FOREWORD INTRODUCTION

Cyanoguanidine

CAS N°: 461-58-5

SIDS Initial Assessment Report

For

SIAM 17

Arona, Italy, November 11-14, 2003

1. Chemical Name:	Cyanoguanidine
2. CAS Number:	461-58-5
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4. Shared Partnership with:	Mr. Akira Sakai Nippon Carbide Industries Co., Inc. E-mail: asakai@carbide.co.jp
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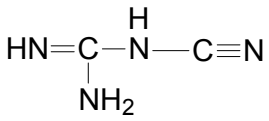
11. Comments:	None

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	461-58-5
Chemical Name	Cyanoguanidine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No metabolism data specific to cyanoguanidine is available.

The oral LD_{50} is greater than 30,000 mg/kg bw in female rats. Data on inhalative and dermal acute toxicity are not available.
This substance is considered to be irritating to the skin in guinea pigs. Data on eye irritation are not available. No sensitising potential has been demonstrated in guinea pigs in three maximization studies. The potential was not clearly demonstrated in human. Most workers did not become sensitive to this substance, however, there might be some workers who became sensitive for specific reasons (cross sensitisation or adjuvant effect of co-factors).

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] was conducted using SD rats at doses of 0, (vehicle; 3% gum arabic solution), 40, 200, and 1,000 mg/kg/day. The dosing period for males was 44 days, and females were dosed from 14 days before mating to day 3 of lactation. This substance had no effect on clinical signs, body weights, food consumption or necropsy findings. The organ weights were similar among all groups. No histopathological changes ascribable to this substance in these organs were found in either sex. The NOAEL for the repeat dose toxicity is considered to be 1,000 mg/kg/day for both sexes.

The reverse mutation studies in bacteria [OECD TG 471 and 472] gave negative results. The *in vitro* chromosomal aberration test with Chinese hamster lung cells (CHL/IU) [OECD TG 473] with and without metabolic activation was also negative. Therefore, this substance is not genotoxic.

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] (0, 40, 200, 1,000 mg/kg/day) was conducted using SD rats. This substance had no effects on reproductive parameters such as the mating index, fertility index, numbers of corpora lutea or implantations, implantation index, delivery index, gestation index, gestation length, parturition or maternal behavior. On examination of neonates there were no significant differences between the control and treated groups in the number of offspring or live offspring, sex ratio, live birth index, viability index or body weight. No abnormal findings ascribable to this substance were found for external examination or clinical signs or on necropsy of the offspring. The NOAEL for reproductive and developmental toxicity is considered to be 1,000 mg/kg/day.

A carcinogenicity study was conducted in male and female Fischer 344 rats fed diets containing this substance at 0, 2.5 and 5% (male: 837.2 and 1958.6, female: 1001.3 and 2169.2 mg/kg bw/day) for up to 2 years. The study did not suggest an association of the substance with an increased tumor incidence.

Environment

Cyanoguanidine is a white crystalline powder, which is soluble in water (40 g/L at 25 °C). Melting point, boiling point, and vapour pressure are 209.5 °C, solidified at 252 °C , and equal or less than 0.0045 Pa (100 °C), respectively. This substance does not hydrolyse under environmental conditions. Indirect photo-oxidation by

hydroxy radicals in the atmosphere is predicted to occur with a half-life of 3.1 hours. This substance is not readily biodegradable under aerobic condition within 28 days (BOD = 0 %). However, a prolonged study showed that this substance is completely biodegraded within 34 weeks under aerobic conditions, while two-thirds of the total is biodegraded within 60 weeks under anaerobic conditions. This substance has a low bioaccumulative potential (BCF (*Cyprinus carpio*, 48days): equal or less than 3.1). Fugacity modeling (Mackay level III) predicts that if the substance is released to water, it will not migrate into other compartments. When this substance is released to air or soil, it is mainly distributed to water and soil.

This substance has been tested in aquatic species (algae, invertebrates and fish). An acute growth inhibition test was performed using green algae (OECD TG 201, *Selenastrum capricornutum*). The EC_{50} (biomass; 0-72 h) was 935 mg/L and the EC_{50} (growth rate; 24-72 h) was > 1,000 mg/L. An acute toxicity test for invertebrates was performed using water fleas (OECD TG 202, *Daphnia magna*). The 48-h EC_{50} was > 1,000 mg/L. An acute toxicity test [OECD TG 203] and a prolonged toxicity test [OECD TG 204] for fish were performed using Medaka (*Oryzias latipes*). The 96-h LC_{50} and the 14-d LC_{50} were both >100 mg/L. A chronic reproduction toxicity test for invertebrates was performed using water fleas (OECD TG 211, *Daphnia magna*). The 21-d EC_{50} and the 21-d NOEC were 69.6 mg/L and 25.0 mg/L, respectively. In microorganisms, this substance is known to have an inhibition activity of the nitrification of ammonium in various systems.

Exposure

The production volume of cyanoguanidine was estimated to be approximately 40,000 t/year worldwide in 2002, and not manufactured at present in Japan. This substance is a basic chemical, and used in industry for electrical/electronic engineering, metal extraction, refining and processing of metals, paper, pulp and board, textile processing, pharmaceuticals and intermediates. This substance is also used as absorbent, adhesive, binding, coloring, electroplating, surface-active agents, and agricultural chemicals (fertilizer).

During production and use of this substance, occupational exposure is possible by inhalation and dermal route. The workplace exposures during manufacturing processes are controlled by personal protective equipment. Consumer exposure is also possible by inhalation and dermal route.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

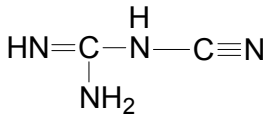
This chemical is currently of low priority for further work because of its low hazard potential.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 461-58-5
IUPAC Name: 1-Cyanoguanidine
Molecular Formula: C2H4N4
Structural Formula:



Molecular Weight: 84.08
Synonyms: Cyanguanidin
Cyanguanidine
Cyanoguanidine
Dicyandiamid
Dicyandiamide
Dicyandiamin
Dicyanodiamide
Didin
1-Cyanoguanidine
DCD
Dicy

1.2 Purity/Impurities/Additives

Purity: 99.1 % (w/w)

Impurities: Melamine: 0.7 % (w/w),

Thiourea: 200 ppm

Heavy metal: 10 ppm

1.3 Physico-Chemical properties

Physical-chemical properties are shown in Table 1.

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Physical state	Solid	CITI Japan,1998
Melting point	209.5 °C	Merck Index, 2001
Boiling point	Solidified at 252 °C	CITI Japan,1998
Density	1.400 g/cm^3 (25 °C)	Merck Index, 2001
Vapour pressure	Equal or less than 4.5 X 10^{-3} Pa (100 °C)	CITI Japan,1998
Water solubility	40 g/L (25 °C) decomposition at 80 °C	CITI Japan,1998
Partition coefficient n-octanol/water (log value)	-0.52 (25 °C)	CITI Japan,1998
Henry's law constant	2.25 X 10^{-10} atm.m^3/mole	HENRYWIN version 1.90, Syracuse Research Co.
Appearence	White crystalline odorless powder	Dutch, 1998 and Gerhartz, 1985

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The production volume of cyanoguanidine was estimated at approximately 40,000 t/year worldwide in 2002. The chemicalis currently not manufactured in Japan. This substance is a basic chemical, and used in industry for electrical/electronic engineering, metal extraction, refining and processing of metals, paper, pulp and board, textile processing, pharmaceuticals and intermediates and approved as an indirect food additive by USFDA. This substance is also used as absorbent, adhesive, binding, coloring, electroplating, surface-active agent, and agricultural chemical (fertilizer).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

This substance has various uses and exposure to the environment is possible. This substance is directly released into the environment through its use as a fertilizer.

2.2.2 Photodegradation

Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life of 3.1 hrs (12-hrs day; 1.5 X 10^6 OH/cm^3, calculated using AOPWIN version 1.90, Syracuse Research Co.).

2.2.3 Stability in Water

This substance is considered abiotically stable in water and not hydrolyzed regardless of pH [CITI Japan, 1998].

2.2.4 Transport between Environmental Compartments

A Mackay level III fugacity model was employed to estimate the environmental distribution of this substance in air, water, soil and sediment. The results are shown below. The results show that if this substance is released into water, 99.6 % stays in water, it is unlikely to migrate into other compartments. When this substance is released to air, it does not stay in air, and 48.3 % is transported to water and 51.5 % to soil. If released into soil, 57.8 % stays in soil, and 42.1 % is transported to water.

Table 2 Estimated distribution under three emission scenarios

Compartment	Release: 100 % to air	Release: 100 % to water	Release: 100 % to soil
Air	0.0 %	0.0 %	0.0 %
Water	48.3 %	99.6 %	42.1 %
Soil	51.5 %	0.0 %	57.8 %
Sediment	0.2 %	0.4 %	0.2 %

2.2.5 Biodegradation

This substance is not readily biodegradable under aerobic condition within 28 days (BOD = 0 %) [Remde et al, 1996]. However, a prolonged study in flooded sediment showed that this substance was completely biodegraded within 34 weeks under aerobic conditions, while two-thirds of the total was biodegraded within 60 weeks under anaerobic conditions [Amberger et al, 1988]. This substance is also biodegradable with isolated soil microorganisms [Hallinger et al, 1990].

2.2.6 Bioaccumulation

This substance has low bioaccumulative potential (BCF (Cypinus carpio, 48 days) of equal to or less than 3.1 at 25 °C) [CITI Japan, 1982].

2.2.7 Other Information on Environmental Fate

No other information is available.

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational exposures at production sites may occur by inhalation and by the dermal route. There is no available monitoring data. Normally, workers wear protections for eye/face, skin, and respiratory tract. There is no available official recommendation and regulation for occupational exposure limit.

2.3.2 Consumer Exposure

Consumer exposures may occur by inhalation and dermal route to articles containing this substance.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There is no available information specific to cyanoguanidine.

3.1.2 Acute Toxicity

There were various studies on the acute toxicity by different administration routes. However one oral and two i.p. reports were reliable, the other reports were not relevant.

Oral

As to the oral toxicity, the study by Matsushima [Matsushima et al., 1991] was considered to be the most reliable and identified as the key study. Fischer 344DuCrj rats (5 females/group) were administered by gavage with doses of 20,000 and 30,000 mg/kg bw. No death was observed at both doses. At 30,000 mg/kg bw, hypothemia and decrease in locomotor activity were observed 1 hour after dosing, lateral position and cyanosis were seen 2 hours after dosing. However, these symptoms disappeared within 18 hours after dosing, except for diarrhea. There were no findings at autopsy 1 week after dosing. The LD50 is greater than 30,000 mg/kg bw.

Other Routes of Exposure

As to the acute toxicity by intraperioneal administration (i.p.), two values were reported in mice or in rabbits. These values are greater than 4,000 mg/kg for mice and greater than 3,000 mg/kg for rabbits [Hald et al., 1952].

Conclusion

The oral LD50 is greater than 30,000 mg/kg bw. Data on inhalative and dermal acute toxicity are not available.

3.1.3 Irritation

Skin Irritation

Studies in Animals

There was one reliable report. The study by Nakano (1977) was identified as the key study. This substance was applied to the intact and abraded skin (6 spots/animal) of Hartley guinea pigs at the dose level of 0, 5, 10, 20, 50, 100 % under the patch for 24 hrs, one animal per dose. Positive response was observed only at a dose of 50%. The other doses gave negative responses. Under these test conditions, this substance was considered to be slightly irritating to the skin.

Studies in Humans

Two reliable studies of patch test have been reported by Akabane (1954) and NIPPON CARBIDE INDUSTRIES CO., INC (1977).

Akabane applied this substance to abraded skin at unspecified concentration. When applied by patch for 3 hours, this substance showed irritation. NIPPON CARBIDE INDUSTRIES CO. reported that patch application of 5% of this substance for 24 hours caused slight irritation.

Eye Irritation

Studies in Animals

Although two reports were available, test conditions were not reported in detail and the reports were considered to be invalid.

Conclusion

This substance is considered to be irritating to the skin.

3.1.4 Sensitisation

Studies in Animals

Skin

There are three sensitization studies in guinea pigs as shown in Table 3. In the study conducted by Boman et al. (1985), no significant differences between the control and the treated groups (0.5, 2.5 5.0 %) was obtained. In the study using this substance (1, 5, 10, 20 %) conducted by Nakano (1977), 8/10 guinea pigs (Hartley) showed negative results and the rest showed ambiguous results. In the study by Senff et al. (1988), it was not possible to sensitise any of the 10 tested guinea pigs. Based on the weight of evidence of these studies, this substance does not have sensitising potential.

Table 3 The summary of sensitisation information

Species	Method	Result	Reference
Guinea pig	Maximization test	Not sensitising	Boman et al, 1985
Guinea pig	Maximization test	Not sensitising (ambiguous)	Nakano, 1977
Guinea pig	Maximization test	Not sensitising	Senff et al, 1988

Studies in Humans

Skin

Two reliable patch test studies have been reported by Senff et al. (1988) and Szczeklik-Frank et al. (1977).

Senff et al. reported that a patient showing contact dermatitis gave no positive reactions in patch test to the standard domestic substance series, rubber chemicals, the paint, plastics and adhesive series or disinfectants. Testing the materials which he was continually in contact with at work, the showed a strongly positive reaction to this substance, and this was clearly evident even in a dilution of 1:100. The high level of sensitisation to this substance was detectable even one year after giving up the job: renewed patch testing again showed strong reactions to this substance. This report is only a consistent case who was sensitised to this substance, while the causative (sensitising) effect of it was uncertain.

Szczeklik-Frank et al. reported about the workers of this substance of the nitrogen works. In all cases patch tests were carried out by the method of Jadassohn-Bloch with 1 % melamine and/or cyanoguanidine. In subjects with skin changes, patch tests with standard allergens were done additionally. During these investigations two types of skin changes were observed. One showed typical morphological features and course of allergic contact dermatitis. These changes were caused by this substance as evidenced by positive results of patch tests. Besides that, erythema of different intensity was observed on the skin exposed to sunlight. 6 and/or 9 out of 80 examined workers showed positive results to melamine and/or this substance, however, only one from the same cohort showed positive results by application of the mixture of melamine and cyanoguanidine. Because of this contradiction the validity of the study was lowered.

Three other surveys on occupational dermatitis by cyanoguanidine were performed. In one study of carpenters at a large construction site in the United State [Sinks, 1991], association between dermatitis and handling of fire-retardant lumber and plywood was shown. In Europe, many cases of allergic contact dermatitis due to derivatives of the substance have been reported among hairdressers [Adams, 1983]. Thirty-four epoxy resin workers who were symptomatic of dermatitis were tested for allergic response by application of a patch with material used in the industry including cyanoguanidine. None of the 34 exhibited positive response to the substance [Jirasek et al., 1960 (Pub. 1962)]. For each survey the conclusions is negative or inconclusive.

These retrospective surveys in humans lead to negative, inconclusive or inconsistent result with regard to the causative (sensitising) effect of this substance. However, there is possibility and a firm evidence that there are persons who became hyper sensitive to this substance among those involved in industries handling this substance among others.

