	0.05	0.06	0.04	0.05	0.06	0.04
Relative liver						
Mean	32.89	32.43	33.22	34.06	33.25	38.34**
SE	0.75	0.54	0.53	0.60	1.08	1.13
Absolute stomach						
Mean	1.063	1.080	1.105	1.151	1.171*	1.316**
SE	0.035	0.0.35	0.025	0.033	0.028	0.040
Relative stomach						
Mean	5.75	5.86	5.87	6.00	6.70**	7.67**
SE	0.17	0.21	0.11	0.19	0.19	0.28

Absolute thymus(g)

Mean	0.233	0.238	0.234	0.240	0.193*	0.150**
SE	0.012	0.014	0.010	0.012	0.015	0.005

Relative thymus

Mean	1.26	1.29	1.24	1.24	1.10	0.87**
SE	0.06	0.08	0.05	0.05	0.09	0.03

Note: *, p<0.05; **, p<0.01

At necropsy, no gross lesions were attributed to methylacrylonitrile administration. Microscopically, the treatment-related changes in the olfactory mucosa were observed in male and female rats of the 60 and 120 mg/kg groups and consisted of necrotic and metaplastic effects. No microscopic effects were observed to account for organ weight differences.

Male

Dose(mg/kg)	0	7.5	15	30	60	120
32-day interim evaluation						
No.of animals examined	10	10	10	10	10	6
Olfactory epithelium, metaplasia	0	0	0	0	4*	1
Olfactory epithelium, necrosis	0	0	0	0	3	1
13-week study						
No.of animals examined	10	10	10	10	10	7
Olfactory epithelium, metaplasia	0	1	0	0	6**	1
Olfactory epithelium, necrosis	0	0	0	0	2	1

Female

Dose(mg/kg)	0					
32-day interim evaluation						
No.of animals examined	10	10	10	10	10	10
Olfactory epithelium, metaplasia	0	0	0	0	6**	10**
Olfactory epithelium, necrosis	0	0	0	0	5**	10**
13-week study						
No.of animals examined	10	10	10	10	10	10
Olfactory epithelium, metaplasia	0	1	0	0	9**	9**
Olfactory epithelium, necrosis	0	0	0	0	1	3

Note: *, p<0.05; **, p<0.01

Reproductive parameters:
There were no significant differences in reproductive organ weights or sperm motility parameters between dosed and the control males. Female rats that received 60 or 120 mg/kg had significantly longer estrus cycles that did the controls. Female in the 60 mg/kg group spent more time in diestrus

than did the control.

Dose(mg/kg)	0	30	60	120
No.of animals examined	10	10	10	9
Estrus cycle length(days)				
Mean	4.95	5.20	5.75**	6.06**
SE	0.05	0.20	0.29	0.41

Note: **,p<0.01

Test substance : The test chemical was obtained in one lot(JY00427ET) from Aldrich Chemical Company(USA).
Purity: 99.9%(determined by gas chromatography)

Conclusion : Death, anemia, decrease in body weight and the gain, olfactory epithelium metaplasia and necrosis, longer estrous cycle were observed at 60 mg/kg (42.9 mg/kg/day) and more. However, since no information were reported on the incidence of clinical signs at each dose, NOAEL for this study was not evaluated.

11.01.2002 (38)

Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : gavage
Exposure period : 13 weeks
Frequency of treatment : once a day, 5 days per week
Post obs. period : none
Doses : 0.75, 1.5, 3, 6, 12 mg.kg
Control group : yes, concurrent vehicle
Method : other
Year : 1992
GLP : yes
Test substance :
Test condition : Dose formulations were prepared by mixing methylacrylonitrile
with deionized, purified water to give the required concentrations. Dosing volumes were 10mL/kg body weight.

Animals were 7 weeks old when the study began. Groups of 20 male and 20 female rats were administered methylacrylonitrile
by gavage. Ten animals from each group were preselected for interim evaluation; those animals were dosed 5 days per week for 32 days and then killed and examined. The remaining 10 male and 10 female rats were administered methylacrylonitrile
5 days per week for 13 weeks.

Animals were observed twice daily. Clinical findings and individual body weight were recorded weekly and at necropsy. At the end of the core study, sperm motility(sperm count and motility) and vaginal cytology evaluations(relative number of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrus cycle stage) were performed on male and female mice in the 0, 3, 6, and 12 mg/kg groups.
Complete necropsies were performed on all animals. The heart, right kidney, liver, lung, stomach, right testis, and thymus of all animals were weighed.

Complete histopathologic examinations were performed on all animals that died before scheduled evaluations, all vehicle control animals, male and female mice in the 12 mg/kg groups. The following tissues were evaluated: adrenal gland, brain (three section), esophagus, eyes (if grossly abnormal), femur with marrow, gallbladder, gross lesions and tissue masses, heart, intestines (large: cecum, colon, rectum; small: duodenum, jejunum, ileum), kidney, liver, lung with mainstem bronchi, lymph nodes (mandibular and mesenteric), mamary gland with adjacent skin, nasal cavity and turbinates (three sections), ovary, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thigh muscle (if neurologic signs were present), thymus, thyroid gland, trachea, urinary bladder, uterus and vagina (females in vaginal cytology studies only).
Statistical method:
The Fisher exact test was used for analysis of lesion incidences. Organ and body weight data were analyzed with the parametric multiple comparison procedures of Williams and Dunnett. Clinical chemistry, hematology, spermatid, and spermatozoal data, were analyzed with the nonparametric multiple comparison method of Shirley and Dunn. Average severity values were analyzed for significance using the Mann-Whitney U test.

Result **:** Among groups scheduled for interim evaluation on day 32, one male in the 12 mg/kg group died during week 3. Two females that received 1.5 mg/kg died due to dosing errors. The final mean body weights and mean body weight gains of dosed and the control mice were similar.
Clinical findings of toxicity were dose dependent and included lethargy, tremors, ataxia, convulsions, and abnormal breathing. These were observed within minutes of dosing and disappeared within 2 to 3 hours after dosing. No information were reported on the incidence of clinical signs at each dose.
Among groups evaluated at the end of the 13-week study, two female mice in the 12 mg/kg group died. One of them was due to a dosing error. The final mean body weights and mean body weight gains of dosed and the control mice were similar.
Clinical findings of toxicity were dose dependent and included lethargy, tremors, ataxia, convulsions, and abnormal breathing. These effects were observed within minutes of dosing and disappeared within 2 to 3 hours after dosing. No information were reported on the incidence of clinical signs at each dose.

At the 32-day interim evaluation, stomach weights of male mice that received 3 mg/kg or greater were greater than those of the control. And, thymus weights of males in the 12 mg/kg group were less than those of the controls. At the 13 weeks evaluation, males in the 12 mg/kg group had increased stomach weights. No differences in organ weights at the 32 day and 13 week evaluations were detected in female mice.

Dose(mg/kg)	0	0.75	1.5	3	6	12
Male						
32-day interim evaluation						
No.of animals examined	10	10	10	10	10	9
Absolute stomach(g)						
Mean	0.175	0.189	0.187	0.197*	0.195*	0.201*

	SE	0.005	0.005	0.009	0.006	0.007	0.007
Relative stomach							
	Mean	5.90	6.52	6.39	6.84**	6.66**	6.89**
	SE	0.18	0.19	0.26	0.14	0.30	0.20
Absolute Thymus(g)							
	Mean	0.053	0.052	0.047	0.047	0.051	0.043*
	SE	0.003	0.003	0.002	0.001	0.002	0.002
Relative Thymus							
	Mean	1.78	1.80	1.63	1.63	1.74	1.48*
	SE	0.08	0.10	0.07	0.04	0.06	0.06

Week 13

No.of animals examined						
	10	10	10	10	10	10
Absolute stomach						
Mean	0.198	0.212	0.221	0.214	0.220	0.233*
SE	0.003	0.007	0.008	0.008	0.006	0.016
Relative stomach						
Mean	5.77	5.91	6.16	5.84	6.60*	6.99**
SE	0.12	0.24	0.17	0.20	0.22	0.50

Note: *, p<0.05; **, p<0.01

No treatment-related gross or microscopic lesions were observed in mice exposed to methylacrylonitrile.

Reproductive parameters:
There were no significant differences in reproductive organ weights or sperm motility parameters between dosed and control males. There were no biologically significant differences in estrus cycle length or in the relative length of time spent in the estrus stages between dosed and control females.

Test substance : The test chemical was obtained in one lot(JY00427ET) from Aldrich Chemical Company(USA).
Purity: 99.9%(determined by gas chromatography)

Conclusion : One male and one female died early in the 12 mg/kg (8.6 mg/kg/day) group. Clinical findings such as lethargy, tremors, ataxia, convulsions, and abnormal breathing were observed. However, since no information were reported on the incidence of clinical signs at each dose, NOAEL for this study was not estimated.

11.01.2002 (38)

Species : rat
Sex : male/female
Strain : other:Harlan-Wistar
Route of admin. : inhalation
Exposure period : nine days
Frequency of treatment : seven hours per day, five days per week
Post obs. period : no data
Doses : 110, 50, 20 ppm
Control group : yes
Method : other
Year : 1968
GLP : no data
Test substance : Purity: minimum of 99.0 wt.%
Remark : No.of animals:six per sex per group
Young animals were exposed to methylacrylonitrile vapor.
Details of test condition such as age of animals at study initiation, clinical

observations performed and frequency, the items examined, and statistical methods used, were not reported.

Result : Two male rats died without convulsions during the first day at the 110 ppm level. No other rat at any level showed symptoms at any time during the nine-day exposure period. No gross lesions were observed in the dead animals or survivors. The latter had normal body weight gains and normal liver and kidney weights.

Conclusion : NOAEL was not established because there were no information on hematological, biochemical and histopathological examination.

