FOREWORD INTRODUCTION

2,2'-dimethyl-4,4'-methylene bis(cyclohexylamine)

CAS N°: 6864-37-5

SIDS Initial Assessment Report

For

SIAM 13

Bern, Switzerland, 6-9 November 2001

1. **Chemical Name:** 2,2'-dimethyl-4,4'-methylene bis(cyclohexylamine)
2. **CAS Number:** 6864-37-5
3. **Sponsor Country:** Germany
   National SIDS Contact Point in Sponsor Country
   BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit)
   Contact person: Prof. Dr. Ulrich Schlottmann
   Address: Postfach 12 06 29
   D- 53048 Bonn- Bad Godesberg
4. **Shared Partnership with:**
5. **Roles/Responsibilities of the Partners:**

- Name of industry sponsor /consortium
- Process used

6. **Sponsorship History**

- How was the chemical or category brought into the OECD HPV Chemicals Programme ?

7. **Review Process Prior to the SIAM:**
8. **Quality check process:**
9. **Date of Submission:** 14 September 2001
10. **Date of last Update:**

11. Comments:

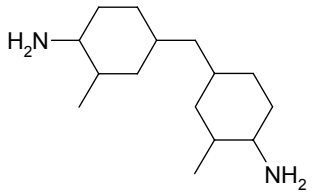
OECD/ICCA - The BUA* Peer Review Process

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications
  (if original reports are missing: reliability (4) not assignable)
- Review o f validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)
- In case of data gaps, review of testing plan or rationale for not testing

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6864-37-5
Chemical Name	2,2'-dimethyl-4,4'methylenebis(cyclohexylamine)
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In humans (epoxy resins production workers) scleroderma-like skin changes have been described revealing 2,2'dimethyl-4,4'methylenebis(cyclohexylamine) as most probable causative agent. In DMD production workers unspecific skin changes, but no scleroderma-like symptoms were seen. DMD is harmful via the oral route and toxic via the dermal and inhalation route:

LD_{50} rat (oral): > 320 < 460 mg/kg bw, symptoms: unspecific;
LC_{50} rat (inhalation, liquid aerosol): 420 mg/m^3/4h, symptoms: irritation of the airways;
LD_{50} rabbit (dermal): > 200 < 400 mg/kg bw, symptoms: cyanosis, necrotic changes at the test site.

The substance is highly corrosive to skin (full thickness necrosis after 3 minutes of exposure) and may cause severe damage to eyes. In the guinea pig maximization test the substance showed no sensitizing effect. In a well conducted rat 90-day inhalation study (OECD TG 413) body weight development was impaired, local irritative effects observed for the skin and upper airways (nasal mucosa) and target organ toxicity indicative of a mild anemic effect as well as effects on the liver, testes and kidneys were seen at 48 mg/m^3. No histopathological correlate was found with respect to increased absolute lung weights. At 12 mg/m^3 the only effect seen was an increase in GPT levels in males. The NOAEC was 2 mg/m^3.

In a subchronic oral toxicity study with rats (OECD TG 408), the animals were exposed to 0, 2.5, 12 and 60 mg/kg bw/day by gavage over 3 months. Liver, white and red blood cells, kidneys, adrenal glands and heart were the target organs for toxic effect showing also histopathological alterations. At the high dose level (60 mg/kg bw/day) body weight development/food consumption were clearly impaired and the general state of health was poor. The absolute testes weight was decreased and an atrophy of the seminiferous tubuli and a reduced content of the seminal vesicle were noted. These changes were interpreted as consequence of the marked impairment on body weight. While the toxic effects at the mid dose of 12 mg/kg bw/day were generally less pronounced, a NOAEL was achieved at 2.5 mg/kg bw/day.

The substance showed no genotoxic effects in the Ames test (OECD TG 471), cytogenetic assay with CHO cells (OECD TG 473) and HGPRT assay (OECD TG 476) when tested up to the cyto-/bacteriotoxic range.

In rat 90-day oral and inhalation studies the substance showed no direct adverse effects to the male and female reproductive organs (testes, ovaries and uterus examined). The observed effects on testes being a secondary non-specific consequence of the severe systemic toxicity (e.g. decrease in body weight) seen at the same dose level. A fertility study is not required under SIDS due to the existence of good 90 day repeated dose toxicity studies with

histopathological evaluation of the sex organs.

In a developmental toxicity study (OECD TG 414) the test substance (0, 5, 15 or 45 mg/kg bw/day) was administered from day 6 to 19 post-coitum orally by gavage to rats. The NOAEL for maternal toxicity was 5 mg/kg bw/day. Slight fetotoxicity (retardation of ossification of skull bones) without teratogenicity was observed at 45 mg/kg bw/day, together with severely reduced body weight of the dams. The NOAEL for developmental toxicity was 15 mg/kg bw/day.

Environment

2,2'-dimethyl-4,4'methylenebis(cyclohexylamine) has a water solubility of 3.6 g/l, a vapour pressure of 0.08 Pa and a measured log Kow of 2.51. However, due to the Lewis base character of the substance the experimental determination of the log Kow is inaccurate.

From the physico-chemical properties the hydrosphere is identified as target compartment for the substance. According to OECD criteria the substance is not biodegradable even with adapted inoculum (OECD TG 302B <1 % after 28 days) and can only be poorly eliminated in sewage water treatment plants. Due to the chemical structure of 2,2'-dimethyl-4,4'methylenebis(cyclohexylamine) hydrolysis is not likely to occur under environmental conditions. In the atmosphere the substance is quickly degraded by photochemical attack (half life =3.1 hours). The log K_{OC} was calculated to 3.26. It has to be considered however, that as a basic compound cyclohexylamine can additionally be bound to the soil by ion exchange. The following aquatic effects concentrations are available:

Leuciscus idus: LC_{50} (96 h) > 22 < 46 mg/l,
Daphnia magna: EC_{50} (48h) = 15.2 mg/l,
Scenedesmus subspicatus: ErC_{50} (72 h) > 5 mg/l; EbC_{50} (72 h) = 2.1 mg/l

With these data the substance is considered as toxic to aquatic organisms. With an assessment factor of 1000 a PNECaqua of 2.1 µg/l can be derived. Results from prolonged or chronic studies are not available. No data are available on terrestrial organisms.

Exposure

The global production volume of 2,2'-dimethyl-4,4'methylenebis(cyclohexylamine) (DMD) in 2000 amounts to 1000 – 5000 t. The total volume was produced in Germany by one company. The substance is mainly used as a hardener in epoxy resins and polyamides. No relevant releases to the environment could be identified. The exposure of workers at the manufacturing and processing site is controlled.

NATURE OF FURTHER WORK RECOMMENDED

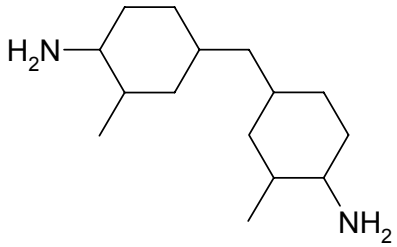
No further work is recommended unless information regarding significant exposure becomes available.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 6864-37-5
Chemical Name: 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine)
Molecular Formula: $C_{15}\ H_{30}\ N_2$
Structural Formula:



Synonyms: 3,3'-Dimethyl-4,4'-diaminodicyclohexylmethan
4,4'-Diamino-3,3'-dimethyldicyclohexylmethane
4,4'-Methylenebis[2-methylcyclohexanamine]
4,4'-Methylenebis[2-methylcyclohexylamine]
Bis(3-methyl-4-aminocyclohexyl)methane
Bis(4-amino-3-methylcyclohexyl)methane

1.2 General Substance information

Substance type: organic (BASF AG 1999)

Physical status: liquid (BASF AG 1999)

Purity: ≥ 99 % w/w (BASF AG 1999)

1.3 Physico-Chemical properties

2,2'-dimethyl-4,4'methylenebis(cyclohexylamine) (DMD) is a colorless/yellowish liquid, with a water solubility of 3.6 g/l at 20°C and a vapor pressure of 0.08 Pa at 20°C. The measured log K_{OW} is 2.51 at 25 °C. However, due to the Lewis base character of the substance, the experimental determination of the log K_{OW} is inaccurate. The density of the substance (ca. 0.95 g/cm^3 at 20°C) is virtually the same than that of water. Sedimentation, flotation or stratification processes are not to be expected in case of accidental losses (BASF AG 1978, 1981, 1984, 1985, 1988a, 1988b).

2 GENERAL INFORMATION ON EXPOSURE

The global production volume of DMD in 2000 amounts to 1000 – 5000 t. The total volume was produced in Germany by one company. Considerably more than half of the production volume was exported. The substance was not imported in 2000 into the European Union. The substance is used as an monomer for specialty plastics and for coatings industry. In Germany DMD is used as hardener in epoxy resins and polyamides.

Information from the Swedish, the Danish and the Swiss product registers confirm the above described use of the substance.

The following exposure information is taken from BUA report 143 (BUA 1994):

The reactivity of the 4 H atoms of the amino groups permits a multiple cross-linkage of DMD with reactive epoxy groups, and thus chemical binding in the cross-linked resins. Among the best known areas of application for DMD-cured resins are the coating of concrete and other building materials, lacquer raw materials and anti-corrosive paints. Such resins can also be employed in shipbuilding and pipeline coating.

An application of the substance without chemical conversion is not known.

During production at the German site no emissions into the atmosphere occur. Approximately 2/3 of DMD-cured epoxy resins are hardened at room temperature. Assuming that, in the case of incomplete reaction, amine traces should remain in the material, emissions are rather unlikely due to the difficulty of diffusion in the cross-linked system. Analytical results of DMD are not available, however. The low vapor pressure is an additional indication against any appreciable introduction of DMD into the atmosphere.

In a very few large plants the curing is carried out at two different temperature levels. The process is initiated at ambient temperature. Only after a marked decrease of the monomer concentration, the final curing of the mixture is then performed at increased temperatures of 60 - 80 °C. The curing process for epoxy resins, if done at increased temperatures, has to be performed in closed chambers. Their equipment with exhaust purification systems is an effective measure to control the inhalation exposure, and can be applied also by small companies. Independent from that, several strategies are pursued to lower the inhalation exposure during the process steps manually done at room temperature. Among these measures are to be named:

- setup of ventilation units at work places;

- mixture of dimethyldicykan with reactive amines to accelerate the initial reaction, and thus shorten the phase of potential exposure for workers;

- use of metering units, to avoid manual mixing;

- implementation of the so-called RTM process, which integrates the two latter measures into a fully automated process.

In DMD production no waste water forms during synthesis which could result in emissions into the hydrosphere. In the distillation of the crude product, waste water is formed during the generation of a vacuum for the distilling apparatus. Analysis of the waste water samples from DMD distillation showed that < 42 kg/a was emitted into the waste water.

No waste-water accumulates during the cross-linkage of epoxy-resins with DMD. Releases into the hydrosphere from processing is thus unlikely to occur.

Releases into the environment due to possible residues of DMD in epoxy resins cannot be quantified but are expected to be low.

2.1 Environmental Exposure and Fate

Distribution modeling using Mackay, Level I, indicates water to be the main environmental compartment (95 %) followed by soil (2 %) and sediment (2 %). However, due to the Lewis base character of the substance, the determination of the log K_{OW} is inaccurate and therefore, also the

distribution modeling with Mackay is not quite correct. However, a qualitative estimation of the environmental distribution also identifies the hydrosphere as target compartment. Due to the chemical structure of DMD, hydrolysis is not likely to occur under environmental conditions. The half-life for photochemical degradation in the atmosphere was calculated to 3.1 h. According to OECD criteria the substance is not biodegradable even by adapted inoculum (OECD 302B < 1 % after 28 days) and can only poorly eliminated in sewage water treatment plants. The log K_{OC} was calculated to 3.26. It has to be considered however, that as a basic compound DMD can additionally be bound to the soil by ion exchange. With a measured log K_{OW} of 2.51 DMD has a low bioaccumulation potential in aquatic organisms (AOP 1992, BASF AG 1990, BASF AG 2001, BUA 1994, Schamp and van Langenhove 1986).