Conclusion

This substance is considered to be irritating to the skin in guinea pigs. Data on eye irritation are not available. No sensitising potential has been demonstrated in guinea pigs in three maximization studies. The potential was not clearly demonstrated in human. Most workers did not become sensitive to this substance, however, there might be some workers who became sensitive for specific reasons (cross sensitisation or adjuvant effect of co-factors).

3.1.5 Repeated Dose Toxicity

One study is reliable. The oral study by MHW Japan (1998) was conducted according to OECD TG 422 in compliance with GLP and was identified as the key study.

According to the OECD test guidelines for combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], SD (Crj: CD) rats (12 animal/group/sex) were administered by gavage with the doses of 0 (vehicle; 3% gum arabic solution), 40, 200, and 1,000 mg/kg/day. The dosing period for males was 44 days, and females were dosed from 14 days before mating to day 3 of lactation.

This substance had no effect on clinical signs, body weights, food consumption or necropsy findings. The organ weights of the kidney, testes and epididymides were similar among all groups. No histopathological changes ascribable to this substance in these organs were found in either sex. The NOAEL for the repeat dose toxicity is considered to be 1,000 mg/kg/day for both sexes.

Conclusion

The NOAEL for the repeat dose toxicity is considered to be 1,000 mg/kg/day for both sexes.

3.1.6 Mutagenicity

Six study results are available. These were four bacterial *in vitro* test reports and two non-bacterial *in vitro* test reports.

In vitro Studies

Bacterial test

Four studies are available, however only one study was considered to be reliable.

The study by MHW Japan (1997) was conducted according to OECD TG 471 and TG 472 in compliance with GLP. The MHW studies were identified as the key studies and summarized below.

Indicating strains were *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA, and doses were 0, 156, 313, 625, 1250, 2,500, 5,000 ug/plate. Dimethylsulfoxide was used as vehicle (vehicle control). The test was conducted two times with and without metabolic activation (rat S9). No increase of revertants was observed at each dose in all strains with or without metabolic activation, and the test was concluded to be negative. Toxic effects were not observed at any dose.

Non-bacterial in vitro test

Two studies were available, however only one study was considered reliable.

MHW Japan (1998) conducted a chromosomal aberration in vitro test according to OECD TG 473 with cultured Chinese hamster lung cells (CHL/IU). The study by MHW was conducted in compliance with GLP and was identified as the key study. Twenty-four and 48 hr continuous treatment without metabolic activation, 6 hr short-time treatment with or without metabolic activation were conducted. The tested concentrations were 210, 420 and 840 ug/mL as the highest dose (comparable to 10 mmol/L) were set. Saline was used as vehicle (vehicle control).

This substance did not induce chromosomal aberrations, and the result for all treatments was negative. No growth inhibition was observed at any dose.

In vivo Studies

There are no available test results.

Conclusion

The reverse mutation studies in bacteria gave negative results. The *in vitro* chromosomal aberration test with Chinese hamster lung cells (CHL/IU) with and without metabolic activation was also negative. Therefore, this substance is considered to be non-genotoxic.

3.1.7 Carcinogenicity

Studies in Animals

Oral

One carcinogenicity study in rats was reliable. The study was conducted in male and female Fischer 344 rats which were fed pulverized diets containing 0, 2.5 and 5 % cyanoguanidine (converted values: male; equivalent to 837.2 and 1958.6 mg/kg/day, female; equivalent to 1001.3 and 2169.2 mg/kg/day) for up to 2 years [Yasuhara et al., 1997]. The mean body weight gains in both sexes of the 5 % group and in females of the 2.5 % group were significantly lower than the

control values after week 1 of treatment. No other signs of toxicity were seen in any of the rats throughout the treatment period. Histopathologically, various tumors developed in all groups, including the control group, but these were all similar to those known to occur spontaneously in this strain of rats, and no toxicologically significant increase was found for any lesion type in the treated group.

Studies in Humans

In an occupational surveillance, increased incidences of colon and prostate cancers were seen in 790 men working at a calcium carbide plant for at least 1.5 years [Kjuus et al., 1986]. Some of the men would have been exposed to cyanoguanidine. Although, a 30-years follow- up of 117 workers who were specially engaged in cyanoguanidine and calcium cyanamide production revealed no increases in cancer incident. No excess of cancer was observed among workers in the cyanamide/cyanoguanidine production.

Conclusion

Therefore, this substance has no carcinogenetic potential. The study did not suggest an association with increased tumor incidence.

3.1.8 Toxicity for Reproduction

One study has been available. The study was conducted according to the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] in compliance with GLP [MHW Japan, 1998] and was identified as the key study.

Studies in Animals

According to the OECD test guideline for the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422], SD (Crj: CD) rats (12 animal/group/sex) were administered by gavage with doses of 0 (vehicle; 3% gum arabic solution), 40, 200, and 1,000 mg/kg/day. The dosing period for males was 44 days, and females were dosed from 14 days before mating to day 3 of lactation, the mating period was a maximum of 7 days. The autopsy was conducted 1 day after the dosing

This substance had no effects on reproductive parameters such as the mating index, fertility index, numbers of corpora lutea or implantations, implantation index, delivery index, gestation index, gestation length, parturition or maternal behavior. On examination of neonates there were no significant differences between the control and treated groups in the number of offspring or live offspring, sex ratio, live birth index, viability index or body weight. No abnormal findings ascribable to this substance were found for external examination or clinical signs or on necropsy of the offspring. The NOAEL for reproductive and developmental toxicity is considered to be 1,000 mg/kg/day in rats.

Conclusion

The NOAEL for reproductive and developmental toxicity is considered to be 1,000 mg/kg/day in rats.

3.2 Initial Assessment for Human Health

No metabolism data specific to cyanoguanidine is available. The oral LD50 is greater than 30,000 mg/kg bw in female rats. Data on inhalative and dermal acute toxicity are not available.

This substance is considered to be irritating to the skin in guinea pigs. Data on eye irritation are not available. No sensitising potential has been demonstrated in guinea pigs in three maximization studies. The potential was not clearly demonstrated in human. Most workers did not become sensitive to this substance, however, there might be some workers who became sensitive for specific reasons (cross sensitisation or adjuvant effect of co-factors).

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] was conducted using SD rats at doses of 0, (vehicle; 3% gum arabic solution), 40, 200, and 1,000 mg/kg/day. The dosing period for males was 44 days, and females were dosed from 14 days before mating to the day 3 of lactation. This substance had no effect on clinical signs, body weights, food consumption or necropsy findings. The organ weights were similar among all groups. No histopathological changes ascribable to this substance in these organs were found in either sex. The NOAEL for the repeat dose toxicity is considered to be 1,000 mg/kg/day for both sexes.

The reverse mutation study in bacteria [OECD TG 471 and 472] gave negative result. The *in vitro* chromosomal aberration test with Chinese hamster lung cells (CHL/IU) [OECD TG 473] with and without metabolic activation was also negative. Therefore, this substance is not genotoxic.

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [OECD TG 422] (0, 40, 200, 1,000 mg/kg/day) was conducted using SD rats. This substance had no effects on reproductive parameters such as the mating index, fertility index, numbers of corpora lutea or implantations, implantation index, delivery index, gestation index, gestation length, parturition or maternal behavior. On examination of neonates there were no significant differences between the control and this substance-treated groups in the number of offspring or live offspring, sex ratio, live birth index, viability index or body weight. No abnormal findings ascribable to this substance were found for external examination or clinical signs or on necropsy of the offspring. The NOAEL for reproductive and developmental toxicity is considered to be 1,000 mg/kg/day.

A carcinogenicity study was conducted in male and female Fischer 344 rats fed diets containing this substance at 0, 2.5 and 5% (male: 837.2 and 1958.6, female: 1001.3 and 2169.2 mg/kg/day) for up to 2 years. The study did not suggest an association with increased tumor incidence.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

The reliable toxicity data of aquatic organisms are summarized in Table 4 and 5. All of these toxicity tests were performed with GLP and in accordance with OECD test guidelines. Cyanoguanidine concentrations in the testing media were monitored during the course of the experiments.

Acute toxicity data have been reported for three kinds of aquatic organism (algae, invertebrates and fish) by the Environmental Agency of Japan. A growth inhibition test for algae was performed in accordance with OECD TG 201 using green algae (*Selenastrum capricornutum*). The EC50s for algae were calculated based on biomass and growth rate. The EC50 (biomass; 0-72 h) was 935 mg/L and the EC50 (growth rate; 24-72 h) was > 1,000 mg/L (EA. Japan, 1998a). An acute toxicity test for invertebrates was performed in accordance with OECD TG 202 part 1 using water flea (*Daphnia magna*). The 48-h EC50 and 48-h NOEC (immobilizations) were > 1,000 mg/L and 1,000 mg/L (EA Japan, 1998b), respectively. An acute toxicity test and a prolonged toxicity test for fish were performed in accordance with OECD TG 203 and TG 204, respectively using Medaka

(*Oryzias latipes*). The 96-h LC50, 14-d LC50 and 14-d NOEC were >100 mg/L, >100 mg/L and 100 mg/L, respectively (EA Japan, 1998c; EA Japan 1998d). The lowest acute toxicity value for this substance has been reported as 14-d LC50 of > 100 mg/L in the fish prolonged toxicity test using Medaka.

Table 4 Summary of acute toxicity effects of cyanoguanidine on aquatic organisms

Organism	Test duration	Result (mg/L)	Reference
Aquatic plant eg. Algae			
Green algae (*Selenastrum capricornutum*)	72 h	EC_{50} (bms) = 935 NOEC (bms) = 171 EC_{50} (gr) > 1,000 NOEC (gr) = 556 (nc)	EA, Japan 1998a
Invertebrates			
Water flea (*Daphnia magna*)	48 h (s)	EC_{50} (imm)> 1,000 NOEC (imm) = 1,000	EA, Japan 1998b
Fish			
Medaka (*Oryzias latipes*)	96 h (ss)	LC_{50} > 100	EA, Japan 1998c
	14 d (ft)	LC_{50} > 100 NOEC = 100	EA, Japan 1998d

s: static, ss: semi-static, bms: biomass, gr: growth rate, imm: immobilization, ft: flow through Cyanoguanidine concentrations of the test solutions were measured and all the measured values were within ± 20% of the nominal concentrations.

Chronic Toxicity Test Results

A chronic toxicity test for daphnids (*Daphnia magna*) on reproduction was performed according to OECD TG 211, and the 21-d LC50, 21-d EC50, 21-d NOEC, 21-d LOEC for daphnids were > 100 mg/L, 69.6 mg/L, 25.0 mg/L, 50.0 mg/L, respectively [EA, Japan ,1998e].

Table 5 Summary of chronic toxicity effects of cyanoguanidine on aquatic organisms

Organism	Test duration	Result (mg/L)	Reference
Invertebrates			
Water flea (*Daphnia magna*)	21 d (ss)	LC_{50} > 100 EC_{50} (rep) = 69.6 NOEC (rep) = 25.0 LOEC (rep) = 50.0	EA, Japan 1998e

ss: semi-static rep: reproduction, Cyanoguanidine concentrations of the test solutions were measured and all the measured values were within ± 20% of the nominal concentrations.

4.2 Terrestrial Effects

This substance has been investigated for inhibition activity of the nitrification of ammonium in various systems: in sewage (75% inhibition at 250 ppm) [Tomlinson et al., 1966], in a highly nitrifying culture isolated from nitrifying activated sludge (IC50 = 8.2 mg/l for respirometry) [Wagner et al., 1990], in N-fixing bacteria (Rhizobium leguminosarum and Azotobacter chroococcum) (IC50 = 8.2 mg/l for respirometry) [Zacherl et al., 1990], in Nitrosomonas europaea, Nitrosococcus oceanus and Nitrosomonas sp. 4W30 (a marine isolate) (70% inhibition at 250 mg/l)

[Zacherl et al., 1984]. The mode of action is considered bacteriostatic rather than bactericidal (100 mg/l for complete inhibition but not bactercidal) [Rodgers et al., 1982]. Adaptation may be acquired in the long term [Tomlinson et al., 1966]. To increase the efficacy of ammonium fertilizer by the inhibition activity, this chemical has been applied to agricultural soil intentionally.

4.3 Initial Assessment for the Environment

This substance is a white crystalline powder, which is soluble in water (40 g/L at 25 °C). Melting point, boiling point, and vapour pressure are 209.5 °C, solidified at 252 °C, and equal or less than 0.0045 Pa (100 °C), respectively. This substance does not hydrolyse under environmental conditions. Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life of 3.1 hours. This substance is not readily biodegradable under aerobic conditions within 28 days (BOD = 0 %). However, a prolonged study showed that this substance is completely biodegraded within 34 weeks under aerobic conditions, while two-thirds of the total is biodegraded within 60 weeks under anaerobic conditions. This substance has a low bioaccumulative potential (BCF (Cyprinus carpio, 48days): equal or less than 3.1). Fugacity modelling (Mackay level III) predicts that if released to water, this substance will not migrate into other compartments. When this substance is released to air or soil, it is mainly distributed to water and soil.

This substance has been tested in aquatic species (algae, invertebrates and fish). An acute growth inhibition test was performed using green algae (OECD TG 201, *Selenastrum capricornutum*). The EC50 (biomass; 0-72 h) was 935 mg/L and the EC50 (growth rate; 24-72 h) was > 1,000 mg/L. An acute toxicity test for invertebrates was performed using water flea (OECD TG 202, *Daphnia magna*). The 48-h EC50 was > 1,000 mg/L. An acute toxicity test [OECD TG 203] and a prolonged toxicity test [OECD TG 204] for fish were performed using Medaka (*Oryzias latipes*). The 96-h LC50 and the 14-d LC50 were >100 mg/L, >100 mg/L, respectively. A chronic toxicity test for invertebrates was performed using water flea (OECD TG 211, *Daphnia magna*) on reproduction. The 21-d EC50 and a 21-d NOEC were 69.6 mg/L and 25.0 mg/L, respectively. In microorganisms, this substance is known to inhibit the nitrification of ammonium in various systems.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work because of its low hazard potential.