11.01.2002 (3)

Species	:	rat
Sex	:	male/female
Strain	:	other:Harlan-Wistar
Route of admin.	:	inhalation
Exposure period	:	91 days
Frequency of treatment	:	seven hours per day, five days per week
Post obs. period	:	no data
Doses	:	19.3, 52.6, 109.3 ppm
Control group	:	yes
NOAEL	:	= 19.3 ppm
LOAEL	:	= 52.6 ppm
Method	:	other
Year	:	1968
GLP	:	no data
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	Groups consisting 12 young male and 12 young female rats were exposed to methylacrylonitrile vapor. The observed criteria of toxic stress included symptomatology, body weight changes, liver and kidney weights, and gross and microscopic pathology. All animals were examined carefully at autopsy and 19 tissues, but not the brain, were sampled from each rat for microscopic examination. Statistical methods: Body weight changes and kidney and liver weights as percentage of body weight of all animal groups were intercompared statistically by use of the following tests: Bartlett's homogeneity of variance, analysis of variance and Duncan's multiple range. The last test was used if F for analysis of variance was significantly high, to delineate which group differed from the control. If Bartlett's test indicated heterogeneous variances, the F-test was used for each group versus the control. If these individual F-tests were not singficant, Student's t-test was used; if significant, the means were compared by the Cochran t-test. The fiducial limit of 0.05 ("P") was employed as the critical level of difference believed not to have been produced by chance. There were no clear infromation on age of animals at study initiation, clinical observations performed and frequency, and organs examined at necropsy.
Result	:	Seven male rats died during the first day of exposure to 109.3ppm vapor and one male died during the second day at 52.6 ppm vapor. Loss of consciousness preceded death. One male rat was found prostrated by the end of the 11th exposure day at the 109.3 ppm level, but appeared normal the next morning. The body weight gains of both sexes at the 109.3 ppm level and of the females at the 52.9 ppm level were significantly lower than those of the control after five exposure days. After 91 exposure days the mean liver weights as percentage of the body weight of the males at the 109.3 ppm and 52.6 ppm levels and of the females at the 109.3 ppm level were significantly higher than those of the

control. There was no significant alternation of the relative kidney weights. No observable gross or microscopic lesions in the dead animals or survivors.

26.12.2001 (3)

Species	:	other:dog
Sex	:	female
Strain	:	Beagle
Route of admin.	:	inhalation
Exposure period	:	eight days
Frequency of treatment	:	seven hours per day, five days per week
Post obs. period	:	no data
Doses	:	20 ppm
Control group	:	no data specified
NOAEL	:	< 20 ppm
LOAEL	:	= 20 ppm
Method	:	other
Year	:	1968
GLP	:	no data
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	A female beagle weighing 6.3 kg was exposed to 20 ppm vapor for eight days. After the inhalation period the dog was sacrificed to examine macroscopically and microscopically. Details of the items examined were not reported. Details of test condition such as age of animals at study initiation, clinical observations performed and frequency, the items examined and statistical methods used, were not reported.
Result	:	The dog vomited early during the first day and experienced a 20% weight-loss by the eighth exposure day, but the dog had no other observable signs of toxic stress by that time. No pertinent gross or microscopic lesions were found.

26.12.2001 (3)

Species	:	dog
Sex	:	male
Strain	:	Beagle
Route of admin.	:	inhalation
Exposure period	:	90 days
Frequency of treatment	:	seven hours per day, five days per week
Post obs. period	:	no data
Doses	:	3.2, 8.8, 13.5 ppm
Control group	:	yes
NOAEL	:	= 8.8 ppm
LOAEL	:	= 13.5 ppm
Method	:	other
Year	:	1968
GLP	:	no data
Test substance	:	Purity: minimum of 99.0 wt.%
Remark	:	Groups of three young animals were exposed to methylacrylonitrile vapor. The observed criteria of toxic stress included body weight changes (statistically compared after the 6th, 31st, 61st, and 90th exposure days), symptomatology, hematocrit, total white blood cell count, differential count, blood urea nitrogen, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase and serum alkaline phosphatase values, as well as liver and kidney weights and gross and micropathology. The hematological and blood chemistry tests were performed 15 days before the start of the study and after the 21st,41st,

61st and 89th exposure days. Twenty-seven tissues, including the brain, from each dog were sampled for microscopic examination.
Statistical methods: Body weight changes and kidney and liver weights as percentage of body weight of all animal groups were intercompared statistically by use of the following tests: Bartlett's homogeneity of variance, analysis of variance and Duncan's multiple range. The last test was used if F for analysis of variance was significantly high, to delineate which group differed from the control. If Bartlett's test indicated heterogeneous variances, the F-test was used for each group versus the control. If these individual F-tests were not singficant, Student's t-test was used; if significant, the means were compared by the Cochran t-test. The fiducial limit of 0.05 ("P") was employed as the critical level of difference believed not to have been produced by chance.
There were no clear infromation on age of animals at study initiation, clinical observations performed and frequency, and organs examined at necropsy.

Result : At least on dog had diarrhea during the fifth exposure day at 13.5 ppm. Between the 39th day and 64th exposure days, two of the three male dogs at 13.5 ppm showed clinical signs such as tonic convulsions, rapid pulse, rapid respiration, loss of control over the hind quarters and congested optic discs. One of them had microscopic lesions in the brain: microscopic malacia of the floor of the third ventricle of the brain with massive accumulations of gitter cells and some demyelinization of the corpus callosum above this area. One of three dogs at the 8.8 ppm level experienced a marked but transitory elevation of SGOT and SGPT values. One of the three dogs at 3.2 ppm showed a slight and transitory reversal in the neutrophil-lymphocyte ratio, to which no significance is attached.

26.12.2001 (3)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Test species/strains : Sallmonella typhimurium TA100, TA1535, TA98, TA1537, Escherichia coli WP2 uvrA
Concentration : 0, 313, 625, 1250, 2500, 5000 ug/plate
Cytotoxic conc. : Cytotoxicity was not observed.
Metabolic activation : with and without
Result : negative
Method : other:Chemical Substance Control Law of Japan and OECD Guide-line 471
Year : 2001
GLP : yes
Test substance :
Remark : Procedures: Pre-incubation method
Solvent: Dimethyl sulfoxide
S9: Rat liver, induced with phenobarbital and 5,6-benzoflavon
Positive control:
-S9: 2-(Furyl)-3-(5-nitro-2-furyl)acrylamide for TA98, TA100 and WP2uvrA
Sodium azide for TA1535
9-Aminoacridine for TA1537
+S9: 2-Aminoanthracene for all strains
Plates/test: 3(1 for cytotoxicity test)
Number of replicates: 2(plus 1 cytotoxicity test)
Result : There were no precipitation in any test concentration.

Cytotoxic concentration:
Toxicity was not observed up to 5000 ug/mL in five strains with or without S9 mix.
Genotoxic effects :
With metabolic activation: negative
Without metabolic activation: negative

Test substance : Purity: 99%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.12.2001 (31)

Type : Ames test
System of testing : Salmonella typhimurium strain TA97, TA98, TA100, TA1535, or TA1537
Concentration : 0, 100, 333, 1000, 3333, 6666, 10000 ug/plate
Cytotoxic conc. : 10000 ug/plate: cytotoxicity was observed at TA100 without S9 mix and TA1537 with rat S9 mix, and slightly at TA97, TA98, TA100 and TA1535 with hamster S9 mix.
Metabolic activation : with and without
Result : negative
Method : other
Year : 1987
GLP : no data
Test substance : no data
Remark : S9: Sprague-Dawley rat liver or Syrian hamster liver, induced with Aroclor 1254
Positive control:
-S9: 9-Aminoacridine for TA97 and TA1537
4-Nitro-o-phenylenediamine for TA98
Sodium azide for TA100 and TA1535
+S9: 2-Aminoanthracene for all strains
At least two trial of triplicate plate was conducted.
27.12.2001 (13) (38)

Type : Ames test
System of testing : Salmonella typhimurium strains TA98 and TA100
Concentration : Up to concentration which exhibit toxic effects (no detail data)
Cytotoxic conc. : no data
Metabolic activation : with and without
Result : negative
Method : other
Year : 1985
GLP : no data
Test substance : no data
Remark : Since methylacrylonitrile could absorb to plastic and is volatile, closed glass equipment was used in the study. This study was reported only as a brief abstract and there were no detail information.
27.12.2001 (35)

Type : other:Fluctuation test
System of testing : Klebsiella pneumoniae
Concentration : Up to concentration which exhibit toxic effects
Cytotoxic conc. : no data
Metabolic activation : without
Result : positive
Method : other
Year : 1985
GLP : no data
Test substance : no data
Remark : Since methylacrylonitrile could absorb to plastic and is

volatile, closed glass equipment was used in the study.
This study was reported only as a brief abstract and there were no detail information.

27.12.2001 (35)

Type : other:gene mutation test
System of testing : L5178Y mouse lymphoma cells
Concentration : up to concentrations which exhibit toxic effects
Cytotoxic conc. : no data
Metabolic activation : with and without
Result : negative
Method : other
Year : 1985
GLP : no data
Test substance : no data
Remark : Gene mutation was examined at the HPRT- and TK-loci.
Since methylacrylonitrile could absorb to plastic and is volatile, closed glass equipment was used in the study.
This study was reported only as a brief abstract and there were no detail information.

27.12.2001 (35)

Type : Chromosomal aberration test
System of testing : Type of cell used :Chinese hamster lung(CHL/IU) cells
Concentration : -S9 mix(short-term treatment): 0, 0.17, 0.34, 0.67 mg/mL
+S9 mix(short-term treatment): 0, 0.068, 0.14, 0.27, 0.54 mg/mL
-S9 mix(continuous treatment for 24 hours): 0, 0.17, 0.34, 0.67 mg/mL
Cytotoxic conc. : Cytotoxicity was observed at 0.54 mg/mL with S9 mix in short-term treatment.
Metabolic activation : with and without
Result : positive
Method : OECD Guide-line 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"
Year : 2001
GLP : yes
Test substance :
Remark : Solvent: Distilled water
S9: Rat liver, induced phenobarbital and 5,6-benzoflavon
Plates/test: 2
Positive control: -S9: Mitomycin C (0.05 ug/mL)
+S9: Cyclophosphamide (5 ug/mL)
Maximum concentration, 0.67mg/mL, for continuous treatment and short-term treatment without S9 was giving 50% growth inhibition of the cells in cell proliferation inhibition test.
Maximum concentration, 0.54mg/mL, for short-term treatment with S9 was giving two times 50% growth inhibition of the cells in cell proliferation inhibition test.
Result : Cells with structural aberrations were increased dose dependently after short-term treatment with metabolic activation(frequency: 7.5-62.0%). Polyploidy did not show dose-dependent increasing, but was significantly induced at 0.068 mg/mL and 0.14 mg/mL on short-term treatment with metabolic activation.