2.2 Human Exposure

According to information from product registers (DK, S, N, FIN, CH) (SPIN-Database 2003; Swiss Product Register 2001) exposure of the consumer is assumed to be insignificant. Workplace-concentrations are not available. Due to the toxicity, the exposure of workers at the manufacturing and processing site is controlled (BASF AG, 1984b; Bakelite AG, 2005). The producer and customers of composite parts of epoxy resins and hardeners are informed and trained to handle the products correctly and safely (Bakelite AG, 2005). DMD is admitted for synthesis of polyamide foils which are used as packing material in foodstuffs. It is not known if it is used in the food area in Germany or other members of the European states. Significant human exposure via food uptake is not expected since there is no evidence in migration studies of DMD in different food contact materials. The detection limit was about 1.2 µg/dm^2. The investigations were carried out according to the guidance for food contact materials (BUA, 2000).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

No studies available. Toxicological experiments show that the compound can be resorbed via the skin, the lung and the gut, causing systemic toxicity.

3.1.2 Acute Toxicity

DMD is harmful via the oral route and toxic via the dermal and inhalation route:

LD_{50} rat (oral): > 320 < 460 mg/kg bw. In this study 5 male and 5 female rats per dose group were dosed with 316; 464; 681 or 1000 mg/kg body weight in 0.5 % aqueous Carboxymethylcellulose preparation. While complete mortality was observed at the highest dose level, mortality rates in the mid dose groups were 90 resp. 70 % and no rats died when treated with 316 mg/kg body weight. Clinical symptoms were unspecific (BASF AG 1979a).

LC_{50} rat (inhalative, liquid aerosol): 420 mg/m^3/4h. In this study 10 rats per sex and dose group were exposed to analytical concentrations of 53; 310; 410 or 620 mg/m^3. While 9 males and 10 females died at the highest concentration, mortality rates in the mid dose groups were 40 resp. 15%. No rats died at the lowest concentration (BASF AG 1979b).

LD_{50} rabbit (dermal): > 200 < 400 mg/kg bw – cyanosis – necrotic skin changes at the application site when 5 animals per sex and per dose group treated with the undiluted test substance were

examined. While 4 males and 5 females died when treated with 400 mg/kg body weight, none of the males and 3 females died when treated with 200 mg/kg body weight (BASF AG 1979a).

These acute toxicity tests were carried out according to protocols comparable to the respective OECD TG with acceptable restrictions (pre-GLP studies; in the oral study no LD_{50} was calculated; in the dermal study too few dose groups were used to calculate a LD_{50}; however, lethality occurred in both studies).

Due to the low vapor pressure no mortalities or symptoms were noted when rats were exposed for 7 hours to an atmosphere saturated with vapors of the compound at 20°C (BASF AG 1979a).

Conclusion

DMD is harmful to health via the oral route and toxic via the dermal and inhalation route in studies with restricted reliability. The restrictions are considered not to impair the estimation of the range of acute toxicity of DMD, therefore no additional testing according to current guidelines is necessary for these endpoints.

3.1.3 Irritation

The undiluted substance was highly corrosive to the skin of rabbits after 3 minutes exposure to the intact skin when necrotic skin changes were observed in 3 out of 4 rabbits. The study design was comparable to OECD TG 404 with acceptable restrictions (pre-GLP study). Full thickness necrosis was diagnosed on day 8 of the study. Severe damage including corneal opacity (not to be considered reversible) was noted, when 0.1 ml of the unchanged test substance was instilled into the eyes of rabbits. The study design was comparable to OECD TG 405 with acceptable restrictions (pre-GLP study) (BASF AG, 1979a).

Conclusion

DMD is corrosive to the skin and leads to severe damage of the eye of rabbits in tests with restricted reliability. The results on irritation are plausible due to the alkalinity of DMD.

3.1.4 Sensitisation

In the GPMT (guinea pig maximization test; intradermal and topical induction with 0.5 % test compound in acetone, dermal challenge with 2 % test compound in acetone) none of the animals (0/15) showed a positive result. The substance thus showed no sensitizing effect (Thorgeirsson 1978). The study design was comparable to OECD TG 406 with acceptable restrictions (pre-GLP study according to original description of the GPMT; no positive control used, however, several simultaneously tested compounds were positive thus proving the sensitivity of the test system). Induction concentration was selected because of systemic toxicity reported in the literature. No information on concentration selection for challenge and on reactions during induction is provided.

Conclusion

In a GMPT with restricted reliability DMD proved not to be sensitizing.

3.1.5 Repeated Dose Toxicity

In a subchronic inhalation study following OECD Guideline 413, rats were exposed to aerosol concentrations of 0, 2, 12 and 48 mg/m³ for 3 months (6 hours/day and 5 days/week). No mortalities occurred. In the high exposure group local irritative effects, typical for alkaline compounds such as amines were observed for the skin (slight hyperkeratosis in 7/10 animals) and upper airways (nasal

mucosa, slight vacuolization of olfactory epithelium in 2/10 high dose males, and in 1/10 high dose females). A clear and statistically significant depression of body weight development was noted in animals of both sexes. Compared to control animals terminal body weight was significantly reduced by 14 % in males ($p < 0.01$) and 8 % in females ($p < 0.05$). Systemic toxicity was mild. Relative organ weight of liver, lung, and kidney was significantly increased in high dose male and female animals on the 1 % or 5 % level of significance. Relative weight of adrenals ($p < 0.05$) and testes ($p < 0.01$) , and absolute lung weight (1.41 g vs 1.18 g in controls, $p < 0.05$) were significantly increased only in high dose male rats. The relative organ weight changes were largely influenced by reduced body weights and were judged to be of minor relevance. Pathological correlates were not found for any of these organs, and histological alterations in the testes were not seen.

Liver was also a target organ in high dose male rats, but not in high dose females, as substantiated by significant increases of serum transaminases GOT and GPT (glutamate oxalo-acetate transaminase and glutamate pyruvate transaminase, both on the $p < 0.01$ level). Activity of GPT in serum was 1.081 µkat/l in high dose male rats compared to 0.845 µkat in control animals. However, no histopathological correlate was seen. Red blood cells were affected in high dose male rats as substantiated by significant reductions ($p < 0.05$) of hemoglobin, hemoglobin per erythrocyte, mean corpuscular hemoglobin concentration, and polychromatosis. In spleen hemosiderin was noted in all high dose animals and extramedulary haematopoesis (9/10 high dose females) was indicative of a mild anemic effect. A test substancerelated effect on kidneys was of borderline significance (slight tubular nephrosis in 6/10 high dose males vs, 1/10 male controls; in females 7/10 mid dose and 9/10 high dose rats vs. 7/10 control animals) with increased relative kidney weights ($p < 0.01$) and increased urea concentration in females ($p < 0.01$; unchanged in males). In the mid dose animals only a marginal yet significant increase of GPT and alkaline phosphatase levels (both at $p < 0.05$) in the male rats were seen. Alkaline phosphatase (AP) was not significantly increased in animals at the higher dose level. Therefore no dose-relation was given for AP, and this finding was not regarded as a treatment-related effect. The increase of GPT in mid dose males was marginal (1.043 µkat/l vs. 0.845 µkat/l in controls) but was considered as adverse effect on liver. GOT (glutamate-oxaloacetate transaminase) was not affected in this animal group. No substance-related effect was noted in the low dose groups. –Therefore, the NOAEC was 2 mg/m³ and the LOAEC was 12 mg/m³ under the conditions of the study, based on the increase of GPT in the mid dose male rats (BASF AG 1992a).

In a subchronic oral toxicity study following OECD TG 408, rats were exposed to 0, 2.5, 12 and 60 mg/kg bw/day by gavage over 3 months. Deaths occurred in the low dose (one female after 37 exposures) and mid dose group (one male, 47 exposures). No substance-related effect was however noted. At the high dose level (60 mg/kg bw/day) body weight development/food consumption were clearly impaired (body weight -42 % in males, -20 % in females) and the general state of health was poor. The relative weights of liver, kidney, adrenals, and testes were significantly increased in males ($p < 0.01$) whereas absolute weights of adrenals were increased ($p < 0.01$) and absolute weight of testes (-18 %, $p < 0.05$) and liver ($p < 0.01$) were significantly decreased, and absolute kidney weight was unchanged. An atrophy of the seminiferous tubuli (4/10 focal, 2/10 diffuse) and reduced contents of the seminal vesicles in all high dose males was noted. These changes as well as the decreased absolute weight of testes were interpreted as consequence of the marked impairment on body weight. As the body weight was reduced more than the testes weight, the relative testes weight was increased.

Table 1 Comparison of absolute body weight and testes weights

Dose (mg/kg bw/day)	absolute body weight (g)	absolute testes weight (g)
0	408	3.64
2.5	406	3.51
12	388	3.59
60	236** (- 42 %)***	2.96* (- 18.6 %)***

* $p < 0.05$; ** $p < 0.01$

*** weight reduction in % compared to control

Liver, white and red blood cells, kidneys, adrenal gland and heart were the target organs showing also histopathological alterations. At 12 mg/kg bw/day the latter effects were generally less pronounced and no effects on testes were observed. Female but not male body weight was reduced by 7 % at day 85. Relative kidney weight was increased in both sexes, relative liver weight was only increased in male rats. Absolute organ weight change was only noted in kidney of males, no other statistical significant change was noted in any other organ nor in females. A NOAEL was achieved at 2.5 mg/kg bw/day (BASF AG 1990b).

Conclusion

The substance may cause local damage as well as systemic toxicity including histopathological changes in several target organs (damage to hematological system, liver, kidney, adrenal gland and heart) after repeated oral uptake and to a lesser extent after inhalative exposure as shown in animal studies.

3.1.6 Mutagenicity

The substance was negative in the Ames Test meeting OECD TG 471 with and without metabolic activation. The doses ranged from 4 to 5000 µg/plate and bacteriotoxicity was noted at doses of 2500 µg/plate and above (BASF AG 1986).

Negative results were also obtained in the cytogenetic assay with CHO (Chinese hamster ovary) cells according to OECD TG 473. The doses ranged from 78 to 313 µg/ml without and 156 to 625 µg/ml with metabolic activation. Cytotoxicity was observed at doses of 313 µg/ml without and 625 µg/ml with S9-mix (BASF AG 1992b).

The test compound was also negative in the HGPRT assay with Chinese hamster V79 cells (OECD TG 476). The cells were exposed to concentrations ranging from 0.03 to 1.2 mg/ml without metabolic activation and 0.1 to 2 mg/ml with metabolic activation. Higher concentrations could not be tested due to severe cytotoxic effects (BASF AG 1992c).

Conclusion

The substance showed no mutagenic and no cytogenetic effect in three different test systems in vitro.

3.1.7 Reproductive toxicity

A fertility study was not conducted. In both subchronic studies available the gonads of male and female animals were histologically examined. In the oral study the decreased absolute testes weight

(-18 %), the atrophy of the seminiferous tubuli and the reduced content of the seminal vesicle were interpreted as consequence of the marked impairment on body weight at 60 mg/kg bw/day (-42 % compared to control animals). As the body weight was reduced more than the testes weight, the relative testes weight was increased. At 12 mg/kg bw/day no effect on the testes occurred (BASF AG, 1992a). In the inhalation study an increase in relative testes weight at 48 mg/m³ was due to impaired body weight gain. Histological alterations were not seen in this study (BASF AG 1990b).

No other adverse effects to the reproductive organs (ovaries and uterus) were found in those studies, nevertheless, toxicity was reported to other organs like liver, kidneys, adrenals or heart **(**BASF AG 1990b; 1992a).

Conclusion

No effects on the reproductive organs of male and female rats occurred in two subchronic studies with the exception of histological alterations of testes compatible with reduced testes weight at an oral dose that severely impaired body weight gain.

3.1.8 Developmental Toxicity

In a developmental toxicity study in rats, the animals were treated orally via gavage from day 6 to 19 post coitum inclusive with doses of 0, 5, 15 or 45 mg/kg bw/day. The test substance was prepared in 0.5 % aqueous carboxymethylcellulose (OECD TG 414 draft of June 2000). Clear maternal toxicity was observed at the high dose level of 45 mg/kg bw/day. especially with regards to corrected body weight gain (-44%) and macroscopic findings (liver) of the dams. At the mid dose (15 mg/kg bw/day) maternal toxicity was less pronounced. There were no substance related effects with respect to gestational parameters. No external or soft tissue findings in fetuses were noted at all doses. A slight but significant retardation of ossification of the skull bones occurred only at the highest dose. The NOAEL for maternal toxicity was 5 mg/kg bw/day. It was 15 mg/kg bw/day with respect to fetotoxicity. The NOAEL for teratogenicity was 45 mg/kg bw/day, the highest dose tested (CIT 2001).