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SKW Trostberg Aktiengesellschaft. (1985). Firmenprospekt ueber Dicyandiamid

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I U C L I D

Data Set

Existing Chemical	:	ID: 461-58-5
CAS No.	:	461-58-5
EINECS Name	:	cyanoguanidine
EINECS No.	:	207-312-8
TSCA Name	:	Guanidine, cyano-
Molecular Formula	:	C2H4N4

Producer Related Part

Company	:	MITSUBISHI CHEMICAL SAFETY INSTITUTE LTD.
Creation date	:	04.03.2003

Substance Related Part

Company	:	MITSUBISHI CHEMICAL SAFETY INSTITUTE LTD.
Creation date	:	04.03.2003
Memo	:	Cyanoguanidine SIAM 17
Printing date	:	25.02.2004
Revision date	:	
Date of last Update	:	25.02.2004
Number of Pages	:	75
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

Type : lead organisation
Name : NIPPON CARBIDE INDUSTRIES CO.,INC.
Partner :
Date :
Street : 2-11-19, Kohnan, Minato-ku
Town : 108-8466 Tokyo
Country : Japan
Phone : +81-3-5462-8200
Telefax : +81-3-5462-8244
Telex :
Cedex :
25.11.2003

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

Name of recipient : Mr. Yasuhisa Kawamura, Ministry of Foreign Affairs, Economic Affairs Bureau, Second International Organizations Div.
Street : 2-2-1 Kasumigaseki, Chiyoda-ku
Town : 100-8919 Tokyo
Country : Japan
Phone : +81-3-3581-0018
Telefax : +81-3-3581-9470
Telex :
Cedex :
03.06.2003

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organic
Physical status : solid
Purity : = 99.1 % w/w
Flag : Critical study for SIDS endpoint
31.07.2003 (10)

Substance type : organic
Physical status : solid
Purity : = 99 % w/w
31.07.2003 (36)

Substance type : organic
Physical status : solid
Purity : = 99.3 % w/w
31.07.2003 (33)

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

Cyanguanidin
Remark : Common synonyms
Flag : Critical study for SIDS endpoint
31.07.2003

Cyanguanidine
Remark : Common synonyms
Flag : Critical study for SIDS endpoint
31.07.2003

Cyanoguanidine
Remark : Common synonyms
Flag : Critical study for SIDS endpoint
31.07.2003

Dicyandiamid
Remark : Common synonyms
Flag : Critical study for SIDS endpoint
18.03.2003

Dicyandiamide
Remark : Common synonyms
Flag : Critical study for SIDS endpoint
31.07.2003

Dicyandiamin
Remark : Common synonyms
Flag : Critical study for SIDS endpoint
31.07.2003

Dicyanodiamide
Remark : Common synonyms
Flag : Critical study for SIDS endpoint
31.07.2003

Didin
Remark : Common synonyms
31.07.2003

1-Cyanoguanidine
Flag : Critical study for SIDS endpoint
25.11.2003 (9)

DCD
Flag : Critical study for SIDS endpoint
31.07.2003 (9)

Dicy
25.11.2003 (9)

1.3 IMPURITIES

CAS-No : 108-78-1
EINECS-No : 203-615-4
EINECS-Name : melamine
Contents : = .7 % w/w
Remark : water = 0.1 %W/W, thiourea = 200 ppm, heavy metal = 10 ppm

Flag : Critical study for SIDS endpoint
07.07.2003 (33)

1.4 ADDITIVES

1.5 QUANTITY

Production during the last 12 months :
Import during the last 12 months :
Quantity produced : tonnes in
Remark : Worldwide: Approximately 40000 tons in 2002
Flag : Critical study for SIDS endpoint
25.11.2003 (45)

Production during the last 12 months :
Import during the last 12 months :
Quantity produced : tonnes in
Remark : IN JAPAN
1000 - 10000 tons in 2001,
not manufactured in 2002
Flag : Critical study for SIDS endpoint
25.11.2003 (38)

Production during the last 12 months :
Import during the last 12 months :
Quantity produced : 10 000 - 50 000 tonnes in 1990
Remark : About 30000 tones in worldwide
Flag : Critical study for SIDS endpoint
31.07.2003 (33)

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

Type : industrial
Category : Basic industry: basic chemicals
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : industrial
Category : Electrical/electronic engineering industry
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : industrial
Category : Metal extraction, refining and processing of metals

Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : industrial
Category : Paper, pulp and board industry
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : industrial
Category : Textile processing industry
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : use
Category : Absorbents and adsorbents
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : use
Category : Adhesive, binding agents
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : use
Category : Colouring agents
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : use
Category : Electroplating agents
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : use
Category : Surface-active agents
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type : use
Category : other: agriculture chemical (fertiliser)
Remark : This substance has been used in agriculture for long time.
Flag : Critical study for SIDS endpoint
25.11.2003

Type :
Category : Intermediates
Remark : Industry use
Flag : Critical study for SIDS endpoint
31.07.2003 (53)

Type :
Category : Pharmaceuticals
Remark : Industry use
Flag : Critical study for SIDS endpoint
31.07.2003 (8)

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : other
Limit value :
Remark : There is no available official recommendation and regulation.
13.06.2003

1.9 SOURCE OF EXPOSURE

Memo : Consumer Exposure
Remark : Consumer exposures may occur by inhalation and dermal route to articles containing this substance. Dermatitis caused by contact with the article containing cyanoguanidine.
25.11.2003

Memo : Occupational exposure
Remark : Occupational exposures at production sites may occur by inhalation and dermal route. There is no available monitoring data. Normally, workers wear protections for eye/face, skin, and respiratory. There is no available official recommendation and regulation for occupational exposure limit.
25.11.2003

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

Memo : STRUCTUAL FORMULA: H2N-C(=NH)-NH-CN
Flag : Critical study for SIDS endpoint
31.07.2003

Memo : ODOR: ODORLESS

Flag : Critical study for SIDS endpoint
31.07.2003 (21)

Memo : APPEARANCE: white crystalline powder
Source : International Chemical Safety Card (ICSC) ICSC No. 0650
Flag : Critical study for SIDS endpoint
31.07.2003 (13)

1.16 LAST LITERATURE SEARCH

Type of Search : Internal and External
Chapters covered :
Date of search :
Remark : ACGIH
AQUIRE (CIS, STN)
BEILSTEIN (STN)
BIOSIS (STN, Dialog)
CHEMCATS (STN)
CHRIS (CIS, CHEM-BANK)
CSCHEM (STN)
ChemFinder
ECDIN
GMELIN (STN)
HODOC(STN)
HSDB (CIS, STN, DataStar, CHEM-BANK)
IARC
IRIS (CIS, CHEM-BANK)
IUCLIDMSDS-CCOHS (STN, Dialog)
MEDLINE (STN, Dialog, Datastar)
MSDS-OHS (STN)
NCI
NIOSHOHMTADS (CIS, CHEM-BANK)
NIOSHTIC(STN, Dialog)
PROMT(STN, Dialog)
REGISTRY (STN, Dialog)
RTECS(STN, CIS, Dialog, CHEM-BANK)
SPECINFO (STN)
SRC PhysPro Database(SRC: Syracuse Research Corporation)
TOXCENTER (STN)
TOXFILE (Dialog, Datastar)
TSCATS (CIS)

Date of the literature search: 15 July, 2003
09.10.2003

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

Type : AICS
Additional info :
27.06.2003

Type : DSL
Additional info :
27.06.2003

Type : EINECS
Additional info :
27.06.2003

Type : PICCS
Additional info :
27.06.2003

Type : TSCA
Additional info :
27.06.2003

Type : EINECS
Additional info :
27.06.2003

Type : ECL
Additional info :
27.06.2003

Type : CHINA
Additional info :
27.06.2003

2.1 MELTING POINT

Value : = 209.5 ° C
Remark : quotation: The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ, Merck and Co., Inc., No. 544(2001)
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (8)

Value : = 211 ° C
Source : International Chemical Safety Card (ICSC) ICSC No. 0650
Reliability : (4) not assignable
25.11.2003 (13)

Value : = 210 ° C
Sublimation :
Method : other: WHO capillairmethode
Year :
GLP :
Test substance :
Reliability : (4) not assignable
25.11.2003 (60)

Value : = 207.3 ° C
Sublimation :
Method : other: FCI micromethode
Year :
GLP :
Test substance :
Reliability : (4) not assignable
09.10.2003 (60)

2.2 BOILING POINT

Value : = ° C at
Decomposition :
Method : OECD Guide-line 103 "Boiling Point/boiling Range"
Year : 1998
GLP : no
Test substance :
Result : Not measurable (solidified at 252 degree)
Test substance : purchase: WAKO Chemical LTD
Purity: 99.1 %
Lot No. : LEJ1138
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (10)

Value : = ° C at
Decomposition :
Method : OECD Guide-line 103 "Boiling Point/boiling Range"
Year : 1998
GLP : no
Test substance :
Result : Not measurable (solidified at 252 degree)
Test substance : purchase: WAKO Chemical LTD
Purity: 99.1 %

Lot No. : LEJ1138
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (10)

Value : = ° C at
Decomposition :
Method : OECD Guide-line 103 "Boiling Point/boiling Range"
Year : 1998
GLP : no
Test substance :
Result : Not measurable (solidified at 252 degree)
Test substance : purchase: WAKO Chemical LTD
Purity: 99.1 %
Lot No. : LEJ1138
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (10)

Value : = ° C at
Decomposition :
Method : OECD Guide-line 103 "Boiling Point/boiling Range"
Year : 1998
GLP : no
Test substance :
Result : Not measurable (solidified at 252 degree)
Test substance : purchase: WAKO Chemical LTD
Purity: 99.1 %
Lot No. : LEJ1138
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (10)

2.3 DENSITY

Type : density
Value : = 1.4 g/cm3 at 25° C
Remark : Value is 1.400 g/cm3
quotation: The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ, Merck and Co., Inc., No. 544(2001)
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (8)

Type : density
Value : = 1.405 at ° C
Remark : Unit: g/cc (calculated)
Reliability : (4) not assignable
25.11.2003 (28)

Type : density
Value : = 1.404 at ° C
Remark : Unit: g/cc (observed)
Reliability : (4) not assignable
09.10.2003 (28)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	<= .000045 hPa at 100° C
Decomposition	:	
Method		OECD Guide-line 104 "Vapour Pressure Curve"
Year	:	1998
GLP	:	no
Test substance	:	
Method	:	n=1 rate of flow :20mL/min collection vehicle: purified water carrier gas: N2 gas (99.99%)
Test substance	:	purchase: WAKO Chemical LTD Purity: 99.1 % Lot No. : LEJ1138
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

25.11.2003 (10)

2.5 PARTITION COEFFICIENT

Log pow	:	= -.52 at 25° C
Method		OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year	:	1998
GLP	:	yes
Test substance	:	
Method	:	Volume of test substance: 5.09mg Condition to measure: water(saturated)-1-octanol layer and 1-octanol(saturated)-waterlayer: condition 1; 5 and 30 condition 2;10 and 25 condition 3; 20 and 15 25 plus or minus 1 degree, 20 cycle/minute, 5 minutes, n=2 Analysis: HPLC
Result	:	condition 1: -0.58 condition 2: -0.48 condition 3: -0.48 mean = -0.52 SD = 0.06 pH of water layer: 6.2 - 6.3
Test substance	:	purchase: WAKO Chemical LTD Purity: 99.1 % Lot No. : LEJ1138
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

25.02.2004 (10)

Log pow	:	= -1.15 at ° C
Method		other (calculated): QSAR
Year	:	
GLP	:	
Test substance	:	
Reliability	:	(4) not assignable

26.12.2003 (24)

2.6.1 WATER SOLUBILITY

Value : = 40 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 : 1998
GLP : no
Test substance :
Remark : degree plus or minus 1 degree
Test substance : purchase: WAKO Chemical LTD
Purity: 99.1 %
Lot No. : LEJ1138
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (10)

Value : = 22.6 g/l at ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Reliability : (4) not assignable
25.11.2003 (46)

Value : at ° C
Qualitative :
Pka : at 25 ° C
PH : at .84 g/l and 25 ° C
Method : other: OECD guide-line 112
Year : 1998
GLP : yes
Test substance :
Remark : No dissociation constant; not dissociated
Test substance : purchase: WAKO Chemical LTD
Purity: 99.1 %
Lot No. : LEJ1138
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.11.2003 (10)

Value : = 22.6 g/l at 13 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Reliability : (4) not assignable
25.11.2003 (8)

Value : = 41.3 g/l at 25 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Source : International Chemical Safety Card (ICSC) ICSC No. 0650
Reliability : (4) not assignable
25.11.2003 (13)

Result : 12.7 g/L at 0 degree C
22.6 g/L at 13 degree C

25.6 g/L at 15 degree C
41.3 g/L at 25 degree C
77.6 g/L at 39.9 degree C
118 g/L at 49.8 degree C
187.5 g/L at 60.1 degree C
325.8 - 334.1 g/L at 74.5 degree C

Reliability : (4) not assignable
25.02.2004 (27)

Remark : Dissociation constant: 6X10E-15
Reliability : (3) invalid
25.11.2003 (33)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

Result : non flammable
Reliability : (4) not assignable
25.11.2003 (26)

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

Memo : Henry's law constant
Result : 2.25 X 10E-10 atm.m3/mole
Method: Calculated
Calculated using HENRYWIN version 1.90 - 2000 U.S. Environmental Protection Agency, Syracuse Research Co.
Test condition : Parameter
CLASS / BOND CONTRIBUTION DESCRIPTION / COMMENT / VALUE
HYDROGEN / 4 Hydrogen to Nitrogen Bonds / No / 5.1341
FRAGMENT / 2 C-N / No / 2.6020
FRAGMENT / 1 C=N / ESTIMATE / 0.0000
FRAGMENT / 1 N-CN / ESTIMATE / 0.3000
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.02.2004

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.	:	1500000 molecule/cm3
Rate constant	:	= .000000000042 cm3/(molecule*sec)
Degradation	:	= 50 % after 3.1 hour(s)
Deg. Product	:	
Method	:	other (calculated)
Year	:	2003
GLP	:	no
Test substance	:	
Remark	:	Indirect photo-oxidation by hydroxy radicals in the atmosphere is predicted to occur with a half-life of 3.1 hrs (12-hrs day; 1.5 X 10E6 OH/cm3, calculated using AOPWIN version 1.90, Syracuse Research Co.). calculated using: AOPWIN version 1.90 - 2000 U.S. Environmental Protection Agency
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

26.11.2003

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
Degradation	:	% after 5 day at pH and 50 degree C
Deg. Product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	1998
GLP	:	no
Test substance	:	
Remark	:	Test period: 5 days Temperature: 50 plus or minus 1 degree C (Not decomposed at 50 degree C) Concentration: ca. 100 mg/L pH: 4, 7, 9 n=2
Result	:	t1/2 pH4: not hydrolyzed at 50 plus or minus 1 degree t1/2 pH7: not hydrolyzed at 50 plus or minus 1 degree t1/2 pH9: not hydrolyzed at 50 plus or minus 1 degree
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

26.11.2003 (10)

Remark	:	DECOMPOSITION: Solutions above 80 degree decomposes slowly, yielding ammonia.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

09.10.2003 (8)

3.1.3 STABILITY IN SOIL

Type : field trial
Radiolabel :
Concentration :
Soil temp. : degree C
Soil humidity :
Soil classif. :
Year :
Method : Cyanoguanidine at 20mg/L was added to flooded sediment.
Remark : Investigations on leaching of dicyandiamide and its decomposition in flooded soil.
Leaching of the nitrification inhibitor dicyandiamide (DCD) after mineral fertilizing and slurry manuring and decomposition of DCD under simulated ground water conditions (silty loam, pH 6.5) was investigated lysimeters. After mineral feeding, only 0.6 - 0.9 % of DCD applied in 5 years were leached.
Highest leaching rates of DCD occured after slurry application in October (with 5.6 % of added amount).
In sediment fooled sediment with water to a height of 10 to 60 cm, DCD (20 mg/L) was fully degrated within one year in almost all experiments at aerobic conditions while at anaerobic conditions two thirds were decomposed.
Result : Completed degradation was reported within 34 weeks for aerobic conditions, while under anaerobic conditions two-thirds of initial concentration was degraded within 60 weeks.