Chromosome analysis in short-term treatment with S9 mix

Concentration: methylacrylonitrile(mg/mL)					CPA (ug/mL)
0(solvent)	0.068	0.14	0.27	0.54	5
No. of cells analysed					
200	200	200	200	tox	200

No. of cells with aberrations
TAG(%)
5(2.5) 19*(9.5) 31*(15.5) 129*(64.5) tox 127*(63.5)

TA(%)
4(2.0) 15*(7.5) 30*(15.0) 124*(62.0) tox 124*(62.0)
Polyploid(%)
0.50 3.13* 1.88* 0.14 tox 0.13
Cell number (%)
100.0 80.3 80.7 67.5 20.2 -
Mitotic index (%)
- - - 1.6 tox -

Note: TAG, total no. of cells with aberration
TA, total no. of cells with aberration except gap
*, p<0.05
tox: Not examined because of cytotoxicity

Genotoxic effects:

	clastogenicity			polyploidy		
	+	?	-	+	?	-
Without metabolic activation	[ ]	[ ]	[*]	[ ]	[ ]	[*]
With metabolic activation	[*]	[ ]	[ ]	[*]	[ ]	[ ]

Test substance : Purity: 99%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.12.2001 (32)

Type : Unscheduled DNA synthesis
System of testing : HepG2 cells
Concentration : 10, 20, 40 nm/plate
Cytotoxic conc. : no data
Metabolic activation : without
Result : ambiguous
Method : other
Year : 1997
GLP : no data
Test substance : no data
Remark : Solvent: acetone
Increase in the incorporation of [3H] thymidine indicated the induction of unscheduled DNA synthesis.
Result : Maximal unscheduled DNA synthesis activity was observed at 20 nm/plate. At 40 nm/plate, a modest depression of unscheduled DNA synthesis response was yielded. There were no clear data on cytotoxicity.
Conclusion : The result of this study was inconclusive.
27.12.2001 (6)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : rat
Sex : male
Strain : no data
Route of admin. : i.p.
Exposure period : 3 days (three times at 24-hour intervals)

Doses : 12, 25, 50, 100, 200 mg/kg
Result : negative
Method : other
Year : 1993
GLP : no data
Test substance : no data
Method : The standard three-exposure protocol was described in details by Shelby et.al.(Environ. Mol. Mutagen., 21,160-179,1993)
Remark : Male rats (five per group) were injected intraperitoneally three times at 24-hour intervals with methylacrylonitrile dissolved in corn oil at doses of 12, 25, 50, 100, and 200 mg/kg. Solvent control animals were injected with corn oil only. The positive control animals received injections of cyclophosphamide (25 mg/kg). The animals were killed 24 hours after the third injection, and slides were prepared from bone marrow cells obtained from the femurs. 2000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each group.
Result : A initial trial(25, 50, 100, 200 mg/kg i.p.) showed a significant induction of micronuclei in the 25 mg/kg group (Micronucleated PCEs/1000 PCEs: 1.40±0.37 compared with 0.25±0.14 in control); however, a second trial(12, 25, 50mg/kg i.p.) showed no induction of micronuclei in born marrow polychromatic erythrocytes, and the test was determined to be negative overall.
200 mg/kg in a initial trial and 50 mg/kg in a second trial was lethal. In addition, erythrocytes were scored with only 3 and 2 animals at 50 mg/kg and 100 mg/kg, respectively, in a initial trial, probably due to toxicity (no data).

11.01.2002 (38)

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : gavage
Exposure period : 13 weeks (once a day, five days per week)
Doses : 0, 0.75, 1.5, 3, 6, or 12 mg/kg
Result : negative
Method : other
Year : 1993
GLP :
Test substance :
Remark : At the end of 13-week study, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2000 normochromatic erythrocytes (NCEs) in up to ten aminals per dose group. In addition, the percentage of polychromatic erythrocytes (PCEs) among the totalerythrocyte population in the peripheral blood was scored for each dose group as a measure of toxicity.
Result : Methylacrylonitrile did not significantly induce micronuclei.
See section 5.4 REPEATED DOSE TOXICITY on observed toxicity.

Dose(mg/kg)	Number of mice with erythrocytes	Micronucleated NCEs/1000 NCEs

Male		scored	
Corn oil		10	0.45±0.15
Methylacrylonitrile	0.75	10	0.50±0.16
	1.5	10	0.60±0.12
	3	10	0.70±0.13
	6	10	0.55±0.11
	12	10	0.60±0.17
Female			
Corn oil		10	0.55±0.18
Methylacrylonitrile	0.75	10	0.50±0.07
	1.5	10	0.35±0.10
	3	10	0.40±0.15
	6	10	0.35±0.16
	12	8	0.31±0.09

Test substance : The test chemical was obtained in one lot(JY00427ET) from Aldrich Chemical Company(USA). Purity: 99.9%(determined by gas chromatography)
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
22.01.2002 (37)

Type : Micronucleus assay
Species : mouse
Sex : male
Strain : no data
Route of admin. : i.p.
Exposure period : 3 days(three times at 24-hour intervals)
Doses : 6.25, 12.5, 25 mg/kg
Result : negative
Method : other
Year : 1993
GLP : no data
Test substance : no data
Method : The standard three-exposure protocol was described in details by Shelby et.al.(Environ. Mol.Mutagen., 21,160-179,1993)
Remark : Male mice(five per group) were injected intraperitoneally three times at 24-hour intervals with methylacrylonitrile dissolved in corn oil at doses of 6.25, 12.5, 25, 50, 100, and 200 mg/kg. Solvent control animals were injected with corn oil only. The positive control animals received injections of cyclophosphamide (25 mg/kg). The animals were killed 24 hours after the third injection, and slides were prepared from bone marrow cells obtained from the femurs. 2000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each group.
Result : No increase in the frequency of micronucleated polychromatic erythrocytes was observed in the born marrow of male mice treated with 6.25 to 25 mg/kg methylacrylonitrile.
At 25 mg/kg, erythrocyte was scored only in three mice, probably due to toxicity (no data).
27.12.2001 (38)

5.7 CARCINOGENITY

Species : rat
Sex : male/female
Strain : other: F344/N

Route of admin.	:	gavage
Exposure period	:	2 years
Frequency of treatment	:	once a day, 5 days per week
Post. obs. period	:	none
Doses	:	3, 10, 30 mg/kg
Result	:	negative
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1997
GLP	:	yes
Test substance	:	other TS
Test condition	:	Vehicle: deionized water(dosing volume 5 mL/kg). 50 male and 50 female animals per group were approximately 6 weeks old at the beginning of the studies. Animals were observed twice daily and weighed at the beginning of the studies, every 4 weeks, and at necropsy. Clinical findings were recorded on days 8 and 29, every 4 weeks thereafter, and at necropsy. Five male and five female rats per group were randomly selected for urine collection at 2 weeks and 3, 12, and 18 months. The volume and creatinine concentration of urine and urinary metabolites were determined. Complete necropsies and microscopic examinations were performed on all rats. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, and processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 micro m, and stained with hematoxylin and eosin for microscopic examination. The following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung with mainstem bronchi, lymph nodes (mandibular and mesenteric), mamary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.
Result	:	Survival of all dosed groups was similar to that of the vehicle control groups. Mean body weights of the 30 mg/kg groups were lower by at most 9 % than those of the vehicle controls after weeks 21 and 37 for males and females, respectively. There were no clinical findings related to methylacrylonitrile. No changes in the incidences of neoplasms were attributed to exposure to methylacrylonitrile. The incidences of olfactory epithelial atrophy and metaplasia of the nose were significantly greater in 30 mg/kg males and females than those in the vehicle controls. Increased incidences of cytoplasmic vacuolation occurred in the liver of males and females. Summary of the 2-year Carcinogenesis Body weights: 30 mg/kg group less than the vehicle control group. Survival rates: Male: 0 mg/kg, 25/50; 3 mg/kg, 34/50; 10 mg/kg, 35/50; 30 mg/kg, 31/50 Female: 0 mg/kg, 38/50; 3 mg/kg, 33/50; 10 mg/kg,34/50; 30 mg/kg, 36/50

Nonneoplastic effects
Nose: Olfactory epithelial atrophy:
Male: 0 mg/kg, 0/50; 3 mg/kg, 0/50; 10 mg/kg, 0/49; 30 mg/kg, 48/50
Female: 0 mg/kg, 0/50; 10 mg/kg, 0/50; 10 mg/kg, 1/50; 30 mg/kg, 19/50
Olfactory epithelial metaplasia:
Male: 0 mg/kg, 0/50; 3 mg/kg, 0/50; 10 mg/kg, 0/49; 30 mg/kg, 47/50
Female: 0 mg/kg, 0/50; 3 mg/kg, 0/50; 10 mg/kg, 0/50; 30 mg/kg, 47/50
Liver: Cytoplasmic vacuolization:
Male: 0 mg/kg, 14/50; 3 mg/kg, 18/50; 10 mg/kg, 23/50; 30 mg/kg, 28/49
Female: 0 mg/kg, 7/50; 3 mg/kg, 14/49; 10 mg/kg, 17/48; 30 mg/kg, 30/50
Pancreas: Hyperplasia:
Male: 0 mg/kg, 4/50; 3 mg/kg, 10/49; 10 mg/kg, 11/50; 30 mg/kg, 12/50

Neoplastic effects: None in all the groups

Urinalysis and Urinary metabolite analyses:
No biologically significant differences in urine volume or urinary creatinine concentrations were observed between dosed and vehicle control rats. Urinary excretion of N-acetyl-S-(2-cyanoproryl)-L-cysteine and N-acetyl-S-(2-hydroxypropyl)-L-cysteine increased in male and female rats as a function dose. The ratios of ug N-acetyl-S-(2-cyanopropyl)-L-cysteine/mg creatinine were generally greater in males than in females. In females, the ratios of ug
N-acetyl-S-(2-hydroxypropyl)-L-cysteine/mg creatinine were generally greater than the corresponding ratios of ug N-acetyl-S-(2-cyanopropyl)-L-cysteine/mg creatinine. However, opposite is generally observed in male rats.