Conclusion

In a study in rats DMD was neither teratogenic nor embryotoxic. The NOAEL for maternal toxicity was 5 mg/kg bw/day. It was 15 mg/kg bw/day with respect to fetotoxicity. The NOAEL for teratogenicity was 45 mg/kg bw/day, the highest dose tested.

3.1.9 Carcinogenicity

There are no carcinogenicity studies available with the substance.

3.1.10 Human Data

Paleness, lip edema, paralysis of neck muscles, and severe cardio-vascular collapse with characteristic electocardiographic anomalies, which could also be induced in rabbits by the test compound, was reported in a subject who unintentionally ingested a "zip" of DMD. Corrosive lesions were not seen in the subject´s mouth (BASF AG 1965).

Scleroderma-like skin changes were reported in 6 of 233 workmen engaged in the polymerization of epoxy resins. A heavily exposure through inhalation was postulated and DMD was indicated as the most probable causative agent. Follow-up investigation in two of the six men showed disappearance of the skin changes within five years (Ishikawea et al. 1982, 1995, Yamakage et al. 1980). In a cross-sectional study 3 of 91 employees in DMD production showed unspecific skin changes, but

no scleroderma-like symptoms. Average employment duration was 11.8 years. Workplace conc. were not reported (BASF AG 1984b).

3.2 Initial Assessment for Human Health

In humans (epoxy resins production workers) scleroderma-like skin changes have been described revealing 2,2'dimethyl-4,4'methylenebis(cyclohexylamine) as most probable causa-tive agent. In DMD production workers unspecific skin changes, but no scleroderma-like symptoms were seen. DMD is harmful via the oral route and toxic via the dermal and inhalation route:

LD50 rat (oral): > 320 < 460 mg/kg bw, symptoms: unspecific;

LC50 rat (inhalation, liquid aerosol): 420 mg/m^3/4h, symptoms: irritation of the airways;

LD50 rabbit (dermal): > 200 < 400 mg/kg bw, symptoms: cyanosis, necrotic changes at the test site.

The substance is highly corrosive to skin (full thickness necrosis after 3 minutes of exposure) and may cause severe damage to eyes. In the guinea pig maximization test the substance showed no sensitising effect. In a well conducted rat 90-day inhalation study (OECD 413) body weight development was impaired, local irritative effects observed for the skin and upper airways (nasal mucosa) and target organ toxicity indicative of a mild anemic effect as well as effects on the liver, testes and kidneys were seen at 48 mg/m³. No histopathological correlate was found with respect to increased absolute lung weights. At 12 mg/m³ the only effect seen was an increase in GPT levels in males. The NOAEC was 2 mg/m³.

In a subchronic oral toxicity study with rats (OECD TG 408), the animals were exposed to 0, 2.5, 12 and 60 mg/kg bw/day by gavage over 3 months. Liver, white and red blood cells, kidneys, adrenal glands and heart were the target organs for toxic effect showing also histopathological alterations. At the high dose level (60 mg/kg bw/day) body weight development/food consumption were clearly impaired and the general state of health was poor. The absolute testes weight was decreased and an atrophy of the seminiferous tubuli and a reduced content of the seminal vesicle were noted. These changes were interpreted as consequence of the marked impairment on body weight. While the toxic effects at the mid dose of 12 mg/kg bw/day were generally less pronounced, a NOAEL was achieved at 2.5 mg/kg bw/day.

The substance showed no genotoxic effects in the Ames test (OECD TG 471), cytogenetic assay with CHO cells (OECD TG 473) and HGPRT assay (OECD TG 476) when tested up to the cyto-/bacteriotoxic range.

In rat 90-day oral and inhalation studies the substance showed no direct adverse effects to the male and female reproductive organs (testes, ovaries and uterus examined). The observed effects on testes being a secondary non-specific consequence of the severe systemic toxicity (e.g. decrease in body weight) seen at the same dose level. A fertility study is not required under SIDS due to the existence of good 90 day repeated dose toxicity studies with histopathological evaluation of the sex organs.

In a developmental toxicity study (OECD TG 414) the test substance (0, 5, 15 or 45 mg/kg bw/day) was administered from day 6 to 19 post-coitum orally by gavage to rats. The NOAEL for maternal toxicity (reduced corrected body weight gain) was 5 mg/kg bw/day, for fetotoxicity (slight retardation of ossification of skull bones) 15 mg/kg bw/day and for teratogenicity 45 mg/kg bw/day. Thus, DMD showed no substance-specific developmental toxicity, since, the only effects seen, slight fetotoxicity, was observed in the presence of maternal toxicity.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The following aquatic effects concentrations of DMD were found in acute toxicity studies on fish, daphnia, algae and bacteria (BASF AG 1987, 1988c, 1988d, 1989):

Leuciscus idus:	LC_{50} (96 h) > 22 < 46 mg/l
Daphnia magna:	EC_{50} (24 h) = 25.5 mg/l
	EC_{50} (48 h) = 15.2 mg/l
Scenedesmus subspicatus:	ErC_{50} (72 h) > 5 mg/l
	EbC_{50} (72 h) = 2.1 mg/l
	ErC_{10} (72 h) = 1.25 mg/l
	EbC_{10} (72 h) = 0.44 mg/l
Pseudomonas pudita:	EC_{50} (17 h) = 96 mg/l

Based on these data DMD is considered as toxic to aquatic organisms (lowest EC/LC_{50} > 1 < 10 mg/l). Results from prolonged or chronic studies are not available (BASF AG 1987, 1988c, 1988d, 1989).

The lowest effect value found was the 72h-EbC_{50} for *Scenedesmus subspicatus* of 2.1 mg/l. Although growth rate can regarded as more reliable parameter in algae growth inhibition tests, the ErC_{50} is not used as basic value for the PNECaqua derivation as no exact value was found for this endpoint and the difference between the two values is only a factor of 2.

With an assessment factor of 1000 a PNECaqua of 2.1 µg/l can be derived. This assessment factor is proposed as only short-term tests are available.

4.2 Terrestrial Effects

No relevant releases to the environment could be identified. Therefore, studies on terrestrial organisms are considered not to be necessary.

4.3 Other Environmental Effects

None.

4.4 Initial Assessment for the Environment

The worldwide production volume of DMD was 1000 - 5000 t in 2000. The total volume was produced in Germany by one company. The substance is used as hardener in epoxy resins and polyamides. No relevant releases into the environment could be identified.

The substance has a low bioaccumulation potential in aquatic organisms. According to OECD criteria the substance is not biodegradable even with adapted inoculum (OECD 302 B: < 1 % after 28 days) and can only be poorly eliminated in sewage treatment plants. Due to the chemical structure hydrolysis is not likely to occur under environmental conditions. The half-life for photochemical oxidative degradation in the atmosphere was calculated to 3.1 h.

From the physico-chemical properties the hydrosphere is identified as target compartment for the substance. A PNEC of 2.1 µg/l was derived from the lowest available effect value by the application of an assessment factor of 1000.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

There is no need for further work, unless information regarding significant exposure becomes available.

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I U C L I D

D a t a S e t

Existing Chemical	ID: 6864-37-5
CAS No.	6864-37-5
EINECS Name	2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine)
EC No.	229-962-1
Index number	612-110-00-1
Molecular Weight	238.42 g/mol
Molecular Formula	C15 H30 N2

Producer Related Part

Company:	BASF AG
Creation date:	12-NOV-1992

Substance Related Part

Company:	BASF AG
Creation date:	12-NOV-1992

Status:	other: The consortium wants to state that this document is declared confidential within the framework of the ICCA/HPV-Prog. and not ready for publication via OECD/WHO. This has to be derestricted by BASF before publication is allowed.
Memo:	master

Printing date:	14-MAR-2005
Revision date:	
Date of last Update:	**14-MAR-2005**

Number of Pages: **77**

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
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Flag: Critical study for SIDS endpoint
14-MAR-2005

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

Mol. Formula: C15 H30 N2
Mol. Weight: 238.41 g/mol

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003

1.1.1 General Substance Information

Substance type: organic
Physical status: liquid
Purity: >= 99 - % w/w
Colour: colourless - yellow
Odour: amine-like

Method: GC
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (1)

1.1.2 Spectra

1.2 Synonyms and Tradenames

2,2'-Dimethyl-4,4'-methylenbis(cyclohexylamin)

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

3,3'-Dimethyl-4,4'-diaminodicyclohexylmethan

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

4,4'-Diamino-3,3'-dimethyldicyclohexylmethane

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

4,4'-Methylenebis[2-methylcyclohexanamine]

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

4,4'-Methylenebis[2-methylcyclohexylamine]

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Bis(3-methyl-4-aminocyclohexyl)methane

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Bis(4-amino-3-methylcyclohexyl)methane

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Cyclohexanamine, 4,4'-methylenebis[2-methyl- (9CI)

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Cyclohexylamine, 4,4'-methylenebis[2-methyl- (6CI, 7CI, 8CI)

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Epi-Cure 113

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Laromin C

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Laromin C 260

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

1.3 Impurities

CAS-No: 7732-18-5
EC-No: 231-791-2
EINECS-Name: water
Mol. Formula: H2 O
Contents: <= .5 - % w/w

Method: DIN 51777
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (1)

1.4 Additives

1.5 Total Quantity

Quantity: 1000 - 5000 tonnes produced in 2000

Flag: Critical study for SIDS endpoint
07-JUL-2003

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: (T) toxic
(C) corrosive
(N) dangerous for the environment
Specific limits: no
R-Phrases: (22) Harmful if swallowed
(23/24) Toxic by inhalation and in contact with skin
(35) Causes severe burns
(51/53) Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-Phrases: (26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(36/37/39) Wear suitable protective clothing, gloves and eye/face protection
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

Remark: INDEX-No.: 612-110-00-1
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (2)

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: corrosive
R-Phrases: (35) Causes severe burns

Remark: INDEX-No.: 612-110-00-1
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (2)

Classified: as in Directive 67/548/EEC
Class of danger: dangerous for the environment
R-Phrases: (51/53) Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Remark: INDEX-No.: 612-110-00-1
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (2)

Classified: as in Directive 67/548/EEC
Class of danger: harmful
R-Phrases: (22) Harmful if swallowed

Remark: INDEX-No.: 612-110-00-1
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (2)

Classified: as in Directive 67/548/EEC
Class of danger: toxic
R-Phrases: (23/24) Toxic by inhalation and in contact with skin

Remark: INDEX-No.: 612-110-00-1
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (2)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Flag: non confidential, Critical study for SIDS endpoint
09-MAR-1994

Type: industrial
Category: Chemical industry: used in synthesis

Flag: non confidential, Critical study for SIDS endpoint
09-MAR-1994

Type: use
Category: other: monomer

Flag: non confidential, Critical study for SIDS endpoint
11-MAR-2004

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

Classified by: other: VwVwS (Germany) of 17.05.1999, Annex 2
Labelled by: other: VwVwS (Germany) of 17.05.1999, Annex 2
Class of danger: 3 (strongly water polluting)

Remark: ID-Number: 1335
Flag: non confidential, Critical study for SIDS endpoint
20-AUG-2003 (3)

1.8.4 Major Accident Hazards

Legislation: Stoerfallverordnung (DE)
Substance listed: yes

Flag: non confidential, Critical study for SIDS endpoint
26-FEB-2001 (1)

1.8.5 Air Pollution

Classified by: TA-Luft (DE)
Labelled by: TA-Luft (DE)
Number: 3.1.7 (organic substances)
Class of danger: I

Flag: Critical study for SIDS endpoint
10-JAN-2003 (4)

1.8.6 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: EINECS No. 229-962-1

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (5)

Type: ENCS
Additional Info: ENCS No. 4-102

Remark: ENCS CLASSIFICATION:
Low Molecular Carbo-polycyclic Organic Compounds.
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (5)

Type: ECL
Additional Info: ECL Serial No. KE-23839

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (5)

Type: other: SWISS
Additional Info: SWISS No. G-8698

Remark: SWISS CLASSIFICATION:
Giftliste 1 (List of Toxic Substances 1), 31 May 1999.
Toxic Category 3.
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (5)

Type: TSCA

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (5)

Type: DSL

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (5)

Type: PICCS

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (5)

Type: AICS

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (5)

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

Memo: Hazardous reactions: Strong exothermic reaction with acids

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (4)