Time (week)	0	20	34	44	60
Concentration (mg/L)					
aerobic	20	14.1	0	0	0
anaerobic	20	13.4	11.3	10.6	8.2

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (3)

Type : field trial
Radiolabel :
Concentration :
Soil temp. : degree C
Soil humidity :
Soil classif. :
Year :
Remark : The application of dicyandiamide (DCD) in agricultural and horticultural practice, in order to reduce nitrate losses from soils, has gained considerable importance in the past years. DCD specifically inhibits the ammonium oxidation by Nitrosomonas europaea, thus keeping applied nitrogen in a form which is less prone to leaching.
It has been observed that the degradation of DCD depends mainly on soil temperature, moisture, and clay contents. Metallic oxides, especially amorphous iron oxides, are able to catalyze the reaction of water with the nitrile moiety to guanylurea. This is supposed to react further to guanidine and then to urea which, in soils, is readily cleaved into ammonia, CO2, and water.
There is, however, a biological degradation of DCD in soils, too. This has recently been confirmed with bacterial isolated form soils. But, so far, detailed information concerning the microorganisms involved and the pertinent reactions are lacking.
To further characterize the catabolism of DCD, different bacteria have been

isolated from DCD-treated composts and grown in pure cultures. Two lines have been selected which are able to break down DCD rapidly. The first one (line No. 16-1) is likely to belong to the genus Phodococcus (the identification on the species level is still under way), the second one (line No. 11-1) is presumably a Pseudomonas sp.
The degradation of DCD by the isolate 16-1=Phodococcus sp. (conditions : mineral nutrient with DCD as the sole N source, 27 degree C , 0.2 ml inoculum at the stationary phase, rotary shaker at 60 rpm) was very rapid : 200 ug DCD-N/ml were metabolized within 3 days. There was no change of DCD concentrations in the sterile controls. Considerable growth was observed only by the DCD-supplied bacteria, as measured by optical density and viable counting by plating. Psudomonas sp. Behaved similarly : concomitantly with a rapid decrease in DCD concentration there was rapid bacterial growth.
DCD metabolism was further followed by thin-layer chromatography (TLC) on silica gel. Plates were run in ethyl acetate : ethanol : glacial acetic acid : water (75 : 10 : 7.5 : 7.5, v/v), and spots visualized by spraying with KI/starch after chlorination. It could be shown that there is no decomposition of DCD in the sterile control. When incubated with Rhodococcus sp., three different degradation products could be seen after 3 days of culture, which never appeared in the controls. Psudomonas sp. also metabolized DCD in 3 days, yielding two metabolites.
Apparently there are at least two different ways of DCD degradation by bacteria. The main metabolites formed by Rhodococcus sp. are supposed to be cyanourea which appears as the first metabolite (unpublished observations), urea (confirmed by enzymatic testing; Boehinger "Harnstoff-Test"), and a third still unidentified product. When incubating DCD with Psudomonas sp., we found on the chromatogram a substance together with guanidine and a further, unknown product. It is notable that Phodococcus and Psudomonas seem to be unable to metabolize urea (unpublished observations). In contrast to the DCD degradation with metallic oxides, we never observed guanylurea in biological DCD cleavage.
Cell-free phosphate buffer extracts from Rhodococcus sp. were able to degrade DCD quantitatively into cyanourea at a very high rate. Urea was never detected as a degradation product. The DCD-degrading principle is heat-labile, as could be shown by boiling for 30 s. So far, no buffer-extractable DCD-degrading system could be found in Psuedomonas sp.
The following conclusions can be drawn from the above mentioned experiments:
1) DCD can be decomposed by soil bacteria.
2) There are at least two different ways of DCD catabolism. Both seem to be different from the inorganic catalytic DCD breakdown with metallic oxides.
In phodococcus, the possible metabolites are cyanourea, urea, an unidentified substance, whereas in Psudomonas sp. guanidine and another unknown product appear during the degradation.
3) From Rhodococcus, a heat-labile substance could be extracted with buffer which is able to decompose DCD readily, suggesting enzymatic control.
Experiments are under way to further characterize the different metabolic pathways of DCD degradation and the identification of the bacteria on a species level. The results might be of importance for the application of DCD in clean water areas and predicting the behavior of DCD in groundwaters.
The authors are indebted to Dr. M. Medina and Dr. W. Ziegler for helpful discussions, the Deutsche Forschungsge-meinschaft for financial support, and the DSM for help in the identification of the bacterial species.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (23)

Type	:	field trial
Radiolabel	:	
Concentration	:	
Soil temp.	:	degree C
Soil humidity	:	
Soil classif.	:	
Year	:	
Remark	:	Breakdown of Dicyandiamide in quartz sand and soils Under different moisture conditions the breakdown of dicyandiamide (DCD) was investigated in quartz sand with metal oxides and in soils. 1. In quartz sand without metal oxides DCD did not change over 100 days. 2. In the presence of amrphous Fe(III)-hydroxide DCD was transformed to guanyluera after 5 days to 50 % and after 40 days to 90 %. The transformation rate depended on the kind of metal oxides and increased with low humidity. Other metabolites were not detected in quartz sand medium. 3. In two soils (pH 6.5, 6.3; sandy silty loam and sand) the breakdown of DCD to guanylurea followed the same pattern, but continued to ammonium. About 20 - 70 % of the added amount was transformed within 100 days. 4. With increasing soil moisture the transformation of DCD to guanylurea was slower, but the further breakdown to ammonium increased. 5. As long as DCD was present the formation of nitrate was blocked.
Reliability	:	(4) not assignable

26.11.2003 (4)

Type	:	field trial
Radiolabel	:	
Concentration	:	
Soil temp.	:	degree C
Soil humidity	:	
Soil classif.	:	
Year	:	
Remark	:	Effect of temperature on the breakdown of dicyandiamide in the soil The breakdown of dicyandiamide in a soil (sandy silty loam, pH 6.2, 0.13 % N) was investigated in relation of temperature. 1. The rate of conversion of dicyandiamide (DCD) (20 mg DCD-N/100 g soil) to guanylurea increased with rising temperature (10-90 degree C). After 20 days, 14 - 100 % of the added DCD was metabolized. Small amounts of DCD (0.67 resp. 1.34 mg DCD-N/100 g soil) were broken down completely within 20 - 80 days at 8 - 20 degree C. 2. Guanylurea was transformed to guanidine and then to ammonium. Increasing temperature in the region of 10 and 30 degree C accelerated the transformation. At higher temperatures (up to 70 degree C) an accumulation of guanidine occurred.
Reliability	:	(4) not assignable

26.11.2003 (59)

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

Media	:	air - biota - sediment(s) - soil - water
Method	:	Calculation according Mackay, Level III
Year	:	2003

Method : Distribution were calculated with the following factors
cyanoguanidine
weight: 84.08
melting point [degree]: 209.5
vapour pressure [Pa]: 4.50E-03
water solubility [g/m3]: 40000
log Kow: -0.52 [25 degree]
half life [hr]
in air: 3.1
in water: 5712
in soil: 5712
in sediment: 17136

Result : The potential environmental distribution of cyanoguanidine obtained from a generic fugacity model Mackay level III under three emission scenarios is shown as below.

Compartment	Amount % Release 100% to air %	Release 100% to water %	Release 100% to soil %
Air	0.0	0.0	0.0
Water	48.3	99.6	42.1
Soil	51.5	0.0	57.8
Sediment	0.2	0.4	0.2

Source : Chemicals Evaluation and Research Institute, Japan (2002):report on generic fugacity model (Mackay level III)

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

31.07.2003

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic

Inoculum : activated sludge

Concentration : 25mg/l related to
related to

Contact time :

Degradation : = 0 % after 28 day

Result : under test conditions no biodegradation observed

Deg. Product :

Method : other: OECD guide-line "Ready biodegradability test"

Year :

GLP : no data

Test substance :

Remark : OECD manometric respirometry test: various source of inoculum; test substance as sole source of organic carbon, oxygen uptake as percent of the ThOD or COD.
Source of inoculum: location; Schmallenberg (number of inhabitants: 15000), Lennestadt-Maumke (number of inhabitants: 30000) in Germany

Result : No biodegradation was observe in both tests.

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

26.11.2003 (47)

Type : aerobic

Inoculum : activated sludge
Contact time :
Degradation : = 0 % after 14 day
Result : under test conditions no biodegradation observed
Deg. Product :
Method : other: equivalent of OECD TG 302 C
Year : 1976
GLP : no
Test substance :
Result : BOD 0%
Test condition : Activated Sludge Concentration: 100 ppm
Test Substance Concentration: 30 ppm
Reliability : (2) valid with restrictions
10.10.2003 (11)

Type : aerobic
Inoculum : activated sludge
Concentration : 100mg/l related to
related to
Contact time :
Degradation : = 0 % after 14 day
Result : under test conditions no biodegradation observed
Deg. Product :
Method : other
Year :
GLP : no
Test substance :
Remark : Biodegradability of cyanoguanidine was estimated by the use of activated sludge under aerobic conditions and soil bacteria under anaerobic conditions and soil perfusion apparatus. Soil bacteria were isolated from the sediment in a sewage drainage.
Activated sludge did not biodegradate cyanoguanidine which was formed calcium cyanamide fertilizer and known to be biodegrabated to ammonia in soil. The change of nitrogen source from polypeptone to cyanoguanidine affected the composition and population of microorganisms in activated sludge but it did not endow activated sludge with the biodegradating activity for cyanoguanidine.
BOD 0%
Reliability : (4) not assignable
26.11.2003 (14)

Type : anaerobic
Inoculum :
Concentration : 100mg/l related to
related to
Contact time :
Degradation : ca. 40 % after 40 day
Result : inherently biodegradable
Deg. Product :
Method : other
Year :
GLP : no
Test substance :
Remark : Soil bacteria anaerobically degradating activity of cyanoduanidine which were not degradated by activated sludge.
Reliability : (4) not assignable
26.11.2003 (14)

Remark : Dicyandiamide (DCD) is well known to be an efficient nitrification inhibitor and, hence, applied in agriculture and horticulture (Hauck, 1984). DCD blocks the first step in the oxidation of ammonium and, as a consequence,

inhibits the formation of nitrate (Reddy, 1964). Although produced and applied at a large scale the degradation of DCD, So far, has not been elucidated in detail. In soil DCD seems to be gradually degraded via guanyl urea, guanidine and urea (Rathsake, 1955; Vilsmeir, 1980). The first step in this degradation has been assumed to be catalyzed by the interaction with metal oxides, such as Fe(OH)3, MnO(OH)2, Cu(OH)2, Zn(OH)2 and Mn(OH)2, rather than being due to microbial and, hence, enzymatic mineralization (Amberger and Vilsmeier, 1979; Amberger, 1986).

In order to test this assumption we have inoculated a nutrient medium with DCD as the single N source, with soil suspension, and determined the decrease in the DCD concentration with time. From such DCD-utilizing mixed cultures we have isolated a number of bacterial strains capable of degrading DCD under pure culture conditions. In the present study we analyze the effect of temperature, aeration and DCD concentration on the degradation of DCD by one of the isolates.

The isolate EK1 is a Gram-positive, strictly aerobic, rod-shaped bacterium. This strain was isolated from an enrichment culture of an agricultural soil (alfisol derived from loss), established on a nutrient medium (Stranksky and Amberger, 1973) with DCD (1.60 g l-1) as the single N source. The same medium (25ml in 100ml Erlenmeyer flasks inoculated with 0.1ml of a culture in stationary phase) was used in the following experiments.

The DCD concentration of the nutrient medium was determined colorimetrically (Vilsmeier, 1982) or by the use of HPLC. In the colorimetric assay DCD reacts with 1-naphthol and diacetyl to give a red complex with an absorption maximum at 538 nm. The HPLC method is based upon separation of DCD on a fast acid column (100 X 7.8 mm) with 0.01 N H2SO4 as eluent (0.8 ml min-1) in an isocratic system, and on the absorption of DCD at a wavelength of 210 nm.

DCD is degraded at 25 degree C at a slightly higher rate than at 33 degree C . At 18 degree C degradation of DCD is slowed down. But even at 10 degree C DCD is mineralized, however, at a significantly lower rate. Aeration favors the degradation of DCD. At 40 degree C the bacterial strain EK1 could not grow in the nutrient medium or degrade its DCD content, wether the culture was shaken or not.

The quantity of DCD which is degraded by EK1 depends upon the amount present in the nutrient medium. During 7 days growth at 25 degree C and 100 rev min-1, 0.70 g DCD were mineralized when the nutrient medium contained 0.72 g l-1, whereas 1.32 g were degraded under the same conditions during 7 days provided the DCD content of the nutrient medium was 2.80 g L-1. If the DCD mineralization is expressed on a percentage basis, the degradation rate decreases with increasing concentration of the substrate, following normal degradation kinetics in batch cultures.

The results outlined above clearly demonstrate the capability of a bacterium to mineralize DCD completely. For example, DCD at 0.72 g l-1 is completely depleted at 7 days, and all other concentrations are approaching complete depletion. Thus, our results are in agreement with an early study carried out by Ulpinani (1906) who claimed to have been able to isolate two bacterial strains capable of degrading DCD.

Using the same nutrient solution with DCD as a single N source as in this study, Paulmichl (1986) found an 89% decrease in DCD concentration within 24 days at 25 degree C at 100 rev min-1. The soil suspension inoculum was from the same soil sample as in this study. Paulmich hypothesized from these results obtained with enrichment cultures that complete microbial degradation of DCD would take place. Our results verify this hypothesis.

The microbial mineralization, as demonstrated in the present study, includes also the first step in the breakdown of this molecule which, previously, has been ascribed to a more inorganic interaction with metal oxides as postulated by Amberger (1986) and Amberger and Vilsmeier (1979). Further studies are required to assess in detail the ecological

significance of this form of degradation in comparison to an entire microbial mineralization of DCD in soil.
Detailed knowledge of the microbial DCD degradation may help to explain, for example why in acid soils less DCD in mineralized than in near-neutral soils (Rodgers et al., 1985), or what determines the duration of the nitrification inhibiting effect of DCD (e.g. Guiraud et al., 1989). In addition, a better understanding of the microbial mineralization of DCD may help to optimize its application in agriculture.