Remark : Hematological and blood biochemical examination was not conducted. The doses were selected based on the results of the NTP 13-week studies (NTP toxicity studies 47 (2000)).
NOAEL for repeated dose toxicity was considered 10 mg/kg b.w. (7.14 mg/kg b.w./day) for both sexes, based on histopathological changes in olfactory epithelium and bone marrow.
Test substance : Purity: greater than 99%
Conclusion : It was suggested that the increase in hepatic glycogen observed in the rats represents an adaptive response to the extensive hepatic metabolism of this compound in this species. And the incidences of acinar hyperplasia noted in the dosed group are within the historical control range. These changes were not considered related to treatment.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.12.2001 (37)

Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : gavage
Exposure period : 2 years

Frequency of treatment	:	one aday, 5 days per week
Post. obs. period	:	none
Doses	:	1.5, 3, 6 mg/kg
Result	:	negative
Control group	:	yes, concurrent vehicle
Method	:	other
Year	:	1997
GLP	:	yes
Test substance	:	other TS
Test condition	:	Vehicle: deionized water(dosing volume 10 mL/kg). 50 male and 50 female animals per group were approximately 6 weeks old at the beginning of the studies. Animals were observed twice daily and weighed at the beginning of the studies, every 4 weeks, and at necropsy. Clinical findings were recorded on days 8 and 29, every 4 weeks thereafter, and at necropsy. Five male and five female mice per group were randomly selected for urine collection at 2 weeks and 3, 12, and 18 months. The volume and creatinine concentration of urine and urinary metabolites were determined. Complete necropsies and microscopic examinations were performed on all mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, and processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 micro m, and stained with hematoxylin and eosin for microscopic examination. The following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung with mainstem bronchi, lymph nodes (mandibular and mesenteric), mamary gland (except male mice), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.
Result	:	Survival of all dosed groups was similar to that of the vehicle control groups. There were no clinical findings related to methylacrylonitrile administration. The mean body weights of all dosed groups were generally similar to those of the vehicle controls throughout the study. There were no neoplasms or nonneoplastic lesions that were attributed to methylacrylonitrile administration. Summary of the 2-year Carcinogenesis Survival rates: Male: 0 mg/kg, 35/49; 1.5 mg/kg, 43/50; 3 mg/kg, 43/50; 6 mg/kg, 22/50 Female: 0 mg/kg, 35/50; 1.5 mg/kg, 35/50; 3 mg/kg, 43/50; 6 mg/kg, 25/50 Nonneoplastic effects: None in all the groups Neoplastic effects: None in all the groups Urinalysis and Urinary metabolite analyses: No biologically significant differences in urine volume or urinary creatinine concentrations were observed between dosed and vehicle control rats. Urinary excretion of

N-acetyl-S-(2-cyanoproryl)-L-cysteine and
N-acetyl-S-(2-hydroxypropyl)-L-cysteine increased in male
and female mice in a dose-dependent manner. The ratios of
ug N-acetyl-S-(2-cyanopropyl)-L-cysteine/mg creatinine were
generally greater in females than in males. Further, the
ratios of ug N-acetyl-S-(2-hydroxypropyl)-L-cysteine/mg
creatinine were significantly greater at all time points
and doses than the corresponding ratios of ug
N-acetyl-S-(2-cyanopropyl)-L-cysteine/mg creatinine in male
and female mice.

Remark : Hematological and blood biochemical examination was not conducted.
The doses were selected based on the results of the NTP 13-week studies (NTP toxicity studies 47 (2000)).
NOAEL for repeated dose toxicity was considered 6 mg/kg b.w. (4.29 mg/kg b.w./day).

Test substance : Purity: greater than 99%

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

27.12.2001 (37)

5.8 TOXICITY TO REPRODUCTION

Type : other

Species : rat

Sex : male/female

Strain : other:Crj:CD(SD)IGS

Route of admin. : gavage

Exposure period : Males:46 days, females:from 14 days before mating to day 4 of lactation

Frequency of treatment : once a day

Premating exposure period

Male : 14 days

Female : 14 days

Duration of test : Males: 47 days, females:from 14 days before mating to day 5 of lactation

Doses : 7.5, 15, 30 mg/kg

Control group : yes, concurrent vehicle

NOAEL Parental : = 30 mg/kg bw

NOAEL F1 Offspr. : = 30 mg/kg bw

Method : other:OECD Test guideline 422

Year : 2001

GLP : yes

Test substance : other TS

Remark : This study was conducted to examine both repeated dose toxicity and reproductive/developmental toxicity as an OECD screening combined study(Test guideline:422)
Test condition:
Age at study initiation: 10 week old for both sexes
Weight at study initiation: 354-434g for males; 210-259g for females
No.of animals per dose per sex: 12
Study design
Vehicle: Olive oil
Mating period: Male/female per cage;1/1
Determination of pregnancy: formation of vaginal closing or sperm detection in vagina
Clinical observation performed and frequency:
Parental:General appearance once a day

Foetus:General appearance once a day
Urinalysis, and hematological and biochemical analysis: Urinalysis was carried out in 6 male animals per dose at 43 or 44 days of treatment. Hematological and biochemical analysis were carried out in all male animals per dose at the 46 days of treatment and in 6 nursing dams per dose at day 5 of lactation period.
Parameters assessed during study: Body weight and food consumption were determined at days 1(before dosing),2,5,7,10 and 14 of treatment for males and females, thereafter once a week and at autopsy for males, or at days 0,1,3,5,7,10,14,17 and 20 of gestation period and at days 0,1 and 4 of lactation period and at autopsy for females, but food consumption was not determined during mating period for males, and at day 0 of gestation and lactation periods for females. No.of pairs with successful copulation, copulation index(No.of pairs with successful copulation, copulation index(No.of pairs with successful copulation/No.of pairs mated x 100), pairing days until copulation, No.of pregnant females, fertility index=(No. of pregnant animals/No.of pairs with successful copulation x 100), No.of corpora lutea, No.of living pregnant females, No.of pregnant females with parturition, gestation length, No. of pregnant females with live pups on day 0, gestation index(No.of females with live pups/No.of living pregnant females x 100), No.of pregnant females with live pups on day 4, delivery index(No.of lactation, live birth index(No.of female pups),No of pups alive on day 4 of lactation, viability index(No.of live pups on day 4/No.of live pups on day 0 x 100), body wt. of live pups(on 0 and 4).
Organs examined at necropsy:
Parent: Organs examined at necropsy
organ weight: Brain, heart, liver, kidney, spleen, adrenal, thymus, testis and epididymis
microscopic examination: Brain, pituitary, thymus, thyroid, parathyroid, adrenal, spleen, heart, thoracic aorta, tongue, esophagus, stomach, liver, pancreas, duodenum, jejunum, ileum, cecum, colon, rectum, larynx, trachea, lung, kidney, urinary bladder, testis, epididymis, prostate, seminal vesicle, ovary, uterus, vagina, eye, Harderian gland, mammary gland, skin, sternum, femur, spinal cord, skeletal muscle, mesentery lymph node, mandibular lymph node, submandibular gland, sublingual gland, parotid gland, ischiadic nerve
Foetus: Full macroscopic examination on all of pups
Statistical methods:Dunnett's test for continuous data and Mann-Whitney U test for quantal data

Result **:** Clinical signs: No abnormality was detected for males and females.
Body weight: No statistically significant changes for males and females.
Food consumption: No dose-dependent changes for males and females.
Urinalysis: No statistically significant changes.
Hematology: Males: Decreases in RBC, packed cell volume and hemoglobin concentration in 30mg/kg group.
Biochem: Males: Decreases in potassium in 15 and 30mg/kg groups, increase in creatinine in 30mg/kg group.
Females: Increase in total bilirubin and glucose in 30mg/kg group.

Necropsy: Males:Dark red patches on the mucosa of the glandular stomach in one out of twelve animals given 30mg/kg.
Females: Dark red patches on the mucosa of the glandular stomach in one out of twelve animals given 7.5 or 15mg/kg and in two out of twelve animals given 30mg/kg.
Organ weight: Males: Increase in a relative liver weight in 30mg/kg group.
Histopathology: Slight erosions in the dark red patches on the mucosa of the glandularstomach which were observed in a few male and female animals and extramedullary hematopoiesis in the spleen in 3 females given 15mg/kg, and 7 females given 30mg/kg.
Reproductive parameters: No effects were observed on reproductive performance in males and females given each dose
.

Dose(mg/kg)	0	7.5	15	30
No.of pairs mated	12	12	12	12
No.of pairs with successful copulation	12	12	12	11
Duration of mating Mean	2.3	2.9	2.9	3.5
SD	0.8	0.9	1.1	3.6
Copulation Index	100.0	100.0	100.0	91.7
No.of pregnant animals	11	11	10	11
Fertility Index	91.7	91.7	83.3	100.0

Note: Duration of mating (days, mean and S.D.)
Copulation Index(%)
Fertility Index(%)
Each parameters: No stat.sig.difference from control

Developmental parameters: No effect was detected on viability, general appearance, body weight or autopsy findings of offsprings.