1.12 Last Literature Search

Type of Search: Internal and External
Chapters covered: 3, 4, 5
Date of Search: 22-AUG-2001

Flag: Critical study for SIDS endpoint
13-SEP-2001

Type of Search: Internal and External
Chapters covered: 3, 4
Date of Search: 22-NOV-2002

Remark: update 2003, no new data found
27-JAN-2003

Type of Search: Internal and External
Chapters covered: 5.10
Date of Search: 14-NOV-2002

07-FEB-2003

1.13 Reviews

Memo: BUA report No. 143

Flag: Critical study for SIDS endpoint
31-JUL-2001

2.1 Melting Point

Value: = -7 - -1 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
Flag: Critical study for SIDS endpoint
18-NOV-1999 (6)

2.2 Boiling Point

Value: = 342 degree C at 1013 hPa

Method: other: extrapolated value (based on measured data)

Test substance: Laromin C 260, no further data
Reliability: (2) valid with restrictions
acceptable calculation method
Flag: Critical study for SIDS endpoint
10-APR-2000 (7)

Value: = 346.6 degree C at 1013.25 hPa

Method: other: extrapolated value (based on measured data)

Test substance: Laromin C 260 purity 99.71 % (GC)
Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable and acceptable calculation method
Flag: Critical study for SIDS endpoint
04-FEB-2000 (8)

Value: = 347 degree C at 1013 hPa

Reliability: (4) not assignable
Manufacturer / producer data without proof
18-NOV-1999 (6)

2.3 Density

Type: density
Value: = .944 g/cm³ at 20 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
18-NOV-1999 (6)

Type: density
Value: = .9456 g/cm³ at 20 degree C

Method: other: measured (25 cm3 - glas pycnometer)

Test substance: Laromin C 260 purity 99.9 %
Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
Flag: Critical study for SIDS endpoint
03-AUG-2001 (9)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = .0008 hPa at 20 degree C

Method: other (measured): carrier gas carry along method

Test substance: Laromin C 260 purity 99.5 %
Reliability: (2) valid with restrictions
accepted determination method without detailed documentation
Flag: Critical study for SIDS endpoint
10-APR-2000 (10)

Value: = .0003 hPa at 30 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
18-NOV-1999 (6)

Method: other (measured): static

Result: temperature (°C) / vapour pressure (hPa): 140/1.7; 150/2.8; 160/4.5; 170/6.9; 180/10.4; 190/15.3; 200/22.3; 210/31.9; 220/44.8; 230/61.6; 240/84.0; 250/112; 260/149; 270/195; 280/251
Test substance: Laromin C 260, no further data
Reliability: (2) valid with restrictions
accepted determination method without detailed documentation
Flag: Critical study for SIDS endpoint
10-APR-2000 (7)

Method: other (measured): dynamic with argon

Result: temperature (°C) / vapour pressure (hPa): 107.39/0.20; 113.54/0.30; 121.76/0.50; 127.35/0.70; 133.53/1.00; 146.39/2.00; 154.35/3.00; 165.16/5.00; 172.75/7.00; 181.10/10.00; 198.75/20.00; 209.9/30.00; 224.8/50.00; 235.5/70.00
Test substance: Laromin C 260 purity 99.71 % (GC)
Reliability: (2) valid with restrictions
accepted determination method without detailed documentation
Flag: Critical study for SIDS endpoint
10-APR-2000 (8)

Method: other (measured): dynamic

Result: temperature (°C) / vapour pressure (hPa): 96.38/0.10; 105.97/0.20; 120.53/0.50; 132.74/1.0; 146.18/2.0; 165.30/5.0; 180.27/10.0; 197.83/20.0; 223.7/50.0
Test substance: Laromin C 260 purity 99.5 %
Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
Flag: Critical study for SIDS endpoint
29-NOV-1999 (11)

Method: other (measured): carry along method

Result: temperature (°C) / vapour pressure (hPa): 30.1/0.000337; 40.2/0.00102; 50.0/0.00232; 59.8/0.00585; 79.4/0.0316
Test substance: Laromin C 260 purity 99.71 % (GC)
Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
Flag: Critical study for SIDS endpoint
29-NOV-1999 (12)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = 2.51 at 25 degree C

Method: other (measured): gaschromatographic determination of Laromin C 260 in both equilibrium phases

Method: according to OECD 107
Remark: log Pow is strongly dependent on pH value
Test condition: 25 ml octanol and 25 ml dest. water,
stationary phase: dimethylpolysiloxane-capillary (DB-1),
thickness of film: 1.0 µm, diameter: 0.32 mm, lenght: 30 m,
stove temperature: 230 °C, detector temperature: 250 °C,
sampler temperature: 250 °C,
carrier gas: nitogene, columns heat pressure: 1.75 bar (absolute), total gas flow: 135 ml/min (22 ml/min),
injection amount: 1.0 µl (5.0 µl), instrument: HP 5890 with autosampler, detector: flame ionisation detector
average value from 3 measurements

test was performed in a non-buffered solution (without pH-adjustment)
Test substance: Laromin C 260, no further data
Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
Flag: Critical study for SIDS endpoint
31-JAN-2003 (13)

Partition Coeff.: octanol-water
log Pow: = 3.668

Method: other (calculated): Increment method by Rekker with computerprogramm of firm CompuDrug Ltd.

Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted standard methods, however, due to the LEWIS-base-character of DMD, the determination is inaccurate.
Flag: Critical study for SIDS endpoint
31-JAN-2003 (14)

2.6.1 Solubility in different media

Solubility in: Water
Value: = 3.6 g/l at 20 degree C
pH value: 11
Conc.: 3.6 g/l at 20 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
Flag: Critical study for SIDS endpoint
31-JAN-2003 (6)

2.6.2 Surface Tension

Test type: other: capillary
Value: = 25 mN/m at 230 degree C

Method: other: measured (capillary method)

Test substance: Laromin C 260 unrefined
Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
Flag: Critical study for SIDS endpoint
03-AUG-2001 (15)

2.7 Flash Point

Value: = 173 degree C
Type: closed cup

Method: other: DIN 51 758

Test substance: Laromin C 260, no further data
Reliability: (1) valid without restriction
National standard specification
Flag: Critical study for SIDS endpoint
03-AUG-2001 (16)

2.8 Auto Flammability

Value: = 275 degree C

Method: other: DIN 51 794

Remark: Autoignition temperature
Test substance: Laromin C 260, no further data

Reliability: (1) valid without restriction
National standard specification
Flag: Critical study for SIDS endpoint
03-AUG-2001 (16)

2.9 Flammability

2.10 Explosive Properties

Result: not explosive

Remark: because of chemical structure
Reliability: (2) valid with restrictions
Expert judgement
18-NOV-1999 (17)

2.11 Oxidizing Properties

Result: no oxidizing properties

Remark: because of chemical structure
Reliability: (2) valid with restrictions
Expert judgement
18-NOV-1999 (17)

2.12 Dissociation Constant

2.13 Viscosity

Value: 142 mPa s (dynamic) at 20 degree C

Remark: Hazardous reactions: Exothermic reaction with acids
Reliability: (4) not assignable
Manufacturer / producer data without proof
Flag: Critical study for SIDS endpoint
11-MAR-2004 (6)

2.14 Additional Remarks

Result: Explosion limits in air: 0.5 - 2.8 Vol.%
Test substance: Laromin C 260, no further data
Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
Flag: Critical study for SIDS endpoint
18-NOV-1999 (16)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: = .0000000001249 cm³/(molecule * sec)
Degradation: = 50 % after 3.1 hour(s)

Method: other (calculated): AOP, V 1.5
Year: 1992

Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
03-AUG-2001 (18)

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH

Remark: A rate constant (K(OH)) for the reaction of gaseous DMD with OH-radicals in the atmosphere is not determined up to now. According to Atkinson (1988) an estimated value K(OH)= 1.4*10^-10 cm^3/molecule*sec is derivable. Based on a mean global OH-concentration of 5*10^5 molecules/cm^3 in the troposphere a half life (t1/2) of 2.8 h can be estimated.
05-JUL-2002 (19)

3.1.2 Stability in Water

Method: other
Test substance: as prescribed by 1.1 - 1.4

Remark: hydrolysis of the chemical is unlikely to occur, due to the chemical structure of the compound
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
05-JUL-2002 (20)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: adsorption
Media: water - sediment

Method: other

Remark: Investigations to geoaccumulation are not available. Calculations of the Koc coefficient varried strongly (Koc = 48 - 553). According to Litz (1990) the sorption onto soil is low to moderate. As a basic compound DMD could be better bond onto soil due to ion exchange. DMD has a low mobilization in soil and a transport to groundwater is not expected

equations used to calculate log Koc:

a) log Koc = 48:
log Koc = 3.64 - 0.55 * log water solubility
(water solubiltiy: 3.6 g/L)

b) log Koc = 553:
log Koc = 1.377 + 0.544 * log Pow
(log Pow = 2.51)

Reliability: (2) valid with restrictions
acceptable scientific publications

11-MAR-2004 (20) (21) (22) (23)

Type: adsorption
Media: water - sediment
Method: other: calculated: PCKOCWIN v1.63

Result: log Koc = 3.26 (Koc = 1838)
Reliability: (2) valid with restrictions
scientifically accepted method
Flag: Critical study for SIDS endpoint
11-MAR-2004 (24)

Type: volatility
Media: water - air
Method: other

Remark: Henry's law constant at 20 °C can be calculated for DMD as H = 5.3*10E-3 Pa*m3/mol.
According to THOMAS (1990) DMD is characterized as less volatile than water.
Reliability: (2) valid with restrictions
acceptable scientific publications
22-AUG-2001 (25) (26)

3.3.2 Distribution

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

Remark: due to the Lewis base character of the substance the distribution modeling with Mackay is not quite correct. The modeling is for the uncharged molecule
Result: water: 95.1 %, soil: 2,4 %, sediment: 2.3 %, air: 0.2 %
Reliability: (2) valid with restrictions
acceptable calculation method
Flag: Critical study for SIDS endpoint
11-MAR-2004 (20)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, industrial, adapted
Concentration: 341 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: < 1 % after 28 day(s)
Result: under test conditions no biodegradation observed

Method: other: following OECD 302 B
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: the test was performed with preadapted sludge. To adapt the inoculum, sludge was incubated in the presence of the chemical (400 mg/l DOC) and yeast extract (100 mg/l) for 14 days.
Result: - measured pH-values:

time (day)	pH
0	7.0
3 (hours)	8.0
1	8.3
7	7.7
14	7.2
21	6.5
28	6.8

- the determination of the biochemical oxygen demand gave a BOD5/COD quotient of nearly 0 %.
Reliability: (2) valid with restrictions
comparable to guideline study with acceptable restrictions
Flag: Critical study for SIDS endpoint
05-JUL-2002 (27)

3.6 BOD5, COD or BOD5/COD Ratio

Method: other

C O D

Method: other
Year:
COD: = 2750 mg/g substance

R A T I O B O D 5 / C O D

BOD5/COD: = 0
Method:
Remark: BSB5 <2 mg/g
31-JAN-1994 (28)

3.7 Bioaccumulation

Method: other

Remark: There is no indication of an appreciable bioaccumulation potential (log Pow = 2.51).
No experimental derived data are available.
05-JUL-2002 (29)

BCF: 27

Method: other: calculated

Remark: log BCF = 0.85 log POW - 0.7 = 1.4335 (BCF = 27)
22-AUG-2001 (21)

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: 21.5
LC0: 21.5
LC50: > 22 - 46.4
LC100: 46.4

Method: other: closely followed German Industrial Standard DIN 38 412, Part 15
Year: 1982
GLP: no
Test substance: other TS: 3,3´-Dimethyl-4,4´-Diaminodicyclohexylmethan; purity: >99.5 %