Reliability : (2) valid with restrictions
26.11.2003 (25)

Type : aerobic
Inoculum : activated sludge
Contact time :
Degradation : ca. 0 % after 10 day
Result : under test conditions no biodegradation observed
Deg. Product :
Method : other
Year :
GLP : no
Test substance :
Remark : Activated Sludge Concentration: 100 ppm
Test Substance Concentration: 30 ppm
Test at 25 plus or minus 1 degree
Reliability : (3) invalid
26.11.2003 (55)

Type : anaerobic
Inoculum :
Contact time :
Degradation : ca. 30 - 40 % after 10 day
Result : inherently biodegradable
Deg. Product :
Method : other
Year :
GLP : no
Test substance :
Remark : Activated Sludge Concentration: 100 ppm,
test at 25 degree
Reliability : (3) invalid
26.11.2003 (55)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : Cyprinus carpio (Fish, fresh water)
Exposure period : 42 day at 25 degree C
Concentration :
BCF : <= 3.1
Elimination :
Method : other: equivalent of OECD TG 305C
Year : 1982
GLP : no
Test substance : other TS: > 99.5%
Method : -Tank volume: 100 liter
-Water flow: 582 liter/day

-Mean body weight: 26.1g
-Mean length: 10.0 cm
-Mean content fat: 4.3 %

-Acclimatization: 14 days, 25 plus or minus 1 degree C

Remark : Concentration: 2.0ppm, 0.2ppm (w/v)
Result : -Observation: normal
-Accumulation factor
2.0 ppm concentration division: equal or less than 0.3 (2, 3, 4, 6 Weeks),
0.2 ppm concentration division: equal or less than 3.1 (2, 3, 4, 6 Weeks),
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (12)

BCF : = 3.16
Elimination :
Method : other: calculated
Year : 2003
GLP : no
Test substance :
Source : calculated using: BCFWIN version 2.14 - 2000 U.S. Environmental Protection Agency
Reliability : (2) valid with restrictions
18.03.2003

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : semistatic
Species : Oryzias latipes (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : yes
LC0 : m >= 100
LC50 : m > 100
LC100 : m > 100
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1998
GLP : yes
Test substance : other TS
Result : RESULTS:
- Measured concentrations:

Nominal concentration [mg/L]	Measured concentration [mg/L] (% of nominal) 0-hour (fresh solutions)	48-hour (expired solutions)
Control	<5.00	<5.00
100	104 (104)	104 (104)

- Effect data (Mortality):

Nominal concentration [mg/L]	Cumulative Mortality (% Mortality) 24 hr	48 hr	72 hr	96 hr
Control	0 (0)	0 (0)	0 (0)	0 (0)
100	0 (0)	0 (0)	0 (0)	0 (0)

24 hr LC50 > 100 mg/L
48 hr LC50 > 100 mg/L
72 hr LC50 > 100 mg/L
96 hr LC50 > 100 mg/L
96 hr lowest concentration resulting in 100% mortality > 100 mg/L
96 hr highest concentration resulting in 0% mortality >= 100 mg/L

- Other effects:
No toxicological symptom was observed at during test period.

RESULTS: TEST WITH REFERENCE SUBSTANCE
- Reference substance: CuSO4-5H2O- Results: 96 hr LC50 = 0.930 mg/L

Test condition : TEST ORGANISMS- Strain: Oryzias latipes
- Supplier: NAKAJIMA FISH HATCERY (Japan)
- Size/weight: 1.9 cm (1.8 - 2.1 cm), n = 10 / 0.11 g (0.077 - 0.14 g), n = 10
- Feeding: "TETRAMIN"
- Pretreatment: acclimated for 7 day before testing, mortality was less than 5%. Not fed for 24 hr before the test started.
- Feeding during test: none
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Vehicle, solvent: No solvent was used.
STABILITY OF THE TEST CHEMICAL SOLUTIONS:
Cyanoguanidine was stable, and not hydrolyzed after 48 hrs.

REFERENCE SUBSTANCE: CuSO4-5H2O
DILUTION WATER
- Source: dechlorinated tap water
- Aeration: aerated sufficiently.
- Alkalinity: 29.0 mg/L
- Hardness: 40.5 mg/L as CaCO3
- Residual chlorine: less than 0.02 mg/L as Cl
- pH: 7.6
TEST SYSTEM
- Concentrations: 100 mg/L
- Renewal of test solution: 48 hr
- Exposure vessel type: size; 2.5 L test solution in a 3 L glass beaker
- Number of replicates, fish per replicate: 2, 5
- Test temperature: 24 plus or minus 1 degree
AERATION
- Dissolved oxygen: 6.7 - 8.3 mg/L
- pH: 7.2 - 7.7
- Intensity of irradiation: room light
- Photoperiod: 16 - 8hr light-dark cycle
DURATION OF THE TEST: 96 hr
TEST PARAMETER: mortality, abnormal behavior, abnormal respiration
SAMPLING: immediately after the preparation on 48 hour
MONITORING OF TEST SUBSTANCE CONCENTRATION: analyzed by HPLC at the start and at the 48 hour exposure before renewal.

Test substance : SOURCE: Wako Pure Chemical Industries, LTD (Japan)
PURITY: 99.2%
IMPURITY/ADDITIVE/ETC.: not described
ANY OTHER INFORMATION: Lot No.WTM0467

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
15.07.2003 (19)

Type : flow through
Species : Oryzias latipes (Fish, fresh water)
Exposure period : 14 day
Unit : mg/l
Analytical monitoring : yes
NOEC : m = 100
LC0 : m > 100
LC50 : m > 100
Method : OECD Guide-line 204 "Fish, Prolonged Toxicity Test: 14-day Study"
Year : 1998
GLP : yes
Test substance : other TS
Result : RESULTS:
- Measured concentrations:

Nominal concentration [mg/L]	Measured concentration [mg/L] (% of nominal) 0-day	7-day	14-day
Control	<5.00	<5.00	<5.00
6.25	6.23 (99.7)	6.63 (106)	7.10 (114)
12.5	13.0 (104)	13.1 (105)	13.3 (106)
25.0	23.5	25.7	25.5

	(93.9)	(103)	(102)	
50.0	48.9 (97.8)	51.3 (103)	49.6 (99.2)	
100	93.8 (938)	102 (102)	100 (100)	

- Effect data (Mortality):

Nominal concentration [mg/L]	Cumulative Mortality (% Mortality) 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14-day
Control	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 (0 0 0 0 0 0 0 0 0 0 0 0 0 0 0)
6.25	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 (0 0 0 0 0 0 0 0 0 0 0 0 0 0 0)
12.5	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 (0 0 0 0 0 0 0 0 0 0 0 0 0 0 0)
25.0	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 (0 0 0 0 0 0 0 0 0 0 0 0 0 0 0)
50.0	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 (0 0 0 0 0 0 0 0 0 0 0 0 0 0 0)
100	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 (0 0 0 0 0 0 0 0 0 0 0 0 0 0 0)

7 d-LC50 > 100 mg/L
14 d-LC50 > 100 mg/L
14 day lowest test substance concentration resulting in 100% mortality = 100 mg/L

- Other effects:
No toxicological symptom was observed during test period.
14 day the lowest effective concentration = 100 mg/L

RESULTS: CONTROL
- Nature of adverse effects: none
RESULTS: TEST WITH REFERENCE SUBSTANCE
- Reference substance: CuSO4-5H2O- Results: 96 hr LC50 = 0.930 mg/L

Test condition : TEST ORGANISMS- Strain: Oryzias latipes
- Supplier: NAKAJIMA FISH HATCERY (Japan)
- Size/weight: 2.0 cm (1.9 - 2.1 cm), n = 10 / 0.12 g (0.10 - 0.15 g), n = 10
- Feeding: "TETRAMIN"
- Pretreatment: acclimated for 7 day before testing, mortality was less than 5%. Not fed for 24 hr before the test started.
- Feeding during test: 2% of fish weight daily.
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Vehicle, solvent: No solvent was used.
STABILITY OF THE TEST CHEMICAL SOLUTIONS:
Cyanoguanidine was stable, and not hydrolyzed after 14 days.
REFERENCE SUBSTANCE: CuSO4-5H2O
DILUTION WATER
- Source: dechlorinated tap water
- Aeration: aerated sufficiently.

- Alkalinity: 29.0 mg/L
- Hardness: 40.5 mg/L as CaCO3
- Residual chlorine: less than 0.02 mg/L as Cl
- pH: 7.6

TEST SYSTEM
- Concentrations: 6.25, 12.5, 25.0, 50.0, 100 mg/L
- Renewal of test solution: flow through 25.0 mL/min
- Exposure vessel type: size; 1.8 L test solution in a 3 L glass beaker
- Number of replicates, fish per replicate: 1, 10
- Test temperature: 24 plus or minus 1 degree C
- Dissolved oxygen: 7.5 - 8.2 mg/L
- pH: 7.1 - 7.7
- Intensity of irradiation: room light
- Photoperiod: 16 - 8hr light-dark cycle

DURATION OF THE TEST: 14 day
TEST PARAMETER: mortality, abnormal behavior, abnormal respiration
SAMPLING: immediately after the preparation on 0, 7, 14 day
MONITORING OF TEST SUBSTANCE CONCENTRATION: analyzed by HPLC at the start (0-day), middle (7-day) and the end (14-day) of test period

Test substance : SOURCE: Wako Pure Chemical Industries, LTD (Japan)
PURITY: 99.2%
IMPURITY/ADDITIVE/ETC.: not described
ANY OTHER INFORMATION: Lot No.WTM0467

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
31.07.2003 (20)

Type :
Species : Oryzias latipes (Fish, fresh water)
Exposure period :
Unit :
Analytical monitoring :
Method : other
Year :
GLP : No
Test substance :
Result : 24hr-TLM> 2300 ppm
48hr-TLM> 2300 ppm
Test condition : Dose: 700, 1700, 2319 ppm
Period: 24, 48 hr
n = 10
Reliability : (3) invalid
26.06.2003 (35)

Type :
Species : Rutilus rutilus (Fish, fresh water)
Exposure period :
Unit : mg/l
Analytical monitoring :
Schwellenwert der Giftwirkung (Threshold value of the poison effect) : m = 9000
Method :
Year :
GLP : No
Test substance :
Reliability : (4) not assignable
26.06.2003 (43)

Type :
Species : Perca fluviatilis (Fish, fresh water)
Exposure period :
Unit : mg/l
Analytical monitoring :
Schwellenwert der Giftwirkung (Threshold value of the poison effect) : m = 8000
Method :
Year :
GLP : No
Test substance :
Reliability : (4) not assignable
26.06.2003 (43)

Type :
Species : Salmo gairdneri (Fish, estuary, fresh water)
Exposure period : 4 day
Unit : mg/l
Analytical monitoring :
NOEC : = 3600
LC50 : = 7700
Method : other
Year :
GLP :
Test substance :
Reliability : (4) not assignable
27.06.2003 (5)

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 : m = 1000
EC50 : m > 1000
Method : OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year : 1998
GLP : Yes
Test substance : other TS
Result : RESULTS:
- Measured concentrations:

Nominal concentration [mg/L]	Measured concentration [mg/L] (% of nominal) 0-hour	48-hour
Control	<5.00	<5.00
250	267 (107)	265 (106)
500	537 (107)	529 (106)
1000	1060	1060

(106) (106)

- Effect data (Immobilization):
24 hr EiC50 > 1000 mg/L
48 hr EiC50 > 1000 mg/L
48 hr NOECi >= 1000 mg/L
- Cumulative immobilisation:

Nominal concentration [mg/L]	Cumulative numbers of immobilized Daphniad (% immobility) 24-hour	48-hour
Control	0 (0)	0 (0)
25 0	0 (0)	0 (0)
500	0 (0)	0 (0)
1000	0 (0)	0 (0)

RESULTS: TEST WITH REFERENCE SUBSTANCE
- Reference substance: pure K2Cr2O7
- Results: 48 hr EiC50 = 0.141 mg/L

Test condition : TEST ORGANISMS
- Source/supplier: Sheffield University (United Kingdom)
- Age: juveniles less than 24 hr old
- Feeding: Chlorella vulgaris, 0.1 - 0.2 mgC/day/individual
- Pretreatment: 2 - 4 week
- Feeding during test: none
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Vehicle, solvent: No solvent was used.
STABILITY OF THE TEST CHEMICAL SOLUTIONS:
Cyanoguanidine was stable, and not hydrolyzed after 48 hrs.
REFERENCE SUBSTANCE: pure K2Cr2O7
DILUTION WATER
- Source: dechlorinated tap water
- Aeration: aerated sufficiently
- Alkalinity: 29.0 mg/L
- Hardness: 40.5 mg/L as CaCO3
- Residual chlorine: less than 0.02 mg/L as Cl
- COD: <0.5 mg/L
- Ca/Mg ratio: 10.4 mg/L / 3.52 mg/L
- pH: 7.6 (22 degree C)
- Conductance: 148 micro S/cm
TEST SYSTEM
- Test type: static
- Concentrations: 250, 500, 1000 mg/L
Concentartions set up from the result of a preliminary study.
Pleliminary result: 1000 mg/L-20 % immobility, 250 mg/L-0 % immobility
- Renewal of test solution: none
- Exposure vessel type: 200 mL glass beaker
- Number of replicates, individuals per replicate: 4, 5
- Test temperature: 20.3 - 20.5 degree (setting: 20 plus or minus 1 degree)
- Dissolved oxygen: 8.84 mg/L
- pH: 7.7

- Intensity of irradiation: room light
- Photoperiod: 16 - 8 hr light-dark cycle
DURATION OF THE TEST: 48 hr
TEST PARAMETER: immobility
SAMPLING: immediately after the preparation on 0 and 48 hour
MONITORING OF TEST SUBSTANCE CONCENTRATION: analyzed by HPLC at the start and the end of 48-exposure

Test substance : SOURCE: Wako Pure Chemical Industries, LTD (Japan)
PURITY: 99.2%
IMPURITY/ADDITIVE/ETC.: not described
ANY OTHER INFORMATION: Lot No.WTM0467

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
15.07.2003 (18)

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
NOEC : m = 171
EC50 : m = 935
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1998
GLP : Yes
Test substance : other TS
Result : RESULTS:
- Measured concentrations:

Nominal concentration [mg/L]	Measured concentration [mg/L] (% of nominal) 0-hour	72-hour
Control	<5.00	<5.00
95.3	96.2 (101)	95.6 (100)
171	167 (97.7)	166 (97.0)
309	303 (98.0)	315 (102)
556	560 (101)	568 (102)
1000	1030 (103)	977 (97.7)

Effect data/Element values:
Biomass Method
EbC50 (0-72 hr) = 935 mg/L
NOEC (0-72 hr) = 171 mg/L
Rate Method
ErC50 (24-48 hr) > 1000 mg/L
NOECr (24-48 hr) = 556 mg/L
ErC50 (24-72 hr) > 1000 mg/L

NOECr (24-72 hr) = 556 mg/L

- Cell density data: average

Nominal concentration [mg/L]	Cell density [x10E+4 cells/ml] 0-hr	24-hr	48-hr	72-hr
Control	1.0	4.2	30.1	151.1
95.3	1.0	4.1	30.8	153.2
171	1.0	3.9	29.0	141.0
309	1.0	3.6	28.1	139.0
556	1.0	3.6	27.3	129.0
1000	1.0	3.1	17.2	61.7

- Growth curves:

Nominal concentration [mg/L]	Inhibition area (0-72 hr)%	Inhibition growth rate (24-48 hr)%	Inhibition growth rate (24-72 hr)%
95.3	-1.40	-2.79	-1.33
171	6.06	-1.30	0.119
309	8.06	-4.01	-1.80
556	13.3	-2.60	0.150
1000	54.8	12.5	16.1**

**: <0.01

-pH:

Nominal concentration [mg/L]	pH 0-hr	72-hr
Control	8.0	10.3
95.3	8.0	10.3
171	8.0	10.3
309	8.0	9.9
556	8.0	9.5
1000	8.0	9.1

RESULTS: TEST WITH REFERENCE SUBSTANCE: K2Cr2O7 pure grade- Results: EbC50 (0 - 72 hr) = 0.369 mg/L

Test condition : TEST ORGANISMS
- Strain: ATCC22662
- Source/supplier: American Type Culture Collection
- Method of cultivation: subculturing in OECD medium until use
- Pretreatment: 3 day
- Initial cell concentration: 1 x 10E+4 cells/ml

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Vehicle, solvent: No solvent was used.

STABILITY OF THE TEST CHEMICAL SOLUTIONS:
Cyanoguanidine was stable, and not hydrolysed after 72 hrs.