Test substance : Purity: 99%
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
27.12.2001 (30)

Type : Two generation study
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : See Method
Frequency of treatment : See method
Premating exposure period
Male : See method
Female : See method
Duration of test : See method
Doses : 2, 7, 20 mg/kg

Control group	:	yes, concurrent vehicle
NOAEL Parental	:	= 7 mg/kg bw
NOAEL F1 Offspr.	:	= 7 mg/kg bw
Method	:	other: Reproductive Assessment by Continuous Breeding protocol in National Toxicology Program
Year	:	1997
GLP	:	yes
Test substance	:	no data
Method	:	The Reproductive Assessment by Continuous Breeding(RACB) design in the National Toxicology Program has been used . Each study conducted in accordance with the RACB is separated into four tasks. Task 1 is the dose-range-finding portion. The end points are body weights and food and water consumption. Task 2 is the main portion of an RACB study. In Task 2, control and three dose levels are used, with 20 male and 20 female rodents per dose level. 40 control pairs were used in the study. Exposure begins 1 week prior to cohabitation, and then the animals are housed as breeding pairs for approximately 15 weeks for rats. During this time of continuous chemical exposure, litters are produced approximately 3 to 4 weeks apart. Data collected include developmental parameters on each litter and pregnancy cycle of the dams. After 15 weeks, the pair is separated for 6 weeks, during which the female delivers and nurses to weaning any last litter. Task 3 is the crossover mating trial, performed to determine which sex has affected by treatment. This trial is performed after the last litter from Task 2 has been weaned at postnatal day 21. Task 3 animals are cohabited for a week without being exposed to the test compound, and females are subject to vaginal lavage each day, to check for sperm. The animals are separated when the female is sperm positive or after 1 week, whichever comes first. Thus, alterations in libido or mating success can be identified in this task. The F0 animals can be killed and evaluated for pathology at this point. Task 4 is the evaluation of the second generation. Exposure to the test compound starts at weaning, with each pup receiving the same exposure level as that given his or her parents. When the animals are approximately 80(rats) days of age, they are cohabited within treatment groups for a week. Data collected include developmental parameters on each litter and pregnancy cycle of the dams in the same manner as Task 3. Vehicle: deionized water
Remark	:	In Task 1, decreased body weight and feed consumption, increased water consumption, and mortality were noted. Therefore, dose levels for the continuous breeding phase were set at 2, 7, and 20 mg/kg in deionized water by oral gavage in Task 2.
Result	:	Exposure to methylacrylonitrile by gavage (20 rats/sex/group) did not affect the reproductive performance of F0 rats (Task 2) or F1 rats (Task 4) where only the controls and high-dose groups were evaluated. In Task 4, estrous cyclicity of the F1 animals was not affected by methylacrylonitrile administration. Slight but consistent decreases (3-6%) were noted in the 20 mg/kg F0 male body weights, although none of these reached

statistical significance. F0 female body weights were unchanged. Body weights of the F1 20 mg/kg males and females were consistently less (6-10%) than controls and were occasionally statistically significant. Daily mean feed consumption was decreased by 8-11% in the 20 mg/kg F1 males; F0 male and female and F1 female feed consumption values were unchanged.
No treatment-related changes were noted in hematology or clinical chemistry parameters for either the F0 or F1 animals. At necropsy, no differences were noted in F0 or F1 animals absolute organ weights; however, relative liver weight was increased in the 20 mg/kg males and females from both generations by ~12% when compared to controls. No treatment-related gross or microscopic lesions were observed in either the F0 or F1 animals.
The percent normal sperm was decreased slightly (by ~1%) in the 2 and 20 mg/kg F0 males while no differences were seen in F0 epididymal sperm density. In the F1 generation, epididymal sperm density was decreased by 19% at 20 mg/kg but epididymal sperm morphology was unchanged. F0 and F1 sperm motion parameters and testicular spermatid head counts were unchanged.

Conclusion : The ~1% change in epididymal sperm abnormalities at 2 and 20 mg/kg in the F1 male is believed to be "noise" and not a treatment-related response because the historical control range of percent abnormal sperm is 0.1-1.4% in this laboratory. Therefore, NOAEL for reproductive toxicity was 7 mg/kg/day in males and 20 mg/kg/day in females.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

11.01.2002 (36)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	days 6 to 15 of gestation
Frequency of treatment	:	once a day
Duration of test	:	gestational days 0 to 20
Doses	:	5, 25, 50 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	> 50 mg/kg bw
NOAEL Embryotoxicity	:	> 50 mg/kg bw
Method	:	other
Year	:	1996
GLP	:	yes
Test substance	:	other TS
Method	:	This study was conducted in accordance with the Food and Drug Administrastion 'Good Laboratory Practice Regulations for Nonclinical Laboratory Studies'(FDA,1988).
Remark	:	The test chemical was solved in distilled water(vehicle). Animals: rats(Crj:CD BR VAF/Plus) Female rats weighed from 207 to 275g on gestation day 0(day of vaginal sperm detection). Individual females were placed overnight in the home cage of a singly housed male of the

same stock for mating and then examined the next morning for presence of a vaginal sperm. Number of pregnant females was 25-26 per group.
Animals were weighed on gestation day 0 and daily during treatment (gestational days 6 to 15, organogenesis). Food and water consumption was measured at 2- to 3-day intervals throughout the study, beginning on gestation 0.
Clinical signs were recorded at least once daily during the treatment periods. At necropsy, maternal liver weight and gravid uterine weight were measured. Uterine contents were evaluated for the number of implantation sites, resorptions, late fetal death and live fetuses. The uterus was stained to reveal possible early resorptions when evidence of pregnancy was not apparent. Live fetuses were dissected from the uterus and anesthetized by inducing hypothermia. Each live fetus was weighed and examined for external morphological abnormalities; the viscera were then examined. Half of the fetuses were decapitated prior to dissection, and the heads were fixed in Bouin's solution for examination. All fetal carcasses were cleared and stained with Alcian blue/Alizarin red S and examined for skeletal malformations.

Statistical analysis: Dose-response relationships for selected measures were evaluated with the test for linear trend. The determination whether significant dose effects, replicate effects, or dose replicate interactions had occurred used Analysis of Variance, Williams' multiple comparison test and Dunnett's test. Normal scale measures were analyzed by a test for linear trend on proportion and a chi square test for independence among treatment groups and a Fisher exact probability test for comparison between treatment groups and the control group.

Result : No treatment-related maternal clinical signs or mortality were observed, nor was there any adverse effects on maternal body weight or food or water consumption.
At necropsy, absolute, relative, and adjusted maternal liver weight was increased at the mid- and high-dose groups, an effect that may be indicative of induction of hepatic enzymes rather than toxicity. There was no effect of treatment on postimplantation loss, mean fetal body weight per litter, or morphological development.

Maternal toxicity: Effect of the test chemical on the maternal liver weight

Dose(mg/kg)		0	5	25	50
No. of pregnants		25	26	26	25
Maternal liver weight					
Absolute(g)	Mean	18.3	18.7	19.7**	19.2**
	SE	0.5	0.3	0.3	0.3
Relative(% bw)	Mean	4.5	4.6	4.7**	4.7**
	SE	0.1	0.1	0.1	0.1
Relative(%adjusted wt.)					
	Mean	5.7	5.9	6.0	6.0
	SE	0.1	0.1	0.1**	0.1**

Note: **, p<0.01

There was no effect of treatment on postimplantation loss, mean fetal body weight per litter, or morphological development.

Developmental Toxicity:

Dose(mg/kg)	0	5	25	50

All litters		25	26	26	25
Implantation sites/litter					
	Mean	15.6	15.6	16.0	15.4
	SEM	0.4	0.4	0.3	0.3
Percentage postimplantation/head					
	Mean	3.2	3.5	2.4	4.9
	SEM	1.4	1.2	0.9	2.5
Live litters		25	26	26	25
Live fetuses/litter					
	Mean	15.1	15.0	15.6	14.7
	SEM	0.4	0.4	0.4	0.5
Average fetal body weight/litter(g)					
	Mean	3.73	3.72	3.71	3.76
	SEM	0.06	0.04	0.04	0.06
Percentage live fetuses malformed/litter					
	Mean	5	3	5	5
	SEM	2	1	2	2

Test substance : Purity: 96% (determined by gas chromatography)
Conclusion : NOAEL was not estimated because of maternal toxicity.
Reliability : (2) valid with restrictions
The test guideline used was unknown.
Flag : Critical study for SIDS endpoint
27.12.2001 (17)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : first or second week of gestation period
Frequency of treatment : once a day
Duration of test : day 0 to 20 of gestation
Doses : 50, 100 mg/kg
Control group : yes, concurrent vehicle
Method : other
Year : 1992
GLP : no data
Test substance : other TS
Remark : The study was carried out in three parts as indicated by dosage(groups 1-3). In group 1, first week of gestation was chosen in order to examine the problems that could arise in early pregnancy upon exposure to methylacrylonitrile (50 mg/kg); in group 2, second week of gestation was chosen to examine the effect of methylacrylonitrile on maintenance of pregnancy (50 mg/kg) and in group 3, the pregnant rats received 100 mg/kg(0.5 LD50 value) in second week. The pregnant rats, at the end of the experiments, were sacrificed; their abdominal walls were cut open and the fallopian tubes and uteri were observed for any morphological or physiological abnormalities including edema and the occurrence of any abnormal growth.
All data were calculated and expressed as mean and SD of 6 animals. Statistical analysis was accompanied with student's test.
Result : Within one hour following the test chemical ingestion, the rats developed dose related mild to severe conditions including ataxia, trembling, convulsions, salivation and irregular breathing. The rats recovered from these signs at various times depending on the dose given.
Body weight loss was consistently observed in all the

treated rats following the initial dosing.
None of the group 1 and 3 rats delivered. Only one the group 2 rats delivered a litter of 9 offspring whereas all the control rats delivered normal size litters on the 20th day of gestation.
At necropsy, three out of five treated rats in group 1 animals exhibited mild to severe edema in the fallopian tubes. In group 2 and 3, 4 out of 6 treated rats exhibited severe edema in the fallopian tubes.

Test substance : Purity:>99%

27.12.2001 (7)

Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	gavage
Exposure period	:	day 6 to 19 of gestation
Frequency of treatment	:	once a day
Duration of test	:	gestational days 0 to 30
Doses	:	1, 3, 5 mg/kg
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	> 5 mg/kg bw
NOAEL Embryotoxicity	:	= 3 mg/kg bw
Method	:	other
Year	:	1996
GLP	:	yes
Test substance	:	
Method	:	This study was conducted in accordance with the Food and Drug Administrastion 'Good Laboratory Practice Regulations for Nonclinical Laboratory Studies'(FDA,1988).
Remark	:	The test chemical was solved in distilled water(vehicle). Animals: Rabbits Female rabbits weighed from 2.7 to 4.0kg on gestation day 0(day of artificial insemination). Number of pregnant females was 17-22 per group. Animals were weighed on gestation day 0 and daily during treatment (gestational days 6 to 19, organogenesis). Food consumption was measured at 2- to 3-day intervals throughout the study, beginning on gestation 0. Clinical signs were recorded at least once daily during the treatment periods. At necropsy (gestational day 30), maternal liver weight and gravid uterine weight were measured. Uterine contents were evaluated for the number of implantation sites, resorptions, late fetal death and live fetuses. The uterus was stained to reveal possible early resorptions when evidence of pregnancy was not apparent. Live fetuses were dissected from the uterus and anesthetized by inducing hypothermia. Each live fetus was weighed and examined for external morphological abnormalities; the viscera were then examined. Half of the fetuses were decapitated prior to dissection, and the heads were fixed in Bouin's solution for examination. All fetal carcasses were cleared and stained with Alcian blue/Alizarin red S and examined for skeletal malformations. Statistical analysis: Dose-response relationships for selected measures were evaluated with the test for linear trend. The determination whether significant dose effects, replicate effects, or dose replicate interactions had

occurred used Analysis of Variance, Williams' multiple comparison test and Dunnett's test. Normal scale measures were analyzed by a test for linear trend on proportion and a chi square test for independence among treatment groups and a Fisher exact probability test for comparison between treatment groups and the control group.