Remark: closely followed the German National Standard DIN 38 412, Part 15 (1982):
- animal species: Leuciscus idus L., golden variety (golden orfe)
- test water: reconstituted freshwater was prepared from fully demineralized tap water according to DIN 38 412, Part 11 (1982) that was resalted by the addition of 294.0 mg/L CaCl2.2H2O, 123.3 mg/L MgSO4.7H2O, 63 mg/L NaHCO3 and 5.5 mg/L KCl
- test water had a total hardness of 2.5 mmol/L, an acid capacity of 0.8 mmol/L, ratio Ca/Mg ions = 4:1, ratio Na/K ions = 10:1 and a pH of about 8
- volume of water: 10 L
- aeration: slight
- photoperiod: 16 h light and 8 h darkness
- No. of animals per test concentration: 10
- loading (G fish / L test water): 1.3
- test vessels: all-glass aquarium (30 * 22 * 24 cm)
- temperature: 20 °C +-1 °C
- withdrawal of food: 1 day before and during exposure
- duration of adaptation to test water and test temperature: 3 days
- body length: 5.2 cm (range: 4.3 - 6.0 cm)
- body weight: 1.3 g (range: 0.7 2.1 g)
- positive control of animals conducted with chloracetamide: LC50 (48 h): approx. 31 mg/L (this lethal concentration corresponds to the nominal sensitivity)
- test concentration: 10.0, 21.5, 46.4, 100.0 mg/L
- pH neutralized test solution: to study the effect of the rel. high pH on the toxicity the concentration 100 mg/L was tested in parallel after pH-adjustment (with HCl-solution)
- preparation to test substance: the product was added to the test water without any pretreatment. Subsequently the fish were placed into the aquaria

- pH values after 1 h and 96 h:

concentration (mg/L)	pH (1 h)	pH (96 h)
10.0	7.8	7.7

21.5	8.3	7.7	
46.4	9.1		
100.0	9.7		
control	7.8	7.7	
100.0 (*)	7.7	7.7	

(*) test solution after pH-adjustment

- oxygen values after 1 h and 96 h:

concentration (mg/L)	oxygen (1 h)	oxygen (96 h)
10.0	8.1	8.4
21.5	8.2	8.3
46.4	8.2	
100.0	8.8	
control	8.0	8.1
100.0 (*)	8.5	8.6

(*) test solution after pH-adjustment

- the controls were the test water without the test substance

- median lethal concentration (LC50) were calculated using Probit Analysis (#)

(#) Finney D.J., Probit Analysis, Cambr. Univ. Press, 3. edition, 1971

Result: observed symptoms: tumbling (1 h: 46.4 mg/L); restlessness (48 h, 72 h, 96 h: 100 mg/L, after pH-adjustement)

no observable effect concentration: 21.5 mg/L
maximum concentration causing no mortality: 21.5 mg/L
minimum concentration causing 100 % mortality: 46.4 mg/L

total No. of living fish at the beginning and after 96 h:

concentration (mg/L)	No. of living fish (0 h)	(96 h)
10.0	10	10
21.5	10	10
46.4	10	0
100.0	10	0
control	10	10
100.0 (*)	10	2

(*) after pH-adjustment

a minor reduction of the toxic effect was observed when testing a sample (100 mg/L) after pH-adjustment

Reliability: (1) valid without restriction
closely followed German National Standard

Flag: Critical study for SIDS endpoint

11-MAR-2004 (30)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: = 6.25
EC50: = 15.2
EC100: = 25

Method: other: Directive 79/831/EEC, Annex V, Part C
Year: 1984
GLP: no
Test substance: other TS: Dimethyldicykan; purity: >99.5 %

Method: Procedures to determine EC-values after 48 h:
- EC50: moving average (#)
- EC0: highest concentration tested at which <= 10 % of the animals were immobile
- EC100: lowest tested concentration at which 100 % of the animals were immobile;

static acute toxicity test

(#) Thompson W.R., Bacteriological Reviews, 11, 2, 115-145, 1947

Remark: Test conditions:
- dilution water: source: tap water; pretreatment steps: (1) 6 µm- and charcoal-filtration; (2) H_2SO_4 was added to reduce alkalinity up to pH 4.3; (3) distilled water was added to reduce water-hardness; (4) water was aerated (oil-free air) unil saturated with oxygen; (5) water was stored for at least 24 h for stabilization. Specifications measured at test start: water-hardness: 2.59 mmol/L, alkalinity up to pH 4.3: 0.84 mmol/L, pH: 7.8, conductivity: 620 µSiemens/cm
- water solubility: >100 mg/L at 21 °C (293 K)
- O_2-content: > 2 mg/L
- illumination: diffuse light
- temperature: 20-22 °C (292-294 K)
- test volume: 10 ml
- test vessels: test tubes (glass) with flat bottom (nominal volume 20 ml)
- replicates: 4 per concentration
- volume/animal: 2 ml
- number of animals/vessel: 5
- total number of animals/conc.: 20
- age of animals: 2-24 h
- observation times: visually after 0, 3, 6, 24 and 48 h
- observation parameters: swimming ability, pH, oxygen
- test concentrations: 0.781, 1.56, 3.12, 6.25, 12.5, 25.0, 50.0, 100.0 mg/L

Result: Number of mobile test animals after exposure (48 h) to various test concentrations:

concentration (mg/L)	mobile Daphnids
0.781	19
1.56	20
3.12	19
6.25	18
12.5	17
25	0
50	0
100	0
control	20

effect values after 48 h:
EC50 = 15.16 mg/L
95 % confidence limits: 13.43 - 16.89 mg/L

effect values after 24 h:

EC0 = 12.5 mg/L
EC50 = 25.19 mg/L
95 % confidence limits: 19.26 - 31.12 mg/L
EC100 = 50 mg/L

range of pH at start: 7.58 (control) - 9.98 (100 mg/L)
range of pH after 48 h: 7.91 (3.12, 6.25 mg/L) - 8.59 (100 mg/L)

range of O2 (mg/L) at start: 7.47 (control) - 8.93 (12.5 mg/L)
range of O2 (mg/L) after 48 h: 8.0 (50 mg/L) - 8.38 (control)

Reliability: (1) valid without restriction
guideline study

Flag: Critical study for SIDS endpoint

05-JUL-2002 (31)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: = 1.25
EC50: > 5

Method: other: German Industrial Standard DIN 38412, Part 9, Determination of inhibitory effect on the cell multiplication
Year: 1987
GLP: no
Test substance: other TS: 3,3´-Dimethyl-4,4´-Diaminodicyclohexylmethan; purity: 99.9 %

Method: according to OECD 201 (1984)
Result: - The EC values are calculated (linear regression analysis) from the concentration-response relationship
- The EC - values are given in nominal concentration

- endpoint: biomass
EC10 (72 h) = 0.44 mg/l EC10 (96h) = 0.41 mg/l
EC50 (72 h) = 2.1 mg/l EC50 (96h) = 1.6 mg/l

- endpoint: growth rate
EC10 (72 h) = 1.25 mg/L EC10 (96 h) = 0.98 mg/l
EC50 (72 h) > 5.0 mg/L EC50 (96 h) > 5.00 mg/l

- pH values

concentration (mg/L)	time (0 h)	(72 h)	(96 h)
control	8.2	8.9	9.2
0.313	8.2	8.9	9.1
0.625	8.2	8.7	9.0
1.25	8.2	8.5	8.8
2.5	8.2	8.6	8.7
5.0	8.2	8.3	8.4

Test condition: - Test strain: Scenedesmus subspicatus CHOD
- it is the aim of the study to determine the effect of a substance on the growth of single-cell green algae as

representatives of primary producers in freshwater plankton
- test concentrations: 0.313, 0.625, 1.25, 2.5, 5.0 mg/L
- inoculum density: about 10000 cells/ml
- duration of the test: 96 hours
- test temperature: 23+- 2 °C
- test vessel: Erlenmeyer flaks (nominal volume 250 ml)
- test volume: 50 ml, static test
- illumination: artificial light - permanent illumination,
- light intensity: 120 µE/m2s
- cell counting after 48, 72 and 96h
- measurement of pH-values after 0, 72 and 96 h

Reliability: (1) valid without restriction
following national standard

Flag: Critical study for SIDS endpoint

11-MAR-2004 (32)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: = 72
EC50: = 96
EC90 : = 120

Method: other: German Industrial Standard DIN 38412, Part 8, Determination of the inhibitory effect on the cell multiplication
Year: 1987
GLP: no
Test substance: other TS: Laromin C 260; purity: 99.5 %

Remark: pre-culture:
- species: Pseudomonas putida, DSM 50026
- incubated at 24 °C (297 K +- 1 K), 150 rpm for 7+-1 h
- medium: AK-medium according to DIN 38412, Part 8 (draft)
- test vessel: 300 ml-Erlenmeyer flasks, 1 baffle
- liquid volume: 100 ml

test-culture:
- test vessel: Penicillium glass vessel
- liquid volume: 10 ml
- inoculum: 1 ml pre-culture (adjusted to 10 TE/F)
- test medium: AK-medium according to DIN 38412, Part 8 (draft)
- test concentrations (nominal): 0.977, 1.953, 3.91, 7.81, 15.63, 31.25, 62.5, 125, 250, 500 mg/L mg/L
- replicates: inoculated: 4 per concentration and control; non-inoculated: 1 per concentration
- incubated at 20°C (292 K), 150 rpm for 17 h
- measurements: photometric determination at 436 nm and pH at test start and after 17 h

Result: - range of pH:
at test start: 7.4 (3.91, 1.95, 0.98 mg/L, w/o cells) - 10.4 (500 mg, w/o cells)
after 17 h: 4.8 (62.5, 31.25, 15.63, 3.91, 1.95 mg/L, w cells) - 8.5 (500 mg/L, w cells)

- inhibition (%) after 17 h:

test concentration (mg/L)	inhibition (%)
control	--
0.977	- 8.11 (*)
1.953	- 4.32 (*)
3.91	- 6.87 (*)
7.81	- 8.31 (*)
15.63	- 7.06 (*)
31.25	- 5.56 (*)
62.5	- 4.97 (*)
125	98.4
250	99.4
500	99.5

(*) no inhibition but growth promotion

Reliability: (1) valid without restriction
test procedure following national standard
Flag: Critical study for SIDS endpoint
11-MAR-2004 (33)

Type: aquatic
Species: activated sludge, domestic
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:** no
EC20 : = 160

Method: other: Test for Inhibition of Oxygen Consumption by Activated Sludge, ISO 8192
Year: 1977
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: test concentrations: 1000, 500, 100, 50, 10 mg/L (nominal)
Reliability: (2) valid with restrictions
acceptable study, meets basic scientific principles
Flag: Critical study for SIDS endpoint
05-JUL-2002 (34)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 10
Vehicle: other: 0.5% aqueous CMC
Doses: 316, 464, 681, 1000 mg/kg bw
Value: 320 - 460 mg/kg bw

Method: other: BASF-Test
GLP: no

Result: LD50 >320 <460 mg/kg bw. No deaths were observed at the lowest dose level; 7, 9, and 10 rats dosed with 464, 681, and 1000 mg/kg bw, respectively, died. All deaths occurred within 1 day after dosing. No specific clinical symptoms were noted apart from occasional salivation and blood in stool.
Gross pathology revealed reddening in stomach and gut, scattered occurence of gastric ulcer, and diarrheic gut contents in victims. No changes were noted in organs of sacrificed animals.
Test condition: Groups of 5 male and 5 female rats were administered the test substance at dose levels of 316, 464, 681, or 1000 mg/kg bw; the test substance was administered as a 3.16-10% emulsion in 0.5% aqueous carboxymethylcellulose (CMC) by oral gavage. Dose volume was 10 ml/kg body weight. After dosing, the rats were observed for 14 days.
Test substance: Laromin C 260 liquid
(3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane)
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions (pre-GLP study). The study documentation does not state whether the animals were fed or fasted, as it is often the case in pre-guideline studies. However, the described toxicity fits well into the overall toxicity profile of the test substance.
Flag: Critical study for SIDS endpoint
05-MAY-2004 (35)

Type: LD50
Species: rat
Vehicle: other: Lutrol
Value: ca. 550 mg/kg bw

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Original value: ALD50 = 550 mg/kg

The test substance was administered in Lutrol. Deaths occurred within 1 to 2 days after dosing, without any striking clinical symptoms observed.

Test substance: Laromin C 260 (Dimethyldicykan)

Reliability: (4) not assignable
Documentation insufficient for assessment

12-DEC-2002 (36)

Type: other: lethal dose
Species: rabbit
Vehicle: water
Doses: 50, 100 mg/kg bw
Value: 50 - 100 mg/kg bw

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The test substance, either the hydrochloride or the free amine, was dissolved in water and administered to rabbits (pH = 7). Clinical signs included convulsions and a single case of proteinuria. Autopsy revealed a kidney damage in two animals that died.