GROWTH/TEST MEDIUM CHEMISTRY: OECD medium

TEST SYSTEM
- Test type: closed system, shaking (100rpm)
- Concentration: 95.3, 171, 309, 556, 1000 mg/L
- Renewal of test solution: none
- Exposure vessel type: 100 ml medium in a 500 ml conical flask, 100rpm shaking
- Number of replicates: 3
- Test temperature: 23.2 - 23.6 degree (Setting: 23 plus or minus 2 degree)
- pH: 8.0 at start and 9.1 - 10.3 at end of the test
- Intensity of irradiation: 4400 - 4600 lux (Setting: 4000 - 5000 lux)
- Photoperiod: continuous

TEST PARAMETER: cells/mL

MONITORING OF TEST SUBSTANCE CONCENTRATION: analyzed by HPLC at the start and the end of 72 hour exposure

Test substance : SOURCE: Wako Pure Chemical Industries, LTD (Japan)
PURITY: 99.2%
IMPURITY/ADDITIVE/ETC.: not described
ANY OTHER INFORMATION: Lot No.WTM0467

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

26.11.2003 (16)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Remark : Nitrification inhibitors were investigated in an attempt to establish whether such chemicals actually kill ammonium-oxidizing bacteria (bactericidal action) or whether bacteria remain viable but temporarily incapable of nitrification (bacteriostatic action). In laboratory experiments with nitrifying cultures, nitrification was completely inhibited, but numbers of ammonium-oxidizing bacteria were not significantly affected by a 48-h treatment with dicyandiamide applied at the rate of 100 mg inhibitor/L culture medium.

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

10.10.2003 (48)

Remark : A simple method is described for determining the short term effects of sewages, effluents and individual substances on the nitrifying ability of activated sludge and the results of screening many substances are obatined. The effects of mixtures of inhibitors and the possibility of formation of complexes between some of these inhibitors were investigated. Dicyandiamide showed 75% inhibition at 250 mg/L. The long term effects of inhibitors often differ from their immediate effects, one of the most important factors being the ability of activated sludge to become

adapted to the inhibitor.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.02.2004 (58)

Remark : Chemicals used in industry or housholds and industrial wastewaters were tested for their effects on microbial nitrification. The investigations were carried out as batch-experiments in a manostatic respirometer. Chemical substances were tested in series of definite concentrations and waste waters in series of definite dilutions. The inoculum was a highly nitrifying culture, isolated form a nitrifying activated sludge. Each test series included a corresponding number of blanks to which changes in the amount or rate of the oxygen uptake could be related.
The results of the investigations show that many of these chemicals used in industry as production aids have inhibiting effects on nitrification, in concentrations ranging from 30 ug/L to 230 mg/L. Considerable differences in the slope of the transition between the no-effect level and the level of full toxicity of the different substances were observed.
Cyanoguanidine showed IC50 of respirometry activity at 8.2 mg/L.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.02.2004 (61)

Remark : The nitrification inhibitor dicyandiamide (DCD) did not inhibit growth and respiration of N-fixing bacteria (Rhizobium leguminosarum and Azotobacter chroococcum) in cell suspensions with concentrations of 400 ppm DCD. Growth of Rhizobium leguminosarum was inhibited by 17 % with 100 ppm nitrapyrin (N-Serve), but respiration was not affected. Growth of Azotobacter chroococcum was inhibited by 10 ppm (10%) and 100 ppm nitrapyrin (50%); in the latter case, respiration was also impaired (36%). Thiourea only caused a minor growth inhibition of Azotobacter croococcum with 100 ppm (8%) and had no effect on Rhizobium leguminosarum.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
08.08.2003 (64)

Remark : Inhibition of ammonia oxidation by Nitrosomonas europaea with nitrification inhibitors

Inhibitory effects of dicyandiamide (DCD) on ammonia oxidation were detected in experiments with static cultures as well as cell suspensions. DCD required 200 ppm for 70 % inhibition. DCD effect was shown to be bacteriostatic.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
25.02.2004 (63)

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 : m = 25
LCEC : m = 50

EC50 : m = 69.6
LC50 : m > 100
Method : other: OECD Guide-line 211
Year : 1998
GLP : Yes
Test substance : other TS
Result : RESULTS:

- Measured concentrations:

Nominal concentration [mg/L]	Measured concentration [mg/L] (% of nominal)					
	0-day	2-day	11-day	14-day	18-day	21-day
Control	<5.00	<5.00	<5.00	<5.00	<5.00	<5.00
25	25.7 (102)	25.7 (103)	26.2 (105)	25.8 (103)	25.4 (102)	25.1 (101)
50	50.7 (101)	50.1 (100)	50.3 (101)	50.2 (100)	50.1 (100)	49.3 (98.6)
100	102 (102)	101 (101)	101 (101)	101 (101)	101 (101)	100 (100)

- Effect data:
21 day LC50 > 100 mg/L
21 day ErC50 = 69.6 mg/L
21 day NOECr = 25.0 mg/L
21 day LOECr = 50.0 mg/L

- cumulative reproduction:
(1) Cumulative number of dead parental Daphnia and mortality during exposure of 21day

Nominal concentration [mg/L]	Number of dead parental Daphnia	Mortality (%)
control	1	10
25.0	1	10
50.0	3	30
100	4	40

There was no significant difference.
21 day LC50 > 100 mg/L

(2) mean days required to first brood production during test period:

Nominal concentration [mg/L]	Mean days
control	8.2
25.0	8.3
50.0	8.3
100	-

(3) mean cumulative number of juveniles produced per adult during exposure after 21 day

Nominal	Number

		concentration [mg/L]
		control 126 25.0 135 50.0 125 100 0**
		**:Significantly different from Control at p less than 0.01
		RESULTS: TEST WITH REFERENCE SUBSTANCE- Results: K2Cr2O7 pure grade: 48 hr EiC50 = 0.141 mg/L
Test condition	:	TEST ORGANISMS - Source/supplier: Sheffield University (United Kingdom) - Age: juveniles less than 24 hr old - Feeding: Chlorella vulgaris, 0.1 - 0.2 mgC/day/individual - Pretreatment: 2 - 4 week - Feeding during test: Chlorella vulgaris, 0.1 - 0.2 mgC/day/individual STOCK AND TEST SOLUTION AND THEIR PREPARATION - Vehicle, solvent: No solvent was used. STABILITY OF THE TEST CHEMICAL SOLUTIONS: Cyanoguanidine was stable, and not hydrolysed after 21 days. REFERENCE SUBSTANCE: pure K2Cr2O7 DILUTION WATER - Source: dechlorinated tap water - Aeration: aerated sufficiently - Alkalinity: 29.0 mg/L - Hardness: 40.5 mg/L as CaCO3 - Residual chlorine: less than 0.02 mg/L as Cl - COD: <0.5 mg/L - Ca/Mg ratio: 10.4 mg/L / 3.52 mg/L - pH: 7.6 (22 degree C) - Conductance: 148 micro S/cm TEST SYSTEM - Test type: semistatic - Concentrations: 25, 50, 100 mg/L (Dosage was set up from the result of acute toxicity study to daphnia magna and a preliminary study. Moreover, this study was judged that 3 concentration can enough estimate.) - Renewal of test solution: 3 times/week - Exposure vessel type: 100 mL glass beaker - Number of replicates, individuals per replicate: 10, 1 - Test temperature: 19.5 - 20.8 degree C(setting: 20 plus or minus 1 degree C) - Dissolved oxygen: 7.8 - 8.9 mg/L more than 60% of saturated dissolved oxygen concentration - pH: 7.5 - 7.9 - Intensity of irradiation: room light - Photoperiod: 16 - 8 hr light-dark cycle DURATION OF THE TEST: 21 day TEST PARAMETER: reproduction rate SAMPLING: freshly prepared test solutions on 0, 11 and 18-day, test solutions after 48 or 72 hours on 2, 14 and 21-day. MONITORING OF TEST SUBSTANCE CONCENTRATION: analyzed by HPLC during the exposure period (6 times)
Test substance	:	SOURCE: Wako Pure Chemical Industries, LTD (Japan) PURITY: 99.2% IMPURITY/ADDITIVE/ETC.: not described ANY OTHER INFORMATION: Lot No.WTM0467
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
11.08.2003		(17)

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	:	Fischer 344/DuCrj
Sex	:	female
Number of animals	:	5
Vehicle	:	Water
Value	:	> 30000 mg/kg bw
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS
Result	:	No death was observed in both doses. At 30g/kg bw, hypothermia and decrease in locomotor activity were observed after dosing 1 hour, lateral position and cyanosis were seen after dosing 2 hour. Although, these symptoms were recovered after dosing 18 hours, except diarrhea. There were no findings at autopsy after dosing 1 week.
Test condition	:	Rat: SPF, Charles River Japan Dose: 20, 30g/kg (suspension) Animals were fasted for 4 hours before dosing.
Test substance	:	Sanwa Chemical (purity = 99.9 %)
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

26.11.2003 (37)

Type	:	LD50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	> 10000 mg/kg bw
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Reliability	:	(3) invalid

03.04.2003 (57)

Type	:	other: LD
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	> 500 mg/kg bw
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Reliability	:	(3) invalid

09.06.2003 (41)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Species : mouse
Strain :
Sex :
Number of animals :
Vehicle :
Route of admin. : i.p.
Exposure time :
Value : > 4000 mg/kg bw
Method :
Year :
GLP : no data
Test substance :
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
03.04.2003 (22)

Type : LD50
Species : Rabbit
Strain :
Sex :
Number of animals :
Vehicle :
Route of admin. : i.p.
Exposure time :
Value : > 3000 mg/kg bw
Method :
Year :
GLP : no data
Test substance :
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.06.2003 (22)

Type : LD0
Species : other: frog
Strain :
Sex :
Number of animals :
Vehicle : Water
Route of admin. : other: breast lymph sinus
Exposure time :
Value : > 3000 mg/kg bw
Method :
Year :
GLP : No
Test substance : other TS
Test substance : 99.6%
Reliability : (4) not assignable
10.10.2003 (2)

Type : LD100
Species : Rat
Strain :
Sex :

Number of animals :
Vehicle :
Route of admin. : other: unreported
Exposure time :
Value : = 600 mg/kg bw
Method :
Year :
GLP : no data
Test substance :
Reliability : (4) not assignable
10.10.2003 (65)

Type : LD0
Species : mouse
Strain :
Sex :
Number of animals :
Vehicle : Water
Route of admin. : s.c.
Exposure time :
Value : > 2200 mg/kg bw
Method :
Year :
GLP : no data
Test substance : other TS
Test substance : 99.6%
Reliability : (4) not assignable
10.10.2003 (2)

Type : LD0
Species : Rat
Strain :
Sex :
Number of animals :
Vehicle :
Route of admin. : other: unreported
Exposure time :
Value : = 400 mg/kg bw
Method :
Year :
GLP : no data
Test substance :
Reliability : (4) not assignable
10.10.2003 (65)

5.2.1 SKIN IRRITATION

Species : guinea pig
Concentration :
Exposure :
Exposure time : 24 hour(s)
Number of animals : 1
PDII :
Result : slightly irritating
EC classification : irritating
Method : other: primary irritation test
Year :
GLP : no data
Test substance :
Result : 50%: positive, the other concentration: negative

Test condition	:	Concentration: 100% (undiluted), 50, 20 10, 5% 6 spots/animal were tested. determination of the efficacy at 24 hours after applicating
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

26.11.2003 (40)

Species	:	Rabbit
Concentration	:	
Exposure	:	
Exposure time	:	4 hour(s)
Number of animals	:	
PDII	:	
Result	:	slightly irritating
EC classification	:	
Method	:	Draize Test
Year	:	
GLP	:	
Test substance	:	other TS
Remark	:	This study showed the comparison in vivo and in vitro method, and this result was adventitious to dicyandiamide.
Test substance	:	This substance tested was dicyandiamide/formaldehyde condensate.
Reliability	:	(4) not assignable

10.10.2003 (7)

Species	:	Rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	not irritating
EC classification	:	not irritating
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Reliability	:	(3) invalid

26.11.2003 (52)

Species	:	guinea pig
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	corrosive
EC classification	:	irritating
Method	:	
Year	:	
GLP	:	
Test substance	:	
Result	:	Dicyandiamide was mildly irritating to the skin of guinea-pigs.
Reliability	:	(3) invalid

26.11.2003 (32)

Species	:	Rat
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	

PDII	:	
Result	:	not irritating
EC classification	:	not irritating
Method	:	
Year	:	
GLP	:	
Test substance	:	
Result	:	No skin irritation was seen following application on 12 successive days to the skin of rats.
Reliability	:	(4) not assignable

10.10.2003 (29)

5.2.2 EYE IRRITATION

Species	:	Rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	not irritating
EC classification	:	not irritating
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Reliability	:	(3) invalid

26.11.2003 (52)

Species	:	Rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	not irritating
EC classification	:	not irritating
Method	:	
Year	:	
GLP	:	
Test substance	:	
Reliability	:	(3) invalid

26.11.2003 (32)

5.3 SENSITIZATION

Type	:	Guinea pig maximization test
Species	:	guinea pig
Concentration	:	5 other: % in 0.5mL Petrolatum at challenge 2.5 other: % in 0.5mL Petrolatum at challenge .5 other: % in 0.5mL Petrolatum at challenge
Number of animals	:	20
Vehicle	:	Water
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	other
Year	:	
GLP	:	no data

Test substance : other TS
Method : Guinea Pig Maximisation test:
The guinea pig maximisation test method [Magnusson B and Kligman A (1970), Wahlberg J E and Fregert S (1985)] with the same experimental design as in the study [Wahlberg J E and Boman A (1978)] was used. One group of 20 animals was actively exposed to cyanoguanidine (techn. British Oxygen Co) and another (control) treated in the same way (FCA, vehicle, occlusion etc.) as the first group except for the test compound. The animals were kept in plastic cages, challenged simultaneously after 3 weeks and the readings were performed blind.
Remark : 1-cyanoguanidine has a wide range, e.g., catalyst for epoxy resins, raw material for plastics, intermediate in organic synthesis, and stabiliser in detergent compositions.
Result : The results are summarized in below table. No significant difference between the actively sensitised and the control group was obtained.

cyanoguanidine concentration % (w/w)		5.0	2.5	0.5	Control (pet.)
controls n = 20	24h	0	0	0	0
	48h	1	0	0	0
exposed n = 20	24h	1	1	2	1
	48h	1	0	0	0
Statistical method	24 and 48h	N.S.	N.S.	N.S.	N.S.