Result : Maternal toxicity:
Maternal mortality was not dose-related. Clinical signs, included alopecia and resistance to dosing, were noted more frequently in the treated groups than in the control group, however the incidence and severity of the signs were not dose related. Maternal food consumption, body weight, and liver weight were not adversely affected by treatment.

Dose(mg/kg)		0	1	3	5
No.of assigned female		26	26	26	26
No.of dead animals		0	0	1	1
No.of pregnants at termination		20	22	17	18
Maternal body weight(g) at gestational day 30					
	Mean	4002	3849	3872	3986
	SE	99	65	88	99
Maternal food consumption(g) for gestational days 0-30					
	Mean	187	171	174	193
	SE	7	6	6	8
Gravid uterine weight(g)					
	Mean	359	430	405	447
	SE	62	53	62	60
Maternal liver weight					
Absolute(g)	Mean	116	110	105	122
	SE	7	5	5	4
Relative(% bw)	Mean	2.9	2.9	2.7	3.1
	SE	0.2	0.1	0.1	0.1
Relative(% adjusted weight)					
	Mean	3.2	3.2	3.0	3.5
	SE	0.3	0.1	0.1	0.1

Developmental toxicity:
At necropsy on gestational day 30, 5/20(25%), 4/22(18%), 4/17(24%), and 3/18(17%) of the pregnant animals in the 0, 1, 3 and 5mg/kg groups, respectively, had 100% resorptions, but the effect was not dose related. There was no effect of treatment on the number of implantation sites per litter, percentage post implantation loss per litter, live litter size, or mean fetal body weight per litter. However, the percentage of male pups per litter was decreased at 5 mg/kg group compared to the control group.

Dose(mg/kg)	0	1	3	5
Percentage male fetuses/litter				
Mean	61	58	55	40**
SEM	6	4	5	5

The prevalence of external, visceral, or skeletal malformations or variations was not affected by the test chemical administration to the maternal animals during organogenesis.

Dose(mg/kg)	0	1	3	5
Percentage fetuses with external malformation				

0.0 0.0 1.1 0.0
Percentage litters with external malformation
0.0 0.0 7.7 0.0
Percentage fetuses with skeletal malformation
0.0 0.0 0.0 0.0
Percentage fetuses with visceral malformation
0.0 0.8 2.2 0.0
Percentage litters with visceral malformation
0.0 5.6 15.4 0.0
Percentage fetuses with external variation
0.0 0.0 0.0 0.0
Percentage fetuses with skeletal variation
46.2 62.2 44.3 58.8
Percentage litters with skeletal variation
93.3 100.0 76.9 80.0
Percentage fetuses with visceral variation
0.0 0.8 0.0 2.0
Percentage litters with visceral variation
0.0 5.6 0.0 13.3

Test substance : Purity: 96%(determined by gas chromatography)
Reliability : (2) valid with restrictions
The test guideline used was unknown.
Flag : Critical study for SIDS endpoint
27.12.2001 (17)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : days 6 through 20 of gestation
Frequency of treatment : 6 hr/day
Duration of test :
Doses : 6, 12, 25, 50 and 100 ppm
Control group : other: filtered room air
NOAEL Maternalt. : = 50 ppm
NOAEL Embryotoxicity : = 50 ppm
Method : other
Year : 1993
GLP : no data
Test substance : other TS
Test condition : Animals: Male(350g) and primiparous female(200-220g) rats were used. Female rats were placed with males (one male: three females) overnight and were examined by vaginal smear for the presence of sperm the following morning.
Sperm positive females were considered at day 0 of gestation.
Experimental design: Groups of 20-23 bred rats were exposed to the chemical 6 hr/day on days 6 through 20 of gestation.
Chemical vapor was generated by bubbling an additional air flow through a flask containing the test chemical and was mixed with filtered room air to achieve the desired concentration.
All rats were observed daily throughout pregnancy and maternal body weights were recorded on day 0, 6 and 21 of gestation. On day 21 of gestation , the females were sacrificed and uterus was removed and weighed. The uterus horns were then opened, and the numbers of implantation and resorption sizes and live and dead fetuses were recorded.
Live fetuses were removed from the uterus, and weighed, examined for external anomalies and sex. Half of the live

fetuses from each litter were randomly selected, fixed in Bouin's solution, and examined microscopically. The remaining half of the fetuses were examined microscopically for skeletal anomalies.
Statistical analysis: The number of implantation sites and live fetuses and various body weights were analyzed by the ANOVA and Dunnett's test. The frequency of nonsurviving implants, resorptions, and anomalies among litters was evaluated using the Willcoxon test. Rates of pregnancy and fetal sex ratio were analyzed using Fisher's test. The litter was used the basis for analysis of fetal variables.

Result : Nominal and analytical concentrations of the test chemical:

Nominal conc. :		12	25	50	100(ppm)
Analytical conc.:	Mean	12	25	52	106
	SD	0.6	1.3	2.1	5.1

No maternal deaths were observed. The maternal weight gain between days 6 and 21 of gestation in 100 ppm group decreased significantly. However, when corrected from the uterus weights, weight gain was not different from control. No effects of the test chemical on incidence of pregnancy, number of implantations and live fetuses, male-to-female sex ratio were observed. Male and female fetal body weights were significantly reduced at 100 ppm relative to those of control. Fetal examination did not reveal any gross malformation in any groups. The incidences of external, visceral, and skeletal variants were scattered with no indication of adverse effects in any of the exposed groups when compared to the control.

Dose(ppm)		0	12	25	50	100
Maternal body weight gain on day 6-21(g)						
	Mean	131.5	122.6	136.9	125.7	98.3**
	SD	24.0	21.4	17.9	25.4	35.0
Fetal body weight/litter						
Male	Mean	5.74	5.87	5.83	5.79	5.47**
	SD	0.31	0.37	0.21	0.28	0.35
Female	Mean	5.45	5.53	5.54	5.49	5.19*
	SD	0.22	0.34	0.23	0.31	0.27

Remark : Dosing regimen was based on preliminary studies in which maternal mortality was observed at 150 ppm.
Test substance : Purity: over 99%
Reliability : (2) valid with restrictions
There was no information on test guideline and GLP.
Flag : Critical study for SIDS endpoint
27.12.2001 (15)

5.10 OTHER RELEVANT INFORMATION

Type : other:metabolism and diposition
Remark : After gavage administration of 0.87mmol/kg of 2-14C-methylacrylonitrile to male F344 rats, the chemical was well absorbed from the GI tract and distributed to all major tissues. Approximately 39% of the administered dose was eliminated as CO2 in 24 h after dosing. 31% of the dose was exhaled as organic volatiles in 24 h .
Methylacrylonitrile and acetone were identified by HPLC analysis of expired organic volatiles from treated rats. The urinary excretion was 22%.The major urinary metabolite resulted from conjugate of the epoxide with glutathione. Pretreatment with phenobarbital resulted in decreased

amounts of unchanged methylacrylonitrile elimination in expired air.

Test substance : Radiochemical purity :>=98%

28.12.2001 (5)

Type : other:disposition and distribution

Remark : Following an oral administration of 100mg/kg of 2[14C]methyl-2,3[14C]acrylonitrile in SD rats, 43% of the [14C] was excreted in the urine, 15% in the feces and 2.5% in the expired air as 14CO2 in 5 days. The red blood cells retained significant amounts of radioactivity for more than five days after administration. The [14C]-activity in plasma declined sharply. More than 50% of the radioactivity in erythrocytes was detected as covalently bound to cytoplasmic(hemoglobin) and membrane proteins. A small amount of radioactivity was also found in the heme fraction. About 13% of the total dose administered was recovered as thiocyanate in the plasma and the urine.

Test substance : Purity: 95.5%

02.12.2001 (23)

Type : Metabolism

Remark : One major pathway of methylacrylonitrile metabolism is the direct conjugation with reduced glutathione(GSH), which is catalyzed by GSH S-transferases. Another major pathway involves an epoxide intermediate and is catalyzed by the hepatic microsomal P-450.

28.12.2001 (43)

Type : Metabolism

Remark : Two male albino rabbits were injected intravenously with 12.5 mg/kg of a 1%(w/v) solution of methylacrylonitrile in physiological saline. Four other rabbits were injected with 6.25 mg/kg. All injected rabbits had significant amounts of cyanide ion in their blood. The blood cyanide levels were consistently dose-related, but they all began to fall within four hours after injection. Although the rabbits can produce significant quantities of cyanide from high doses of methylacrylonitrile, the animals can metabolize the cyanide(in large part to thiocyanate), in a relatively short period of time.
In addition, the blood of two dogs from each exposure level, such as 3.2, 8.8 or 13.5 ppm, was examined for cyanide immediately after 87 days of inhalation exposure(seven hours per day, five days per week), and three days later, during which time period the dogs were not exposed. The concentrations of cyanide(micrograms CN- per mL whole blood) were 0.35-0.55 in the dogs given 13.5 ppm level and 0.10-0.15 in the dogs given 8.8 ppm after 87 days of treatment period. No concentrations were determined in the dogs given 3.2 ppm level after 87 days of treatment period and in all dogs after three days of withdrawal.

02.12.2001 (3)

Type : Toxicokinetics

Remark : Groups of male F344 rats were administered methylacrylonitrile intravenously (29, 58, or 116 mg/kg) or perorally (58 mg/kg). Blood samples were collected at various time points after dosing and serum methylacrylonitrile concentrations were measured.