Doses and mortality:

dose and substance	mortality
50 mg/kg bw (amine)	2/6
50 mg/kg bw (hydrochloride)	0/3
100 mg/kg bw (hydrochloride)	2/2

Test substance: Laromin C 260 (Dimethyldicykan)

Reliability: (3) invalid
Significant methodological deficiencies (only two dose levels tested, low number of animals); does not meet the criteria of today's standard methods

13-DEC-2002 (37)

Type: other: lethal dose
Species: rabbit
Vehicle: other: Lutrol, water
Doses: 100, 200 mg/kg bw
Value: < 100 mg/kg bw

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The test substance was administered as the amine (vehicle: Lutrol) or as the hydrochloride (vehicle: water).

Doses and mortality:

dose [mg/kg]	mortality after administration of the amine	hydrochloride (pH = 7)
100	1/1	1/1
200	1/1	1/1

Test substance: Laromin C 260 (Dimethyldicykan)
Hydrochloride of Laromin C 260 (Dimethyldicykan hydrochloride)

Reliability: (3) invalid

Significant methodological deficiencies (only two dose levels tested, low number of animals); does not meet the criteria of today's standard methods

12-DEC-2002 (36)

Type: other: lethal dose
Species: rabbit
Sex: male/female
Vehicle: other: no vehicle
Doses: ca. 47, 94, 189 mg/kg bw (50, 100, 200 µl/kg bw)
Value: < 47 mg/kg bw

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The undiluted test substance was applied to the oral mucosa or by gavage at dose levels of ca. 50, 100, and 200 mg/kg bw (original values: 0.05, 0.1, and 0.2 ml/kg bw, respectively; density = 0.944 g/ml). All animals died/had to be sacrificed between 20 minutes and 3 days after dosing (see table):

Dosing and mortality:
a) application on the oral mucosa

dose	deaths	time of death
0.05 ml/kg bw	3/3	sacrificed 1 day after dosing
0.1 ml/kg bw	1/1	died at 45 min. after dosing
0.2 ml/kg bw	3/3	died at 20 min. - 1 h after dosing

b) administration by gavage

dose	deaths	time of death
0.05 ml/kg bw	2/2	sacrificed 3 days after dosing
0.1 ml/kg bw	2/2	died at 1 h / sacrificed at 2 days
0.2 ml/kg bw	2/2	died at 1 h after dosing

Test substance: Laromin C 260 (Dimethyldicykan)
Reliability: (4) not assignable
Documentation insufficient for assessment

13-DEC-2002 (38)

Type: other: lethal dose
Species: cat
No. of Animals: 6
Doses: 100 mg/kg bw
Value: > 100 mg/kg bw

Method: other
GLP: no
Test substance: other TS: 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamin) hydrochloride

Remark: Administration of 100 mg/kg bw of the hydrochloride to six cats did not cause any death.
Test substance: Hydrochloride of Laromin C 260 (Dimethyldicykan hydrochloride)
Reliability: (4) not assignable
Documentation insufficient for assessment

13-DEC-2002 (37)

Type: other: lethal dose
Species: cat
Vehicle: other: Lutrol, water
Doses: 50, 100, 200 mg/kg bw
Value: <= 100 mg/kg bw

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The test substance was administered as the amine (vehicle: Lutrol) or as the hydrochloride (vehicle: water).

Doses and mortality:

dose [mg/kg]	mortality after administration of the amine	hydrochloride (pH = 7)
50	not tested	0/2
100	0/2	2/3
200	1/1	0/1

Test substance: Laromin C 260 (Dimethyldicykan)
Hydrochloride of Laromin C 260 (Dimethyldicykan hydrochloride)
Reliability: (3) invalid
Significant methodological deficiencies (low number of animals); does not meet the criteria of today's standard methods; documentation insufficient
13-DEC-2002 (36)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 80
Doses: 0.053, 0.31, 0.41, 0.62 mg/l (analytical concentration) [0.31, 1.41, 1.83, 2.13 mg/l (nominal concentration)]
Exposure time: 4 hour(s)
Value: .42 mg/l

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: LC50 (4 h) = 0.42 mg/l (males and females)
LC50 (4 h) = 0.44 mg/l (males)
LC50 (4 h) = 0.40 mg/l (females)

Groups of 10 male and 10 female rats were exposed to the test substance for 4-hours (dynamic head-nose exposure to an aerosol) and were observed for 14 days. Aerosol generator used compressed air to evaporate TS and delivered the atmosphere with a slight pressure of 3 Pascal. TS concentration was analytically monitored. Statistical evaluation included a probit analysis accordinmg to D.J. Finney.

Test concentrations and mortality:

concentration [mg/l]		deaths	
analytical	nominal	male	female
0.62	2.13	9/10	10/10
0.41	1.83	3/10	5/10
0.31	1.41	2/10	1/10
0.053	0.31	0/10	0/10

Clinical symptoms were indicative of a marked irritant effect on the airways and eyes (corneal opacity). Some retardation in body weight gain was observed in the treated animals during the post observation. However, there was no clear dose-response and body weights were not statistically significantly different from control at the end of the postobservation period.

Test substance: Laromin C 260 (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane); according to the authors, purity was >98%

Reliability: (2) valid with restrictions
Comparable to guideline study with restrictions (pre-GLP): concentration was measured, but not humidity, temperature and particle size.

Flag: Critical study for SIDS endpoint

05-MAR-2004 (39)

Type: other: IRT
Species: rat
No. of Animals: 12
Vehicle: other: no vehicle
Exposure time: 8 hour(s)

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: No mortality was observed when 6 rats were exposed for 4 hours to an atmosphere that has been saturated at 20 degrees Centigrade with the volatile part of the compound.
1/6 rats died by 8 hours of inhalation to an atmosphere that has been saturated at 20 degrees Centigrade with the volatile part of the compound. According to the authors, this death may not be substance-related.

Test substance: Laromin C 260 (Dimethyldicykan)

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, acceptable for assessment. Similar to the "Inhalation Hazard Test". Restriction: less animals used than required by OECD TG 403; details of atmosphere generation not reported; no analytical concentration measurement result reported.

21-AUG-2003 (36)

Type: other: IRT
Species: rat
Sex: male/female
No. of Animals: 12
Vehicle: other: no vehicle
Exposure time: 7 hour(s)

Method: other: according to Smyth, H.F. et al.: Am. Ind. Hyg. Ass. J.

23, 95-107
Year: 1962
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: No mortality or clinical symptoms were observed when 12 rats were exposed for 7 hours to an atmosphere that has been saturated at 20 degrees Centigrade with the volatile part of the compound.
Test substance: Laromin C 260 liquid (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane)
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
Flag: Critical study for SIDS endpoint
13-DEC-2002 (35)

Type: other: IRT
Species: mammal
No. of Animals: 2
Vehicle: other: no vehicle
Exposure time: 6 hour(s)

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The inhalation toxicity of the test substance was evaluated in cats, rabbits, and guinea pigs.
No mortality or clinical symptoms/findings were observed when 2 cats, 2 rabbits, and 2 guinea pigs were exposed for 6 hours to an atmosphere that has been saturated at 20 degree Centigrade with the volatile part of the compound.
Test substance: Laromin C 260 (Dimethyldicykan)
Reliability: (4) not assignable
Documentation insufficient for assessment
12-DEC-2002 (37)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Sex: male/female
No. of Animals: 10
Vehicle: other: no vehicle
Doses: 200, 400 mg/kg bw
Value: 200 - 400 mg/kg bw

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: 400 mg/kg bw: After day 7 4/5 males and 5/5 female rabbits died and
mortality ocurred mainly within the first 24 hours
200 mg/kg bw: None of the 5 male rabbits died and 3/5 femnales died within
24 hours. Thus LD50 was >200 and <400 mg/kg bw.

Major clinical symptoms were cyanosis, abnormal position, tremor,
impairment of respiration. All surviving animals developed necrotic skin
changes at the site of application.

Test condition: Two groups of 5 males and 5 females each were applied the undiluted test substance at doses of 200 and 400 mg/kg bw and were observed for 14 days. Area of skin treated: 50 cm² (200 mg/kg bw) and 45 - 102 cm² (400 mg/kg bw). Testsite preparation: the test compound was applied to the shaven, intact skin. The test patch was occlusive. The exposure period was 24 hours. The observation period was 14 days.

Test substance: Laromin C 260 liquid (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane)

Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions. Restriction: two dose levels; scarce study report omitts details of test conditions which are, however, contained in raw data.

Flag: Critical study for SIDS endpoint

28-AUG-2003 (35)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Vehicle: other: Lutrol
Route of admin.: i.p.
Value: ca. 47 mg/kg bw

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Original value: ALD50 ca. 50 µl/kg

ALD50 was determined in a preliminary study for a carcinogenicity study; 21 rats were used; the test substance was administered as a solution in Lutrol.

Test substance: Laromin C 260 (Dimethyldicykan)
Reliability: (4) not assignable
Documentation insufficient for assessment

13-DEC-2002 (40)

Type: LD50
Species: mouse
Vehicle: other: 0.5% aqueous CMC
Route of admin.: i.p.
Value: < 50 mg/kg bw

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: A 0.5 - 10% emulsion of the test substance in 0.5% aqueous carboxymethylcellulose w(CMC) as administered. The animals were
observed for 14 days after dosing. Late deaths were observed; deaths occurred within up to 10 days after dosing.

Marked body weight loss accompanied by unspecific clinical symptoms was reported.
Test substance: Laromin C 260 liquid (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane)
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
26-AUG-2003 (35)

Type: LD50
Species: rat
Vehicle: other: Lutrol
Route of admin.: s.c.
Value: ca. 378 mg/kg bw

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Original value: ALD50 ca. 400 µl/kg

ALD50 was determined in a preliminary study for a carcinogenicity study; 15 rats were used; the test substance was administered as a solution in Lutrol.
Test substance: Laromin C 260 (Dimethyldicykan)
Reliability: (4) not assignable
Documentation insufficient for assessment
13-DEC-2002 (40)

Type: other: lethal dose
Species: rabbit
Vehicle: water
Doses: ca. 9.4, 47.0, 94.0 mg/kg bw (10, 50, 100 µl/kg bw)
Route of admin.: i.v.
Value: <= 9.4 mg/kg bw

Method: other: BASF-Test
GLP: no
Test substance: other TS: 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamin) hydrochloride

Remark: An aqueous solution of the test substance (hydrochloride of Laromin C 260; pH = 7) was injected at dose levels of 10, 50, and 100 µl/kg bw (density = 0.944 g/ml). Deaths occurred during or immediately after injection, accompanied by slight convulsions. Surviving animals recovered within a few minutes.

Doses and mortality:

dose [µl/kg]	dose [mg/kg]	mortality
10	9.4	1/2
50	47.0	1/1
100	94.0	1/1

Test substance: Hydrochloride of Laromin C 260 (Dimethyldicykan hydrochloride)
Reliability: (4) not assignable
Documentation insufficient for assessment
13-DEC-2002 (37)

Type: other: lethal dose

Species: cat
Vehicle: water
Doses: ca. 9.4, 18.8, 47.0, 94.0 mg/kg bw (10, 20, 50, 100 µl/kg bw)
Route of admin.: i.v.
Value: 9.4 - 18.8 mg/kg bw

Method: other: BASF-Test
GLP: no
Test substance: other TS: 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamin) hydrochloride

Remark: An aqueous solution of the test substance (hydrochloride of Laromin C 260; pH = 7) was injected at dose levels of 10, 20, 50, and 100 µl/kg bw (density = 0.944 g/ml). Deaths occurred during or immediately after injection, accompanied by slight convulsions. Surviving animals recovered within a few minutes.