N.S. = not significant
At induction, 1.75% (w/w) cyanoguanidine in water FCA was used for intradermal injection and 25% (w/w) in pet. (after 24h SLS treatment) for topical application. The number of animals with positive test reactions to the different challenge concentrations is given.
Statistical method: chi-square test
Pet.: Petrolatum
Test substance : The purity of test compound is unknown.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (6)

Type : Guinea pig maximization test
Species : guinea pig
Number of animals :
Vehicle :
Result : not sensitizing
Classification : not sensitizing
Method : other
Year :
GLP : no data
Test substance :
Result : It was not possible with this method to sensitize even one guinea pig. These results indicate that the sensitization capacity is exceptionally low.
Test condition : The substance, which was provided in pure from by the manufacturing company and was checked by thin-layer chromatography, was used for sensitization in the FCA (Freund's complete adjuvant) test on 10 albino guinea pigs.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (50)

Type	:	Guinea pig maximization test
Species	:	guinea pig
Number of animals	:	10
Vehicle	:	physiol. saline
Result	:	ambiguous
Classification	:	not sensitizing
Method	:	
Year	:	
GLP	:	no data
Test substance	:	
Remark	:	Guinea pig (species): Hartley
Result	:	----- ---- ---- ----- - +/- + ++ ----- ---- ---- ----- 8 2 0 0 ----- ---- ---- ----- Allergenicity was low.
Test condition	:	Concentration: 20, 10, 5, 1% (challenge) Test period: 24, 48 hour
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

26.11.2003 (40)

5.4 REPEATED DOSE TOXICITY

Species	:	Rat
Sex	:	male/female
Strain	:	Crj: CD(SD)
Route of admin.	:	gavage
Exposure period	:	male: 44 days, female: from 14 days before mating to day 3 lactation
Frequency of treatment	:	once daily
Post obs. period	:	1 day
Doses	:	0 (vehicle), 40, 200, 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 1000 mg/kg
Method	:	OECD combined study TG422
Year	:	1998
GLP	:	Yes
Test substance	:	other TS
Remark	:	Strain: Crj: CD(SD) IGS, A preliminary test to decide the highest level at 100, 300, 1000 mg/kg/day for 14 day was conducted. At each dose, no change was observed. Then the highest dose level for the test was set at 1000 mg/kg/day.
Result	:	This substance had no effect on clinical signs, body weights, food consumption or necropsy findings. The organ weights of kidney, testes and epididymides were similar among all groups. No histopathological changes ascribable to this substance in these organs were found in either sex. The NOAEL for repeat dose toxicity is considered to be 1000 mg/kg/day for both sexes.
Source	:	MHW Japan
Test condition	:	Test Animals - Age: 9 week old - Weight at study initiation: male; 344 - 376 g, female; 204 - 245 g - Number of animals: male; 12, female; 12 Administration / Exposure - Type of exposure: Oral gavage to stomach

- Vehicle: 3% gum arabic solution
- Concentration in vehicle: 0, 8, 40, 200 mg/mL
- Doses: 0, 40, 200, 1000 mg/kg/day
- Volume: 5 mL/kg
Clinical Observation and Frequency:
- Clinical signs: daily
- Mortality: daily
- Body weight and Food consumption: males and females; 0, 3, 7, 14 day from dose start, after then, one day per week. At mated female, 0, 7, 14, 20 day from pregnancy and 0, 4 day from lactation.

Test substance : Purity: 99.8%,
lot No. :L-2271,
NIPPON CARBIDE INDUSTRIES CO.,INC.

Conclusion : The NOAEL for repeat dose toxicity is considered to be 1000 mg/kg/day for both sexes.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

26.11.2003 (39)

Species : rat
Sex :
Strain : Fischer 344/DuCrj
Route of admin. : oral feed
Exposure period : 14 days
Frequency of treatment : ad libitum
Post obs. period : no
Doses : 0, 5, 10% mixed with CRF-1 feed
Control group : yes
NOAEL : = 10 %
Method : other
Year :
GLP : no data
Test substance : other TS
Result : No death was observed during test period.
Decrease in body weight were observed with dose response, although increase in food consumption.
No toxicity was observed to 10% group.
Test condition : Rat: SPF, Charles River Japan
3 animal/group, female
Not converted to mg/kg/day
Test substance : Sanwa Chemical (purity = 99.9 %)
Reliability : (4) not assignable

26.11.2003 (37)

Species : rat
Sex : male/female
Strain : Fischer 344/DuCrj
Route of admin. : oral feed
Exposure period : 13 weeks
Frequency of treatment : ad libitum
Post obs. period : no
Doses : 0, 1.25, 2.5, 5, 10% mixed with CRF-1 feed
Control group : yes
NOAEL : = 2.5 %
Method : other
Year :
GLP : no data
Test substance : other TS
Result : No animals died during the administration period. Inhibition of body weight

gain was more marked in both sexes of the 10 % group and in females of the 5 % group. as compared with the control group. Mean food intake in male of the group treated with 5 % or 10 % and in females of the 10 % group significantly higher than in the control group. Serum biochemical investigation revealed a higher level of serum BUN in both sexes of the 10 % group. On histopathological examination, toxic changes characterized by the occurrence of intranuclear eosinophilic inclusion bodies in the proximal tubular epithelium of the kidney were observed in both sexes of the 10 % group. Similar inclusion bodies were also seen in 2 out of 10 males of 5 % group.
NOAEL is 2.5 %/day for both sexes.

Test condition : Rat: SPF, Charles River Japan
10 animal/group/sex (total 100 animals)

Converted value:
Male;
1.25%: 571 mg/kg/day
2.5%: 1230 mg/kg/day
5%: 2602 mg/kg/day
10%: 5782 mg/kg/day
Female;
1.25%: 707 mg/kg/day
2.5%: 1500 mg/kg/day
5%: 2978 mg/kg/day
10%: 6822 mg/kg/day

Test substance : Sanwa Chemical (purity = 99.9 %)
Reliability : (4) not assignable
26.11.2003 (37)

Species : guinea pig
Sex :
Strain :
Route of admin. : inhalation
Exposure period :
Frequency of treatment : 4 weeks
Post obs. period :
Doses :
Control group :
Method :
Year :
GLP : no data
Test substance :
Result : TCLo = 2400 ug/m3
Reliability : (3) invalid
26.11.2003 (57)

Species : rat
Sex :
Strain :
Route of admin. : inhalation
Exposure period : 4 weeks
Frequency of treatment :
Post obs. period :
Doses :
Control group :
Method :
Year :
GLP : no data
Test substance :

Result	:	TCLo = 2400 ug/m3
Reliability	:	(3) invalid

26.11.2003 (57)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA1535, TA1537 and Escherichia coli WP2uvrA
Concentration	:	0, 156, 313, 625, 1250, 2500, 5000 ug/plate
Cycotoxic conc.	:	No cytotoxicity was observed at any dose.
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: OECD Guide-line 471 and 472
Year	:	
GLP	:	yes
Test substance	:	other TS
Remark	:	Solvent (solvent control): DMSO Positive: Control: Without metabolic activation; 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (TA100, TA98 and WP2uvrA), sodium azide (TA1535), 9-aminoacridine hydrochloride (TA1537) With metabolic activation; 2-aminoanthracene (each strain)
Result	:	Genetoic effect: No increase of revertants was observed at each dose in all strains with or without metabolic activation. - With metabolic activation: Negative - Without metabolic activation: Negative
Test condition	:	System of Testing - Metabolic activation system: S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone Condition: - Number of replicates: 2 - Plates per test: 3 - Application: pre-incubation (37 degree, 20 minutes) - Positive and negative control groups and treatment: - Incubation time: 48 hr Criteria for Evaluating Results: (1) The revertant colony on this substance increase should be more than two times of the control. (2) The concentration dependency should be shown in the revertant colony increase.
Test substance	:	Purity: 99.8% (impurities as melamine are included 0.01-0.02%). lot No. :L-2271, NIPPON CARBIDE INDUSTRIES CO.,INC.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

26.11.2003 (39)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration	:	1, 2.5, 5, 10, 25, 50, 100, 150 ug/plate
Cycotoxic conc.	:	No cytotoxicity was observed at any dose.
Metabolic activation	:	with and without
Result	:	positive
Method	:	other
Year	:	1985
GLP	:	yes
Test substance	:	other TS

Remark	:	The result essentially is not influence of dicyandiamide.
Result	:	The results of the tests conducted on the test material in the absence or presence of a metabolic activation system were positive with the strains TA100 and TA1535. The test material (dicyandiamide included) exhibited genetic activity with the strains TA100 and TA1535 in the nonactivation and activation assays conducted in this evaluation and was considered mutagenic under these conditions according to their evaluation criteria.
Test condition	:	Metabolic activation system: 10% S-9 mix from male Sprague-Dawley induced Aroclor 1254 Solvent: DMSO Negative control: DMSO Positive Control: -S9; Sodium azide, 2-Nitrofluorene, 9-Aminoacridine, +S9; 2-anthramine
Test substance	:	Dicyandiamide was one component of a rigidite. The rigidite was used in this test.
Reliability	:	(4) not assignable

26.11.2003 (30)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration	:	44-9300 ug/plate
Cycotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	positive
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	other TS
Remark	:	The result essentially is not influence of dicyandiamide.
Result	:	Resins tested were weakly mutagenic in strains TA1535 and TA100 in the presence and absence of metabolic activation. The presence of metabolic activation significantly increased the mutagenicity of resins in strain TA1535. However, metabolic activation did not appreciably alter the mutagenicity in strain TA100. Resins were non-mutagenic in strains TA1537, TA1538, and TA98.
Test substance	:	Dicyandiamide was one component of resins as 0.8%. The resin was used in this test. Unknown the influence of cyanoguanidine to the results
Reliability	:	(4) not assignable

26.11.2003 (15)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538
Concentration	:	Without metabolic activation: 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0 mg/plate, With metabolic activation (mouse S-9 mix): 0.1, 0.5, 1.0, 2.5, 5.0 mg/plate, (maize fraction S-14): 0.1, 1.0, 5.0, 10.0 mg/plate
Cycotoxic conc.	:	No cytotoxicity was observed to 1.0 mg/mL.
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	
GLP	:	no
Test substance	:	other TS
Result	:	This substance reduced the numbers of bacterial colonies in plates with 10, 5 or 2.5 mg/plate, respectively. It did not exert mutagenic effects on tester strains incubated was observed in strain TA1535 when tested with 0.1, 0.5 and 1.0 mg per plate.
Test condition	:	Metabolic activation system: S-9 mix from mouse liver homogenate

Plate: Two dish were used.
Application: Preincubation at 37 degree with shaking for 30 minutes.
Solvent: DMSO

Test substance : Chemiekombinat Bitterfeld, G. D. R.
Reliability : (3) invalid
26.11.2003 (56)

Type : Chromosomal aberration test
System of testing : Chinese hamster lung (CHL/IU) cells
Concentration : 24 and 48 hr Continuous treatment without metabolic activation: 210 - 840 ug/mL,
6 hr short-time treatment with or without metabolic activation: 210 - 840 ug/mL
The highest dose (840 ug/mL) was comparable to 10mmoL/L
Cycotoxic conc. : No growth inhibition was observed at any dose.
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"
Year : 1998
GLP : yes
Test substance :
Remark : Solvent (solvent control): saline

Positive: Control:
24 and 48 hr Continuous treatment without metabolic activation: mitomycin C 0.05, 0.025 ug/mL, respectively.
6 hr short-time treatment with or without metabolic cyclophophamide 12.5 ug/mL
Result : Genetoic effect:
No increase of structural or numerical aberration was observed at each dose in all treatments with or without metabolic activation.
- 24 hr continuous treatment without metabolic activation: Negative,
- 48 hr continuous treatment without metabolic activation: Negative,
- 6 hr short-time treatment with metabolic activation: Negative,
- 6 hr short-time treatment without metabolic activation: Negative

Test condition : System of testing:
- Species/cell type: CHL/IU from NISH on Nov.1984
- Metabolic activation system: S9; Rat liver, induced with phenobarbitol and 5,6-benzoflavone
- No. of metaphases analyzed: 200 / dose (100 / dish)
Condition:
- Dose: All treatment; 210, 420, 840 (as 10mmol/L) ug/mL
- Number of replicates: 2
Pre-incubation time: 3 day
Criteria for Evaluating Results:
Negative; < 5%, Equivocal; 5% =< - <10%, Positive; 10% =<

Test substance : Purity: 99.8% (impurities as melamine are included 0.01-0.02%).
lot No. :L-2271,
NIPPON CARBIDE INDUSTRIES CO.,INC.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
26.11.2003 (39)

Type : Sister chromatid exchange assay
System of testing : Chinese hamster ovary cells (CHO-WBL)
Concentration : With metabolic activation: 0.333, 1, 3.3, 10.0 uL/mL,
Without metabolic activation: 0.0333, 0.1, 0.333, 1.0 nL/mL
Cycotoxic conc. : No cytotoxicity was observed to 10 uL/mL.
Metabolic activation : with and without
Result : positive

Method : other
Year : 1985
GLP : yes
Test substance : other TS
Remark : The result essentially is not influence of dicyandiamide.
Result : Without metabolic activation: Statistically significant increases in sister exchanges were observed at 333 nL/mL and 1.0 uL/mL with a dose response established observed the test article is considered positive in the sister chromatid exchange assay under of non-metabolic activation.
With metabolic activation: There were statistically significant increases in sister exchanges were observed at 3.3 uL/mL and 10.0 uL/mL with a dose response established. The test article is considered positive under the condition of metabolic activation in the sister chromatid exchange assay.
Test condition : Metabolic activation system: S-9 from male Sprague-Dawley induced Aroclor 1254, S-9 15 uL/mL of S-9 mix

Controls:
Negative control; McCoy's 5a medium
Solvent control; DMSO
Positive control; Mitomycin C
Test substance : Dicyandiamide was one component of a rigidite.
The rigidite was used in this test.
Reliability : (4) not assignable
26.11.2003 (30)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENITY

Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 104 weeks
Frequency of treatment : ad lib.
Post. obs. period : 9 weeks
Doses : 2.5, 5.0 % (converted values: male; equivalent to 837.2 and 1958.6 mg/kg/day, female; equivalent to 1001.3 and 2169.2 mg/kg/day)
Result : negative
Control group : yes
Method : other
Year :
GLP : no data
Test substance : other TS
Result : -Non-neoplastic lesions

	No. of rats with lesions					
	Male			Female		
Dose (%)	0	2.5	5	0	2.5	5
Effective No. of rats	49	50	49	49	50	50
Liver						
Bile duct hyperplasia	44	46	47	10	15	23**
Hepatocellular altered foci	25	31	33	32	38	40
Kidney						

Intranuclear eosinphilic in the proximal tublar epithelium						
minimal	-	-	6*	-	-	-
Chronic nephropathy						
slight	13	17	21	4	3	3
moderate	10	8	5	1	-	2
severe	1	1	-	-	-	2
Brown pigmentation of proximal tubular epithelium						
minimal	36	12	6	33	14	24
slight	32	34	37	11	32	22
moderate	1	-	1	1	-	1
Heart						
Myocardial fobrosis	48	48	48	26	20	20

*, **: significantly different p<0.05, 0.01, respectively (Fisher's extract test)

There was a dose related inhibition of body weight gain, attaining statistical significance in both sexes of the 5% group and in female s of the 2.5% group as compared with the control from wk 1 to 104 and wk 1 to 65, respectively. After 108 wk , male and females that had received 2.5 or 5% this substance showed a remarkable increase in their body weight. The mean survival times for the control, 2.5 and 5% groups were 109.1, 108.0 and 108.3 wk for males and 109.6, 107.5 and 111.0 wk for females, respectively, with no significant intergroup differences. The survival rates of the 5% female group were higher than the otder groups. The first autopsy was performed at wk 65 when a female rat in the 2.5% group was killed because it became moribund as the result of a malignant fibrous histocytoma. The incidences of tumors in male were almost 100% in all groups, while those for females were within the range 64 to 78%, with the lowest value observed for females of the 5% group. There were no statistically significant differences in overall tumor incidence between the control and treated groups of either sex.
For male of groups, tumors were observed with a high incidence in the testis, followed by the pituitary, adrenal gland, thyroid, pancreas, haematipoietic organs and mammary gland, while in females, tumors of the pituitary, uterus, mammary gland and haematopoietic organs were common. A variety of tumors were also detected in other organs or tissues in all groups of both sexes, but the incidences were very low. The incidence of alveolar/bronchiolar adenomas was significantly increased in males receiving 5% dose, but this was not accompanied by adenocarcinoma development and no comparable increase was observed in females. Significantly decreased incidences of pituitary adenomas in the 2.5% group of males and mammary fibroadenomas in the 2.5% group of females were also noted, but these again were not evident in the other sex and were not dose related. With regard to non-neoplastic lesions, myocardial fibrosis, bile dict hyperplasia, hepatocellular altered foci and chronic nephropathy were seen with a high incidence in bile duct hyperplasia was seen in 5% group of females as compared with the control. However the severity of hyperplasia was slight.
As the earlier 13-wk study indicated the kidney to be a target organ for this substance, it was examined in detail. Two tubular cell adenomas were seen in male of 5% group killed the termination of this study (wk 113) and one nephroblastoma developed in a 2.5% group male but these were without statistical significance. No preneoplastic lesions such as dysplasia of the renal tubular epithelium, were seen. As non-neoplastic lesions, intranuclear eosinophlic bodies in the proximal tubular epithelium were seen in six males attaining significance, and in two females of the 5% group. However, these changes were minimal in severity with a very low occurrence per renal section. Aged-related lesions, such chronic nephropathy and brown pigmentation of proximal tubular epithlium (proved to be haemosiderin by iron stain), were seen in both sexes of all groups,

including the control group, without any statistically significant differences in incidence or severity.