Concentration versus time profiles was characterized by two phases and a two-compartment model was selected to fit the data. Toxicokinetics parameters were determined using SIMUSOLV.

Result:
The 39-min terminal half-life shows that 99% of an i.v. dose is eliminated in less than 5 hr, suggesting that the potential for methylacrylonitrile bioaccumulation is minimal. The volume of distribution at steady-state (747 ml/kg) indicates little distribution of methylacrylonitrile into tissues. Clearance is higher at 29 mg/kg than at the two other doses, suggesting that methylacrylonitrile elimination is saturable at doses above 29 mg/kg. Methylacrylonitrile disposition is route-dependent. Approximately 36% of the i.v. dose was exhaled as unchanged methylacrylonitrile, while only 18% was eliminated via this route following p.o. administration. Methylacrylonitrile disposition data also suggest that a significant first-pass metabolism may occur because a higher percentage of metabolites was produced following oral vs i.v. administration. Perorally, 39% of the dose was exhaled as CO2 and 22% was excreted into the urine as metabolites over the 24-hr dosing interval. In comparison, following i.v. delivery, 26% of the dose was exhaled as CO2 and 16% was excreted into the urine as metabolites. About equal amounts of acetone were excreted following administration by oral and i.v. route (13 % and 17 %, respectively).

Test substance : Radiolabeled methylacrylonitrile, purity: more than 98%
01.12.2001 (41)

Type : other:dispositon
Remark : Following intravenous administration of 0.216 mmol [2-14C]-methylacrylonitrile/kg (14.5 mg/kg), radioactive dose of the tissue distribution, covalent interaction, and elimination were examined (at 5 min to 48 hr) in male Fischer 344 rats using whole-body autoradiography (WBA).

Result:
The respiratory tissues contained high levels of 14C at an early period (5 min), while the gastrointestinal mucosa, adrenal cortex, liver, and kidney contained high levels of radioactivity at later periods (8, 24, and 48 hr). Rats treated with [2-14C]methylacrylonitrile eliminated 65% of the total radioactive dose by exhaled air, urine, and feces. Both WBA and elimination studies indicated that [2-14C]methylacrylonitrile and/or its metabolites, however, were rapidly distributed and eliminated, mostly via the lung.

01.12.2001 (16)

Type : Metabolism
Remark : The animals recieved a single gavage dose of 58 mg/kg. Bilewas collected before and after methylacrylonitrileadministration.

Result:
Bile flow and methylacrylonitrile-derivedradioactivity were determined at each time point.Methylacrylonitrile had a minimal effect on bile flow and 4 to6% of the administered

methylacrylonitrile dose was excretedin the bile within 6 hr after dosing. HPLC analysis of bile showed two major metabolites, which were identified as 1-(S-glutathionyl)-2-propanone and 1-(S-glutathionyl)-2-cyanopropane by using NMR spectra and chemical synthesis. The ratio of the two metabolites in methylacrylonitrile-treated rats was approximately 2:1. Pretreatment of rats with sodium phenobarbital caused minimal quantitative or qualitative changes in the biliary excretion of methylacrylonitrile metabolites. In contrast, pretreatment of rats with beta-diethylaminoethyl diphenylpropylacetate before methylacrylonitrile administration resulted in a significant decrease in the ratio of 1-(S-glutathionyl)-2-propanone to 1-(S-glutathionyl)-2-cyanopropane (1:2).

01.12.2001 (11)

Type : Metabolism
Remark : Male F344 rats and B6C3F1 mice received a single gavage dose of 11.5 or 1.15 mg of [14C] methylacrylonitrile/kg and were placed in glass metabolism cages.

Result:
Elimination of methylacrylonitrile in rats occurred primarily in expired air as unchanged methylacrylonitrile, acetone and CO2. Three major urinary metabolites were identified as N-acetyl-S-(2-cyanopropyl)-L-cysteine (about 0.9 and 1.0 % in rats and mice, respectively), N-acetyl-S-(2-hydroxypropyl)-L-cysteine (7 and 49 %) and a deoxyuridine isomer (7 and 2 %). Methylacrylonitrile elimination was almost complete within 24 hr after dosing and the tissue concentrations of methylacrylonitrile-derived radioactivity were, with the exception of the urinary bladder, consistently higher in rats than in mice.

15.01.2002 (27)

Type : Metabolism
Remark : The interaction of methylacrylonitrile with glutathione (GSH) was evaluated in vitro, and its in vivo potential to delete GSH in rats was investigated. Addition of methylacrylonitrile to a solution of 0.3 mmol GSH in 2 mmol EDTA, pH 7.4, resulted in a time and concentration dependent depletion of GSH determined as nonprotein sulfhydryl. Thin layer chromatography analysis of incubation mixtures of methylacrylonitrile with GSH and cysteine showed the appearance of distinct spots representing the adducts S-cyanopropyl GSH and S-cyanopropyl cysteine. Oral administration of methylacrylonitrile to the rats resulted in significant depletion of GSH in the liver, kidney, heart, lung, brain and spleen. The maximum GSH depletion was noticed in the liver (approximately 39% of control) and in other organs it ranged between 26-34% of control.

11.01.2002 (39)

Type : Toxicokinetics
Remark : Following gavage administration of 115, 11.5, or 1.15 mg methylacrylonitrile /kg in water, male F344 rats were placed

in glass metabolism cages and urine, expired air, and feces were collected. Rats were sacrificed at various times, and the concentration of Methylacrylonitrile-derived radioactivity in tissues was determined. For investigation of the effect of dosing vehicle and the strain on methylacrylonitrile disposition in rats, the following three test was also conducted.

Male F344 rats received a single gavage dose of 115 mg methylacrylonitrile/kg in safflower oil.

Male SD rats received a single gavage dose of 115 methylacrylonitrile/kg in water and were held for 72 hour.

Male SD rats received a single gavage dose of 115 methylacrylonitrile/kg in safflower oil and were held for 72 hour.

Result: Methylacrylonitrile was rapidly absorbed from the gastrointestinal tract and distributed to all major tissues. After gavage administration of 1.15-115 mg/kg, [2-14C]methylacrylonitrile is primarily eliminated in the expired air. Sixty to 70% of the low and medium doses were exhaled as 14CO2 in 72 hr compared with 25% of the highest dose. Whereas about 40% (about 34 % as unchanged methylacrylonitrile and about 8 % as acetone) of the high dose was expired as organic volatiles in 72 hr, only 9-12% of the low and medium doses were exhaled as such. It is therefore apparent that saturation of methyacrylonitrile metabolism occurs at the high dose. HPLC analysis of expired organic volatiles from methylacrylonitrile-treated rats showed that it contained two components that were identified as unchanged methylacrylonitrile and acetone. The methylacrylonitrile:acetone ratio was directly proportional to dose and decreased as a function of time. Urinary excretion accounted for 20-30% of all methylacrylonitrile doses within 72 hr after dosing. As for the tissue distribution, the concentration of methylacrylonitrile-derived radioactivity was dose-dependent and particularly high in the liver, kidney, urinary bladder, intestine, adrenal gland, and thymus. With the exception of brain, the tissue:brood ratio of methylacrylonitrile-derived radioactivity in rats receiving the medium dose exceeded unity at 8, 24, 72 hr after dosing. The percentage of methylacrylonitrile that remained in tissues 72 hours after dosing was less than 3 % of the dose.

Investigating the effect of dosing vehicle on methylacrylonitrile disposition in rats revealed that administration of 115 mg methylacrylonitrile/kg in oil resulted in the death of rats within 24 hr after treatment. Furthermore, monitoring the fate of methylacrylonitrile in these rats before death showed that a significantly higher percentage of the dose was eliminated in urine and expired air. Analysis of this expired air also revealed that significantly more acetone and less unchanged methylacrylonitrile were exhaled by these animals. It is apparent that administration of methylacrylonitrile to F344 rats in oil resulted in slower absorption, decreased elimination of unchanged methylacrylonitrile, and increased metabolism to acetone and/or decreased degradation of acetone to CO2. The combination of these effects of an oil vehicle may have contributed to the death of rats by methylacrylonitrile. Comparison of the metabolism and disposition of methylacrylonitrile in F344 and

Sprague-Dawley rats showed minor differences between the two strains.

Test substance : Radiolabeled methylacrylonitrile, purity: 98 % or greater
11.01.2002 (18)

Type : Toxicokinetics
Remark : Cyanide levels following oral administration of 0.5 or 1 LD50 dose of methylacrylonitrile to Sprague-Dawley rats, Albino-Swiss mice and Mongolian gerbils were determined in the blood and organs. A dose-dependent relationship for the toxicity of methylacrylonitrile and the metabolism to cyanide was found in all of the three species 1hr after oral administration of various doses of methylacrylonitrile. In comparison to other organs, blood and liver contained the highest amounts of cyanide. The organs from gerbils and mice metabolized significantly greater quantities of methylacrylonitrile than by the rats. Methylacrylonitrile metabolism to cyanide by gerbils was about 4-7 times greater than that in mice.
Test substance : purity: 98+ %
11.01.2002 (10)

Type : Neurotoxicity
Remark : The neurotoxicity of methylacrylonitrile was studied in rats. Male Sprague-Dawley rats were orally administrated methylacrylonitrile at 50, 70 or 90 mg/kg b.w. 5 days per week for 12 weeks. Neurophysiological measurement was performed with a Racia-Medelec modular electrophysiological system, equipped with a DAV 62 computer. The motor conduction velocity and sensory conduction velocity of the tail nerves, and the amplitudes of the sensory action potential and of the muscular action potential were measured at least 16 hours after treatment during weeks 3, 6, 9, and 12 of exposure and week 20 (8 weeks after exposure ended). Result: Two and eight rats died in teh low and high dose groups, respectively. The body weight was significantly decreased at 70 and 90 mg/kg b.w.. However, no abnormal behaivors or any significant changes in motor and sensory conduction velocities and amplitudes of the sensory and motor potentials of the tail nerve were seen.
11.01.2002 (22)

Type : other: Hematological and erythrocyte membrane changes
Remark : Administration of methylacrylonitrile at 100 mg/kg/day for 7 days resulted in a significant decrease in the red cell count and in the level of hemoglobin. Methylacrylonitrile altered the fluidity of the erythrocyte membrane by increasing membrane cholesterol while the phospholipid remained unchanged, followed by a decrease in the activities of membrane bound enzyme like (na+, K+)-ATPase, Acetylcholine esterase and NADH-dehydrogenase. A significant decrease in membrane sialic acid and calcium were also observed in the treated animals.
11.01.2002 (42)

Type : Cytotoxicity
Remark : The effects of methylacrylonitrile on lung mitochondria and microsomes was studied using albino rats given 100 mg/kg in sunflower oil for 14 days. Methylacrylonitrile caused significant decrease in the activities of mitochondrial citric acid cycle enzymes and inner mitochondrial enzymes. The concentrations of cytochromes and the energy-linked

properties of lung mitochondria also declined. The respiratory control ratio was lowered in methylacrylonitrile treated rats lung mitochondria, leading to a decrease in net energy product. In the microsomes, administration of methylacrylonitrile resulted in significant increases in cytochrome-P450 and cytochrome b5 contents. The lung mitochondrial phospholipids and cholesterol and microsomal phospholipids were significantly lower.