Doses and mortality:

dose [µl/kg]	dose [mg/kg]	mortality
10	9.4	0/2
20	18.8	1/1
50	47.0	1/1
100	94.0	1/1

Test substance: Hydrochloride of Laromin C 260 (Dimethyldicykan hydrochloride)
Reliability: (4) not assignable
Documentation insufficient for assessment
13-DEC-2002 (37)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: Semiocclusive
Exposure Time: 3 minute(s)
No. of Animals: 6
Vehicle: other: no vehicle
Result: highly corrosive

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The undiluted test substance was applied to the skin. Exposure time was 3 minutes (4 animals) and 1 hour (2 animals). A patch saturated with the unchanged test compound was applied to a size of 1x1 cm (3 minutes exposure) or 2x2 cm (1 hour exposure).
After exposure for 3 minutes, necrotic changes (full thickness necrosis) were observed in 3/4 rabbits at the reading at 8 days after application.
Test substance: Laromin C 260 liquid (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane)
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
Flag: Critical study for SIDS endpoint

05-MAR-2004 (35)

Species: rabbit
Concentration: other: undiluted or 30%
Exposure Time: 15 minute(s)
Vehicle: other: no vehicle or oil
Result: corrosive

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The undiluted test substance and a 30% preparation of the test substance was applied to the dorsal skin of white rabbits for 1, 5, and 15 minutes each. After the end of each application period, the application sites were washed. The test substance, undiluted or as a 30% preparation and applied for 1 to 15 minutes, produced inflammatory erythema followed by desquamation. After application for 15 minutes, slight edema and scabbing was observed, additionally. The skin was normal at 14 days after application.
Test substance: Dimethyldicykan (4,4'-Diamino-3,3'-dimethyldicyclohexylmethane)
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, acceptable for assessment
10-DEC-2002 (41)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
No. of Animals: 3
Vehicle: other: no vehicle
Result: corrosive

Method: other: according to Federal Register 38, No. 187, § 1500.42
Year: 1973
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: One tenth millilitre of the unchanged test substance was instilled into the conjunctival sac of the right eye of each of 3 rabbits. The treated eye was scored at 24 h, 48 h, 72 h, and 8 days after instillation; irritation was graded according to the Draize scheme. Severe damage of ophthalmic tissue including corneal opacity was observed. After 8 days, the study was terminated since reversibility of the findings was not expected. Primary irritation index was >51 (maximum = 110).
Test substance: Laromin C 260 liquid (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane)
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
Flag: Critical study for SIDS endpoint
05-MAR-2004 (35)

Species: rabbit

Concentration: undiluted
Dose: .1 ml
Comment: not rinsed
Vehicle: other: no vehicle
Result: corrosive

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: One drop (ca. 0.1 ml) of the undiluted test substance was instilled into the conjunctival sac of one eye of each rabbit; a 0.9% aqueous sodium chloride solution was instilled into the other eye (control). The eyes were scored at 10 minutes, and 1, 3, and 24 h after beginning of application. The test substance produced strong redness, corneal opacity, purulent lacrimation and scabbing. Depilation was observed at the area around the treated eye.
Test substance: Dimethyldicykan (4,4'-Diamino-3,3'-dimethyldicyclohexylmethane)
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, acceptable for assessment
13-DEC-2002 (41)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Concentration 1st: Induction .5 % intracutaneous
2nd: Induction .5 % occlusive epicutaneous
3rd: Challenge 2 % occlusive epicutaneous
No. of Animals: 15
Vehicle: other: acetone; Freund's Complete Adjuvant
Result: not sensitizing

Method: other: according to Magnusson, B. and Kligman, A.M.: J. Invest. Derm. 52, 268
Year: 1969
GLP: no
Test substance: other TS

Method: The sensitizing properties of the test substance were evaluated in a Guinea pig maximization test in accordance to the protocol of Magnusson and Kligman. Fifteen animals were used in the test group; the number of control animals is not given in the article.

Induction:
The test animals were given subcutaneous and topical applications of the test substance in acetone and/or Freund's Complete Adjuvant at a final concentration of 0.5%. Control animals received the corresponding vehicle.

Challenge:
At two weeks after the last induction, animals of both the test and control group received a topical application of the test substance in acetone at a final concentration of 2% (24-hour occluded patch). The skin was scored at 24 hours

after removal of the test patch.

Criteria for selection of induction concentration was systemic toxicity reported in the literature. Criteria for selection during induction is not given. No criteria for selection of challenge concentration was given. Number of animals reacting during induction is not given.

Result: No skin reactions were observed after challenge in both test (0/15) and control animals.

Test substance: 3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane, commercial grade; no further data

Reliability: (2) valid with restrictions
pre-GLP study according to original description of the GPMT; no positive control used, however, several simultaneously tested compounds were positive thus providing the sensitivity of the test system.

Flag: Critical study for SIDS endpoint

05-MAY-2004 (42)

Type: Skin painting test
Species: guinea pig
Concentration 1st: Induction undiluted open epicutaneous
2nd: Induction 10 % open epicutaneous
3rd: Challenge 1 % open epicutaneous
No. of Animals: 10
Vehicle: other: ethanol (96%)
Result: not sensitizing

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: The sensitizing properties of the test substance were evaluated in 10 guinea pigs (no control group included).

Induction:
The animals were painted once with the undiluted test substance, and then daily with a 10% solution of the test substance in 96% ethanol. This procedure was scheduled to be continued until a defined erythema was observed at the application site. This was achieved after 5 paintings with the 10% solution. All induction applications were applied onto the left flank.

Challenge:
After recovery of the induction application sites (10 days after the last induction application), the animals were painted with a 1% solution of the test substance in 96% ethanol; this was applied onto the right, previously untreated flank. Skin reactions were scored at 8, 12, and 24 hours after challenge application.

Criteria for dose selection were not reported.

Result: Induction:
Scabbing was observed in 10/10 animals at the application site.

Challenge:
No skin reactions were observed.

Test substance: Dimethyldicykan
(4,4'-Diamino-3,3'-dimethyldicyclohexylmethane)
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, basic data given, acceptable for assessment
22-AUG-2003 (41)

5.4 Repeated Dose Toxicity

Type: Sub-chronic
Species: rat **Sex:** male/female
Strain: Wistar
Route of administration: inhalation
Exposure period: 3 months
Frequency of treatment: 6 hours each working day (5 d/w)
Post exposure period: none
Doses: 0.002, 0.012, 0.048 mg/l (2, 12, 48 µg/l)
Control Group: yes
NOAEL: .002 mg/l
LOAEL: .012 mg/l

Method: OECD Guide-line 413 "Subchronic Inhalation Toxicity: 90-day Study"
Year: 1981
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: Groups of 10 male and 10 female Wistar rats (age 9 weesk, mean body weights 247g and 171 g for male and female animals) were exposed by
inhalation to a liquid aerosol of the test substance at concentrations of 2, 12, and 48 µg/l. Analysis confirmed the nominal concentrations. mean values +/- standard deviation were 2.1 +/- 0.58 µg/l, 12.4 +/- 2.63 µg/l, and 48.2 +/-10.48 µg/l. The mass median aerodynamic diameter (MMAD) was 3.5, 1.5, and 2.8 µm, respectively.
The animals were exposed for 6 hours each working day over a period of 3 months (head-nose exposure). A control group (10 males, 10 females) was exposed to fresh air. The body weight was determined once a week. Feed and water consumption was not measured.
Ophthalmologic examinations were carried out at the beginning and at the end of the study. The state of health was checked before, during and after exposure. Clinicochemical and hematological examinations were carried out. All animals were necropsied and assessed by gross pathology, extensive histopathological examinations were done including examination of the testes, ovaries and uterus.
Result: Mortalities:
There were no mortalities in the control and high dose groups. One female at 2 µg/l and one male at 12 µg/l died intercurrently after 37 and 48 exposures, respectively. Deaths were judged to be of spontaneous nature.

Observations and examinations
Clinical observations:
scattered occurrence of observations throughout all test groups without relation to dose. No specific substance-related effect noted.

Body weight parameters:
Compared to control animals statistically reduced mean body weight gain ($p<0.01$) and reduced body weight from day 50 onwards ($p<0.01$) was seen in high dose male rats. Body weight was reduced by approx 14% compared to controls on day 85. In high dose females body weight change was significantly reduced ($p<0.05$) from day 71 onwards. Terminal body weight in females was reduced by 8% and statistically different from controls animals. No other statistically significant effect on body weight parameters were noted.

Ophthalmologic examinations: no changes in any of the dose groups noted.

Clinical chemistry:
Animals at 2µg/l: no substance-related changes noted in either test group.

Animals at 12 µg/l: statistically significant, but marginal increase of alkaline phosphatase (5.658 µkat/l vs. 4.949 µkat/l in controls) and GPT (glutamate pyruvate transaminase; 1.043 µkat/l vs. 0.845 µkat/l in controls) in male rats. GOT (glutamate oxalo-acetate transaminase) was not changed in male rats. Increase of alkaline phosphatase was only seen in this test group. No other change was noted in male or female animals.

Animals at 48 µg/l: statistically significant increase of GOT and GPT (but not alkaline phosphatase) compared with controls in male rats, but not in females rats. Activity of GPT in serum was 1.081 µkat/l vs. 0.845 µkat/l in control animals ($p<0.01$).
A significant ($p<0.01$) decrease of serum triglycerides in high dose males was considered to result from a decreased food consumption which was assumed because of the reduced body weight development in this group. This finding was therefore regarded to be a secondary effect.
Hematology:
Significant ($p<0.05$) reductions in hemoglobin, hemoglobin per erythrocyte, and in mean corpuscular hemoglobin concentration (MCHC) were noted in the male high dose rats only.
Polychromatosis was noted.
Clotting test: statistically significant clotting time increase was only seen in females but not in males. This effect was not considered to be treatment related.

Pathology
Relative organ weight of liver, lung, and kidney was significantly increased in high dose male and female animals on the 1% or 5% level of significance. Relative weight of adrenals ($p<0.05$) and testes ($p<0.01$), and absolute lung weight (1.41g vs. 1.18g in controls) were significantly increased only in high dose male rats.
Histopathology
No effects in low and medium dose animal groups.
Effects in high dose animals included:
Local irritative effects on the skin and slight hyperkeratosis in 7/10 male rats. Minimal to slight vacuolization of the craniodorsal olfactory epithelium in both male (2/10) and female (1/10 animals) rats. Significantly increased incidenz

of slight tubulonephrosis was noted in male rats only (6/10 vs. 1/10 in male controls; 9/10 females vs. 7/10 controls), and extramedulary haematopoesis in spleen was noted only in female rats (9/10). Hemosiderin was noted in spleen of all high dose animals.

Overall assessment:
No treatment-related effect was noted in animal groups at 2 and 12 µg/l apart from the increased GPT level in mid dose male rats.

Although clear effects on body weight gain were noted in the high dose groups target organ toxicity was mild and restricted to red blood cells, including the spleen (extramedulary haematopoesis) indicative of a mild anemic effect.
There were increases in clinical chemical parameters (GPT and GOT) as well as in the relative liver weight; however, no histopathological correlate was found in this study.
A substance-related effect on kidneys (slight tubular nephrosis with increased kidney weights) was of borderline significance. Other organ weight changes were seen (increased relative weights of testes and adrenals), but were considered to be secondary toxic effects due to severe impairment of the body weight.
According to the authors, under the conditions of this study, the NOAEC was 2 µg/l (0.002 mg/l), based on slightly increased GPT level (1.043 µkat/l vs. 0.845 µkat/l in controls) observed in mid dose males representing a borderline toxicity.

Test substance: Laromin C 260; according to the authors, purity was >99.5%

Conclusion: Clear toxicity was noted in animals exposed to 48 µg/l. Local effects included degeneration of the olfactory epithelium. Hepatotoxicity, adverse effects on red blood cells, hemoglobin, and spleen were noted as was a reduced body weight gain. Male animals were more susceptible than females.
The NOAEC was 2 µg/l (0.002 mg/l) in this study, based on a slightly but statistically significantly increased GPT level (1.043 µkat/l vs. 0.845 µkat/l in controls) observed in mid dose male rats.

Reliability: (1) valid without restriction
GLP guideline study

Flag: Critical study for SIDS endpoint

05-MAY-2004 (43)

Type: Sub-chronic
Species: rat **Sex:** male/female
Strain: Wistar
Route of administration: gavage
Exposure period: 3 month
Frequency of treatment: each working day (5 d/w)
Post exposure period: none
Doses: 2.5, 12, 60 mg/kg bw
Control Group: yes
NOAEL: 2.5 mg/kg
LOAEL: 12 mg/kg

Method: OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: Three groups of 10 male and 10 female Wistar rats were administered the test substance by gavage at dose levels of 2.5, 12, and 60 mg/kg bw; a groups of 10 rats/sex was administered the vehicle, 0.5% aqueous carboxymethylcellulose. The animals were dosed on weekdays for 3 months. The feed consumption and body weight of the rats were determined weekly; water consumption was not measured. The state of health was checked daily. During the administration period, two clinicochemical examinations, two hematological examinations and two urinalyses were carried out. In addition, blood samples were collected from all surviving animals of both sexes for immunological determinations after about 8 and 13 test weeks. Ophthalmological examinations were done in the control and the high dose group at beginning and end of the study. The surviving animals were necropsied and assessed by gross pathology; subsequently, a histopathological examination was carried out including examination of the testes, ovaries and uterus.