Test condition : Animal:
Five-wk-old specific pathogen free F344 rats of both sexes, purchased from Charles River Japan Inc. (Kanagawa , Japan), were acclimatized for 1 wk before the initiation of the study. Males and females were housed separately, four to a plastic cage, and maintained in an air conditioned animal room at a temperature of 24 plus or minus 1 degree and a relative humidity of 55 plus or minus 5 % with a 12-hr light/dark cycle. The animals were maintained on pulverized basal diet and tap water. The diets with admixtures were prepared every 3 months and stored at 4 degree in a cold room until use, following the findings from the author's previous 13-wk range findings study which confirmed that the test chemical in diets was stable for 3 months at 4 degree.

Experimental design and procedure:
A total of 300 rats (150 of each sex) was divided into three groups, each containing this substance 0 (control), 2.5 and 5%, respectively, ad lib. During the experimental period, all animals were observed daily and any clinical abnormalities or mortalities were recorded. Body weights were measured once a week during the first 13 wk and then every 4 wk until the end of the experimental. Food consumption was measured at the same time as body weight to calculate this substance intake. This substance was withdrawn from the diet after 104 wk, and observation was continued until wk 113, when all survivors were killed after overnight fasting. Blood was collected from all surviving rats through the abdominal aorta under ether anaesthesia, and the following parameters were determined: red blood cells, haemoglobin, haematocrit, white, blood cells and platelet counts, and differential leucocytes from blood smears stained. all rats that died or were killed in extremis during the experiment were subjected to a full post-modern autopsy and examined macro- and microscopically for the presence of non-neoplastic and neoplastic lesions. All organs and/or tissues, including tumor masses, were routinely fixed 10% neutral buffered formalin, embedded in paraffin wax, sectioned 4-5 micrometer, and stained with haematoxylin and eosin. In addition, Berlin blue and periodic acid-Schiff stains were applied to sections of the kidneys of five male and five females of each group, selected randomly from these at the termination of the study.

Statistical analysis:
Data for body weight were statistically analyzed using Student's t-test, and the generalized Wilcoxon test was applied for comparison of survival times. The incidences of animals with tumors, survival rate, and neoplastic and non-neoplastic lesions were analyzed using Fisher's exact probability test.

Test substance : Cyanoguanidine was obtained from Nihon Carbide Co. Ltd, with a purity 99.9%. The substance was white crystalline powder, slightly soluble in water and alcohol.

Conclusion : The present results indicate that this substance is without carcinogenic potential in F344 rats when given in the diet at high dose for an extended period.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (62)

Result : Two-year oral studies in rats, which presumably examined a range of tissues for the development of tumor, apparently gave no cause for concern.

Reliability : (3) invalid
02.07.2003 (49)

5.8 TOXICITY TO REPRODUCTION

Type	:	One generation study
Species	:	rat
Sex	:	male/female
Strain	:	Crj: CD(SD)
Route of admin.	:	gavage
Exposure period	:	male: 44 days, female: from 14 days before mating to day 3 lactation
Frequency of treatment	:	once daily
Premating exposure period		
Male	:	14 days
Female	:	14 days
Duration of test	:	male: 45 days, female: day 4 lactation (42-47 days)
Doses	:	0 (vehicle), 40, 200, 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	= 1000 mg/kg bw
NOAEL F1 Offspr.	:	= 1000 mg/kg bw
Method	:	OECD combined repeated dose and reproductive/developmental toxicity screening test
Year	:	1998
GLP	:	yes
Test substance	:	other TS
Remark	:	Strain: Crj: CD(SD) IGS, A preliminary test to decide the highest level at 100, 300, 1000 mg/kg/day for 14 day was conducted. At each dose , no change was observed. Then the highest dose level for the test was set at 1000 mg/kg/day.
Result	:	This substance had no effects on reproductive parameters such as the mating index, the fertility index, numbers of corpora lutea or implantations, the implantation index, the delivery index, the gestation index, gestation length, parturition or maternal behavior. On examination of neonates there were no significant differences in numbers of offsprings or live offspring, the sex ratio, the live birth index, the viability index or body weight. No abnormal findings ascribable to this substance were found for external features or clinical signs or on necropsy of the offspring. The NOAEL for reproductive and developmental toxicity is considered to be 1000 mg/kg/day for parental animals and offsprings.
Test condition	:	Test Animals - Age: 9 week old - Weight at study initiation: male; 344 - 376 g, female; 204 - 245 g - Number of animals: male; 12, female; 12 Administration / Exposure - Type of exposure: Oral gavage to stomach - Vehicle: 3% gum arabic solution - Concentration in vehicle: 0, 8, 40, 200 mg/mL - Doses: 0, 40, 200, 1000 mg/kg/day - Volume: 5 mL/kg Clinical Observation and Frequency: - Clinical signs: daily - Mortality: daily - Body weight and Food consumption: males and females; 0, 3, 7, 14 day from dose start, after then, one day per week. At mated female, 0, 7, 14, 20 day from pregnancy and 0, 4 day from lactation. Parameters Assessed During Study P and F1: - Clinical observation: daily
Test substance	:	Purity: 99.8%, lot No. :L-2271,

NIPPON CARBIDE INDUSTRIES CO.,INC.

Conclusion	:	The NOAEL for reproductive and developmental toxicity is considered to be 1000 mg/kg/day for parental animals and offspring.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

26.11.2003 (39)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	male/female
Strain	:	Crj: CD(SD)
Route of admin.	:	gavage
Exposure period	:	male: 44 days, female: from 14 days before mating to day 3 lactation
Frequency of treatment	:	once daily
Duration of test	:	male: 45 days, female: day 4 lactation (42-47 days)
Doses	:	0 (vehicle), 40, 200, 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 1000 mg/kg bw
NOAEL Teratogen	:	= 1000 mg/kg bw
Method	:	other: OECD combined repeated dose and reproductive/developmental toxicity screening test
Year	:	1998
GLP	:	yes
Test substance	:	other TS
Remark	:	Strain: Crj: CD(SD) IGS, A preliminary test to decide the highest level at 100, 300, 1000 mg/kg/day for 14 day was conducted. At each dose , no change was observed. Then the highest dose level for the test was set at 1000 mg/kg/day.
Result	:	This substance had no effects on reproductive parameters such as the mating index, the fertility index, numbers of corpora lutea or implantations, the implantation index, the delivery index, the gestation index, gestation length, parturition or maternal behavior. On examination of neonates there were no significant differences in numbers of offsprings or live offspring, the sex ratio, the live birth index, the viability index or body weight. No abnormal findings ascribable to this substance were found for external features or clinical signs or on necropsy of the offspring. The NOAEL for reproductive and developmental toxicity is considered to be 1000 mg/kg/day for parental animals and offsprings.
Test condition	:	Test Animals - Age: 9 week old - Weight at study initiation: male; 344 - 376 g, female; 204 - 245 g - Number of animals: male; 12, female; 12 Administration / Exposure - Type of exposure: Oral gavage to stomach - Vehicle: 3% gum arabic solution - Concentration in vehicle: 0, 8, 40, 200 mg/mL - Doses: 0, 40, 200, 1000 mg/kg/day - Volume: 5 mL/kg Clinical Observation and Frequency: - Clinical signs: daily - Mortality: daily - Body weight and Food consumption: males and females; 0, 3, 7, 14 day from dose start, after then, one day per week. At mated female, 0, 7, 14, 20 day from pregnancy and 0, 4 day from lactation. Parameters Assessed During Study P and F1: - Clinical observation: daily

Test substance : Purity: 99.8%,
lot No. :L-2271,
NIPPON CARBIDE INDUSTRIES CO.,INC.
Conclusion : The NOAEL for reproductive and developmental toxicity is considered to be 1000 mg/kg/day for parental animals and offspring.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
26.11.2003 (39)

5.10 OTHER RELEVANT INFORMATION

Type : other: effect on blood press, respiratory and circulator system
Reliability : (4) not assignable
26.11.2003 (2)

Type : other: topical action on mucosa of horse small intestine
Reliability : (4) not assignable
26.11.2003 (2)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

Memo : Carcinogenicity: Surveillance, incidence of cancer among workers
Result : Cancer site

No. employed 117 men	
Lung	1/117
Stomach	0/117
Colon	1/117
Prostate	1/117
All sites	11/117

Conclusion : Increased incidences of colon and prostate cancers were seen in 790 men working at the calcium carbide plant for at least 1.5 year. Some of men would have been exposed to dicyandiamide. However, a 30-yr follow-up of the 117 workers who were specifically engaged in dicyandiamide and calcium cyanamide production revealed no increases in cancer incident. No excess of cancer was observed among workers in the cyanamide/dicyandiamide production.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (34)

Memo : Skin Irritation
Result : Patch test was conducted for 3 hours.
Cyanoguanidine caused redness at the patched site.
Skin irritation was confirmed.
Test condition : Application: supernatant liquid with cyanoguanidine and saline
Unspecified concentration
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.06.2003 (2)

Memo : Allergic potential (sensitisation)
Result : The patient gave no positive reactions to the standard domestic substance series, rubber chemicals, the paint, plastics and adhesive series or disinfectants. Testing with the substance which he was continually in contact at work showed a strongly positive reaction to dicyanodiamide, and

this was clearly evident even in a dilution of 1:100. The high level of sensitization to this substance was detectable even one year after giving up to the job: renewed patch testing again showed strong reactions to dicyanodiamide.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
31.07.2003 (50)

Memo : Skin Irritation
Result : slightl negative (qusai-negative mentioned in the original)
Sample number: 20 (human)
Test substance: 50g/L
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
31.07.2003 (44)

Memo : Allergic potential (sensitisation)
Result : The authors examined the workers of the Division of Melamine and Dicyandiamide of the Nitrogen Works. In all cases patch tests were carried out by the method of Jadassohn-Bloch with 1 % melamine and dicyandiamide. In subjects with skin changes patch tests with standard allergens were done additionally.
During these investigations two types of skin changes were observed. One showed typical morphological features and course of allergic contact dermatitis. These changes were caused by melamine and dicyandiamide as evidenced by positive results of patch tests. Besides that, erythema of different intensity was observed on the skin exposed to sunlight. Among 6 and/or 9 out of 80 examined showed positive to melamine and/or this substance, however, only one from the same cohort showed positive by application of the mixture melamine and this substance. Because of this contradiction validity of the study was less profound. History data indicated that the factor causing their development was alcohol ingestion. The development of erythema was connected with the action of lime nitrogen and its aetiology was most probably toxic.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
31.07.2003 (54)

Memo : Allergic potential Surveillance (sensitisation)
Result : Thirty-four epoxy resin workers who were symptomatic of dermatitis were tested for allergic response by application of patch with material. The materials were those used in the industry like epoxy compounds and hardeners in use including dicyandiamid. None of the 34 exhibited positive response to dicyandiamid.

Method: patch test (Laeppchenprobe)
Dissolving material : water
Concentration: 2%
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
31.07.2003 (31)

Memo : Occupational dermatitis: Surveillance (sensitisation)
Result : Among hairdressers in Europe many cases of allergic contact dermatitis due to dicyanodiamide derivatives have been reported. This chemical is used in hair-setting lotion to repair split ends and restore thinning hair. The dermatitis begins on the side of the second, third and fourth fingers of the left hand, including the interdigital spaces. Onycholysis develops laters, associated with a brownish discoloration of the distal part of the nail bed. Once exposure to this lotion ceases, the nails gradually grow. The product has recently replaced the sensitizing chemical with a new substance.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (1)

Memo : Occupational dermatitis: Surveillance (sensitisation)
Result : An outbreak of dermatitis at one of the largest construction site in the United States was evaluated. The Evaluation started as a result of a request from one of the workers at the site a Health Hazard Evaluation to be conducted by NIOSH in August 1986. Two nuclear power facilities were under construction at the site, employing more than 5000 workers. The wood that was used for scaffolding and other temporary structures was treated with fire retardant made by mixing dicyandiamide, phosphorus-acid, and formaldehyde in water and applying it to the wood by a vacuum pressure process. Pruritic, maculopapular lesions were noted on the shoulders and flank. Workers reported the rashes began at work and lasted from days to weeks. Between February 2 and October 19, 1986 there was a total of 445 visits from 407 workers to the medical facility for skin related problem. Only 122 visit were made during the same time period the year before. Carpenters had the highest rate of skin related visits to the medical facility, following by laborers and then iron workers. Of all the carpenters who completed a questionnaires (92% of those eligible), 54% reported skin conditions, and 29% met the case definition of possible contact dermatitis. Total phosphate concentrations for the extracts of the fire retardant treated lumber ranged from 4.7 to 7.1 milligrams/gram of wood. Results indicated that no specific agent could be identified, nor was it conclusive that a causal role for the fire retardant lumber existed. The large number of workers afflicted suggested that the causative agent was more likely to have been an irritant than an allergen. The authors state that phosphates can leach from treated lumber by both water and sweat. The increased temperature during the summer season suggests this possible course of events. Construction workers have been advised to handle this lumber with caution, particularly in high temperature and humidity conditions.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
26.11.2003 (51)

Memo : Probable Routes of Human Exposure
Result : NIOSH (NOES Survey 1982-1983) has statistically estimated that 28806 workers (25810 of these are female) are potentially exposed to cyanoguanidine in the United States. Occupational exposure may be through inhalation and dermal contact with this substance at workspace where cyanoguanidine is produced or used. The general population may be exposed to cyanoguanidine via dermal contact with products containing cyanoguanidine.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
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