11.01.2002 (28)

Type : other:oxidative stress
Remark : Methylacrylonitrile administration (40 mg/kg/day) resulted in increased levels of lipid peroxidation products, conjugated dienes and lipofuscin-like substances in rats liver. Significant decrease in GSH and a decreased activity of hepatic SOD, CAT, and GPx were observed. There was also an increase in glutathione S-transferase and G6PD activities, decreased plasma ceruloplasmin and vitamin C implying oxidative stress caused by methylacrylonitrile.

11.01.2002 (20)

Type : other: effect on lung
Remark : Oral administration of methylacrylonitrile (100 mg/kg body wt/day) to rats for 14 days damaged the lung tissue and altered the bronchoalveolar lavage (BAL) angiotensin-converting enzyme activity (ACE) and levels of phospholipids and surfactant phospholipids. However, there was no alteration in BAL lactate content or lactate dehydrogenase activity. A significant increase in the phosphatidylcholine content in the extracellular surfactant indicates Type-II cell proliferation. Methylacrylonitrile caused the lung injury by increasing alveolar capillary permeability and promoting the accumulation of surfactant phospholipids, which may lead to serious conditions such as fibrosis.

11.01.2002 (24)

Type : other: effect on forestomach cell proliferation and apoptosis
Remark : Methylacrylonitrile was administered by gavage to male F344 rats daily for 6 weeks at 0 (vehicle: water), 0.43 mmol/kg.b.w. (28.9 mg/kg b.w.) or 0.87 mmol/kg b.w. (58.4 mg/kg b.w.). Methylacrylonitrile induced a dose-dependent increase in epithelial cell proliferation in the forestomach but not in the thickness of the forestomach squamous mucosa as determined by bromodeoxyuridine (Brd U) incorporation into DNA. At doses of methylacrylonitrile that induced a 2.3-fold increase in Brd incorporation, apoptosis was 18-fold greater than controls.
Test substance : Purity:unknown; containing hydroquinone as a stabilizer;purchased from Fluka(Ronkokoma, NY)
Reliability : (2) valid with restrictions
11.01.2002 (8)

Type : Other
Remark : The study was carried out to determine the effect of antidotes of the acute toxicity of methylacrylonitrile in Wistar rats. The rats were exposed for 30 minutes to test chemical at concentrations between 3180 and 5700 ppm. Antidotes were given after methylacrylonitrile exposure.

Result: Methylacrylonitrile caused rapid unconsciousness with convulsion, and lethality occurred between 30 and 60 min after exposure. The acute toxicity could be antagonized with cyanide antidotes (4-dimethylaminophenol plus sodium thiosulfate) as well as with N-acetyl-cysteine which directly reacts with alfa, beta-unsaturated nitriles.

28.12.2001 (21)

Type	:	Sex-linked recessive lethal mutation
Species	:	Drosophila melanogaster
Sex	:	male/female
Strain	:	other: Canton-S
Route of admin.	:	oral feed
Exposure period	:	
Doses	:	6000 ppm in feed
Result	:	negative
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	no data
Remark	:	Males and females were mated, and eggs were exposed in vials with standard cornmeal feed containing methylacrylonitrile in solvent (5 %) ethanol or solvent alone. Adult emergent males were mated at approximately 24 hours of age with two successive harems of three to five Basc females to establish two single-day broods. F1 heterozygous females were mated with their siblings and then placed in individual vials. F1 daughters from the same parental male were kept together to identify clusters. If a cluster was identified as vials containing fewer than 5 % of the expected number of wild-type males after 17 days; these were retested to confirm the response.
Result	:	No induction of sex-linked recessive lethal mutations was observed in germ cells of male Drosophila melanogaster treated during the larval stage by feeding on medium containing 6000 ppm methylacrylonitrile.

27.12.2001 (12) (38)

Type	:	other:Sex-linked recessive lethal mutation
Species	:	Drosophila melanogaster
Sex	:	no data
Strain	:	no data
Route of admin.	:	other:injection
Exposure period	:	no data
Doses	:	up to concentrations which exhibit toxic effects
Result	:	negative
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	no data

27.12.2001 (35)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

Memo	:	Human sensory response
Result	:	Human sensory response to methylacrylonitrile: A group of eight to nine volunteers between 22 and 57 years of age inhaled a series of various concentrations for one

minute periods.

The intervals between each inhalation period were at least 45 minutes. the group inhaled the same concentrations two times in the following sequence:24, 14, 0, 7, 14, 24, 7, 2, 0 and 2 ppm (72, 42, 0, 21, 42, 72, 21, 6, 0 and 6 mg/m3).

The results of all of the human experiments indicate that the vapor of the test substance has very poor warning properties.
Incidence of nose irritation: 24ppm, 6%; 14ppm and less, 0%
Incidence of eye irritation: 24ppm, 17%; 14ppm and less, 0%
Incidence of odor detection:24ppm, 89%; 14ppm,88%; 7ppm, 47%; 2ppm, 0%
Incidense of throat irritation: 24ppm, 22%; 14ppm and less,0%

28.12.2001 (3)

Memo : Human sensory response
Result : 9 and 7 volunteers were exposed for 10 min to 2 ppm (6 mg/m3) and 14 ppm (42 mg/m3) vapor of methylacrylonitrile, respectively. Irritation of a transitory nature was caused in nose, throat and eye, which was observed only in one to two subjects.

28.12.2001 (3)

(1) 85JCAE"Prehled Prumyslove Toxikologie; Orgaicke Latky," Marhold,J., et al.,901, 1986

(2) ACGIH, TLVs and BEIs. (2000)

(3) American Industrial Hygiene Association Journal, 29, 202-210, 1968

(4) Archives of Toxicology, 55, 47-54, 1983

(5) Archives of Toxicology, 68, 611-618, 1994

(6) Bulletin of Environmental Contamination and Toxicology, 59, 274-278, 1997

(7) Bulletin of Environmental Contamnation and Toxicology, 48, 696-700, 1992

(8) Carcinogenesis, 18, 4, 675-680, 1997

(9) DHHS #92-100, 1992

(10) Farooqui, M.Y. et al. (1992) Drug Metabolism and Disposition, 20, 156-160, 1992

(11) Drug Metabolism and Disposition, 24, 4, 390-394, 1996

(12) Environ. Mol. Mutagen., 14, 4, 245-251, 1989

(13) Environ.Mutagen.,9, 1-110, 1987

(14) Exploring QSAR (ACS Professional Reference Book)

(15) Foundamental and Applied Toxicology, 20, 365-375, 1993

(16) Foundamental and Applied Toxicology, 33, 1, 49-59, 1996

(17) Foundamental and Applied Toxicology, 34, 249-259, 1996

(18) Ghanayem, BI et al. (1992) Drug Metab. Dispos., 20, 643-652.

(19) Gig-Tr-Prof-Zabol,-ISS-5,-1985,-P37-40

(20) Indian J Biochem Biophys., 34, 6, 540-542, 1997

(21) International Archives of Occupational Environmental Health, 55, 175-177, 1985

(22) Journal of Applied Toxicology, 18, 1, 25-31, 1998

(23) Journal of Applied Toxicology, 9, 1, 53-57, 1989

(24) Journal of Clinical Biochemistry and Nutrition, 23, 1, 27-31, 1997

(25) Journal of Industrial Hygiene and Toxicology, 18-31, 1936-49

(26) Journal of Industrial Hygiene and Toxicology, 31, 113, 1949

(27) Journal of Pharmacology and Experimental Therapeutics, 269, 2, 581-588, 1994

(28) Medical Scinece Research, 25, 2, 129-132, 1997

(29) Ministry of Health, Labour and Welfare;former MHW,Japan(2001)Toxicity Testing Reports of Environmental Chemicals, 8, 635-637

(30) Ministry of Health, Labour and Welfare;former MHW,Japan(2001)Toxicity Testing Reports of Environmental Chemicals, 8, 638-649

(31) Ministry of Health, Labour and Welfare;former MHW,Japan(2001)Toxicity Testing Reports of Environmental Chemicals, 8, 651-653

(32) Ministry of Health, Labour and Welfare;former MHW,Japan(2001)Toxicity Testing Reports of Environmental Chemicals, 8, 654-659

(33) MOE(Ministry of the Environment), Japan (2001)

(34) MSDS, Aldrich Chemical Co., Inc. (2001)

(35) Mutation Research, 147, 303, 1985

(36) NTIS Technical Report(NTIS/PB97-176390)(NTP/RACB-94-019) May 1997

(37) NTP Technical Report 497 (Draft), NIH Publication No. 01-4431

(38) NTP Toxicity Report Series Number 47, May 2000

(39) Research Communication in Chemical Pathology and Pharmacology, 62, 2, 267-278, 1988

(40) The Sigma-Aldrich Library of Regulatory and Safety Data

(41) Toxicology and Applied Pharmacology, 119, 115-121, 1993

(42) Toxicology Letters, 92, 1, 15-20, 1997

(43) Toxicology, 65, 239-250, 1991

(44) Wako Pure Chemical Inductires, Ltd.