Result: Deaths occurred in the low dose (one female after 37 exposures) and mid dose group (one male, 47 exposures). No substance-related effect was however noted.

The following findings were obtained and assessed or discussed as substance-induced:

60 mg/kg group:
Reduced feed consumption and severely retarded body weight gain were observed. Body weight was about 60% of the control value for males and 80% of the control value for females.
Deteriorated general state of health with differently discolored body regions of various localizations were seen in both sexes.
Increase of the alanine aminotransferase, aspartate aminotransferase, leukocyte and lymphocyte value (both sexes).
Increase of lymphocyte value with changed nuclear structure (both sexes).
Increase of the monocyte and neutrophilic polymorphonuclear granulocytes in the females.
Decrease of mean corpuscular volume (MCV), mean hemoglobin concentration (MHC) of individual erythrocytes, and a decrease of the chloride and creatinine values (both sexes).
In males total protein, albumin, globulins and triglyceride levels were decreased.
The inorganic phosphate was increased in females.
In both sexes, the erythrocyte and leukocyte values, of renal and round-cell epithelias, bacterias and round cell epithelias without nucleus in the urine was increased. The relative weights of liver, kidney, and adrenals were increased in both sexes on the $p<0.01$ level of significance as was relative testes weight in males. The absolute weights of liver and adrenals were increased ($p<0.01$) in both sexes. Absolute testes weight ($p<0.05$) was decreased (-18%).

Decreased absolute testes weight was explained by severe depression of body weight gain (see table below). An atrophy of the seminiferous tubules (4/10 focal, 2/10 diffuse) and a reduced content of the seminal vesicle was noted. These

changes were also interpreted as consequence of the marked impairment of body weight. As the body weight was reduced more than the testes weight, the relative testes weight was significantly (p<0.01) increased.

Table: Comparison of absolute body weight and testes weights

Dose (mg/kg bw.)	absolute bw. (g)	absolute testes weight (g)
0	408	3.64
2.5	406	3.51
12	388	3.59
60	236** (42 %)***	2.96* (18.6 %)***

* p < 0.05
** p < 0.01
*** weight reduction in % compared to control

Histopathology revealed microvacuolar degeneration of the liver of most animals. The lesion was qualitatively more distinct in the females than in male animals. Vacuolar tubulopathy was observed in kidneys, vacuolar myocardial degeneration was found in the heart and the adrenal glands showed a picture of a progressive transformation.

The immunological examinations elicited no adverse effects on the humoral parameters examined in any of the test animal groups.

12 mg/kg group:
Slight reduction of feed consumption and significantly retarded body weight gain in females. Body weight was about 93% of the control value for females (p<0.05), but was not affected
in the males.
Increase of the aspartate aminotransferase values in males.
Increase of bacterias and round-cell epithelia without nucleus in the urine (both sexes).
Increase of erythrocytes in the urine of males and single renal and round-cell epithelias (both sexes).
Increase of the relative liver (p<0.05) and absolute kidney weights (p<0.05) (males); relative kidney weights were increased in both
sexes on the p<0.01 level of significance.
Histopathology revealed vacuolar tubulopathy in the kidneys of some male and female animals. The heart of most animals was found to show vacuolar myocardial degeneration.

2.5 mg/kg group:
No differences in comparison with the control in the animals of both sexes.

Test substance: Laromin C 260; according to the authors, purity was >99 %
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
05-MAR-2004 (44)

Type: Sub-acute
Species: rat **Sex:** male
Strain: Fischer 344
Route of administration: gavage
Exposure period: 10 to 28 days
Frequency of treatment: up to 22 doses
Post exposure period: none
Doses: 25, 37.5, 50, 75, 100 mg/kg; see freetext
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: other TS

Method: The aim of the study was to evaluate clinico-pathological changes in rats treated with the test substance. The study was divided into two experiments.

Experiment 1:
Groups of 10 male Fischer rats were administered the test substance in olive oil by gavage at dose levels of 25, 37.5, 50, and 75 mg/kg bw/application. The animals were dosed 20-22 times within 4 weeks. Control animals (10 rats) were administered the vehicle. Two rats given 75 mg/kg bw/d had to be sacrificed halfway in the experiment because they got severely weakened. After completion of administration, the animals were sacrificed, organ weights were measured, hematological and biochemical tests (RBC, WBC, Ht, Hb; GOT, GPT, Al-P, LAP, BUN) and routine histopathological examinations were carried out.

Experiment 2:
The test substance was administered 8-10 times within 10 days (group A) or 17 times within 24 days (group B). Dose levels were 50, 75, and 100 mg/kg bw/application (group A) and 50, and 75 mg/kg bw/application (group B). Groups of five rats were used. After completion of administration, clinico-biochemical tests (CPK, MAO, creatine, creatinine) and histopathological examinations (esp. of the gastrocnemius muscle and the brain choroid plexus) were carried out.

Result: Body weight gain of the dosed rats was decreased in a dose-related manner. Weakness of the limb muscles was observed, especially in the higher dose groups. Hematology revealed significantly decreased leukocyte counts. Clinico-chemical tests revealed an increase of GOT, CPK, MAO, and creatine and a decrease of alkaline phosphatase. Histologically, various degrees of atrophy, degeneration and regeneration of muscle fibres and various degrees of vacuolar changes of epithelial cells of the choroid plexus were observed.
Test substance: Laromin C [bis(4-amino-3-methyl-cyclohexyl)methane]; no data on purity of the compound
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
13-DEC-2002 (45) (46)

Type: Sub-chronic
Species: rat **Sex:** male

Strain: Fischer 344
Route of administration: gavage
Exposure period: 10 weeks
Frequency of treatment: 5 times per week
Post exposure period: none
Doses: 25, 50 mg/kg bw
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: other TS

Method: The aim of the study was to investigate the histological effects of repeated oral administration of the test substance. Two groups of 10 male Fischer 344 rats were administered the test substance by gavage at doses of 25 and 50 mg/kg bw for 10 week, on 5 days per week. A group of 5 control rats received the vehicle, olive oil. After completion of administration, the animals were sacrificed, and organs were examined by light and electron microscopy.
Result: Repeated administration of the test substance induced myopathic changes in skeletal muscle and vacuolar degeneration of the epithelial cells the choroid plexus of the brain. Electron microscopy revealed round osmiophilic inclusion bodies, sometimes showing a lamellar structure, in many organs. Clara cells of the bronchiolar epithelium were swollen; the cytoplasm of the Clara cells showed a marked accumulation of electron-dense inclusion bodies. According to the authors, these inclusion bodies were presumed to be generated by a complex formation of the test substance with phospholipids of lysosomes.
Test substance: Bis(4-amino-3-methylcyclohexyl)methane; no data on purity of the compound
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
13-DEC-2002 (47) (48)

Type: Sub-acute
Species: rat **Sex:** no data
Strain: no data
Route of administration: s.c.
Exposure period: 5 doses
Frequency of treatment: no data
Post exposure period: 16 days
Doses: ca. 47, 95, 189 mg/kg bw/injection (50, 100, 200 µl/kg bw/injection)
Control Group: no

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: Groups of 5 rats received 5 subcutaneous injections of the undiluted, liquid test substance at dose levels of 50, 100, and 200 µl/kg bw/application (ca. 47, 95, and 189 mg/kg bw/injection, respectively; density = 0.944 g/ml). All animals were observed for 16 days. All five animals of the high dose group died; no deaths were observed at the mid and

low dose level. After approximately 10 days, the test substance perforated the skin after the application and was present at the skin surface.
Test substance: Laromin C 260 (Dimethyldicykan)
Reliability: (4) not assignable
Documentation insufficient for assessment
13-DEC-2002 (40)

Type: Sub-acute
Species: mouse **Sex:** male
Strain: other: ddN
Route of administration: i.p.
Exposure period: 10 and 17 days
Frequency of treatment: daily
Post exposure period: 2 days
Doses: ca. 2, 10 mg/kg bw/d; see freetext
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: other TS

Method: The aim of the study was to evaluate the role of glycosaminoglycan in the induction of skin sclerosis. Primary skin sclerosis was induced in mice by intraperitoneal injection of the test substance. The mice were given i.p. injections of 0.1 ml of a 0.04% or 0.2% solution of the test substance (ca. 2 and 10 mg/kg bw/d, respectively). Each solution was injected daily for 10 and 17 days. Control groups were injected with the vehicle (20% ethanol) for 10 and 17 days. Two days after the final injection, the animals were sacrificed. A specimen was taken from the back skin and evaluated by electron microscopy. Additionally, the skin hydroxyproline (collagen) was determined.
Result: The 0.04% solution induced interstitial edema with slight fibrosis in 7/16 animals treated for 10 days. The 0.2% solution induced scleroderma-like changes with homogenization of connective tissue in 6/12 animals (treated for 10 days) and in 7/10 animals (treated for 17 days. Interstitial edema with slight fibrosis was observed in 1/12 and 1/10 animals treated with the 0.2% solution for 10 and 17 days, respectively. Interstitial edema was also observed in 5/9 control animals treated for 17 days. No skin changes were seen in 9 control animals treated for 10 days. Dermal collagen concentration was reduced in animals treated with the 0.2% solution.
Test substance: Bis(4-amino-3-methylcyclohexyl)methane; no data on purity of the compound
Reliability: (2) valid with restrictions
Basic data are given
13-DEC-2002 (49) (50)

Type: Sub-acute
Species: mouse **Sex:** male
Strain: other: ddY
Route of administration: i.p.
Exposure period: 17 days
Frequency of treatment: daily
Post exposure period: none

Doses: ca. 10 mg/kg bw/d; see freetext
Control Group: yes, concurrent vehicle

Method: other: no data
GLP: no data
Test substance: other TS

Method: Seventy-nine male ddY mice were given intraperitoneal injections of 0.1 ml of a 0.2% solution of the test substance in 30% acetone (ca. 10 mg/kg bw/d) for 17 days. Sixty-four control mice were injected with the vehicle. Seventy-two test mice and 61 control mice were stayed at 22-24°C throughout the study; 7 test and 3 control mice were stayed at 3°C for 12 hours and then at 22-24°C for the remainder of the study. After the final injection, the mice were sacrificed, and a small area of the back skin was cut off for histological and electron microscopical examination.
Result: About 30% of the treated animals (27/79 mice) and only 1/64 control animals had sclerodermatous changes (thickening of the skin). Collagen fibres were swollen. Mice stayed at the low temperature for 12 hours appeared to be more affected. There was an increase in type I collagen and dermatan sulfate and a decrease in collagen content. Slight fibrosis was observed in 20/79 test mice and in 17/64 control mice.
Test substance: Bis(4-amino-3-methylcyclohexyl)methane; no data on purity of the compound
Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, well documented and acceptable for assessment
13-DEC-2002 (51)

Type: Sub-acute
Species: rabbit **Sex:** no data
Strain: no data
Route of administration: gavage
Exposure period: up to 9 doses
Frequency of treatment: daily
Post exposure period: none
Doses: 20 mg/kg bw
Control Group: no data specified

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: Two rabbits were administered the test substance at a dose level of 20 mg/kg bw. The test substance was administered by gavage, daily for 9 doses. One of the animals died after the 8the dosing; autopsy revealed acute hemorrhagic nephritis. The other rabbit survived all 9 doses and showed no macroscopic or microscopic changes. Pathological changes of the urine (proteinuria, hematuria and occurrence renal epithelial cells in the urine) were observed in both animals. However, there were no histological changes of the urinary bladder.
Test substance: Laromin C 260 (Dimethyldicykan)
Reliability: (3) invalid
Significant methodological deficiencies (only one dose level tested, low number of animals); does not meet the criteria

of today's standard methods; documentation insufficient
13-DEC-2002 (37)

Type: Sub-chronic
Species: cat **Sex:** no data
Strain: no data
Route of administration: gavage
Exposure period: up to 40 doses
Frequency of treatment: daily
Post exposure period: none
Doses: 50 mg/kg bw
Control Group: no data specified

Method: other: BASF-Test
GLP: no
Test substance: other TS: 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) hydrochloride

Result: Three cats were administered the test substance by gavage at a dose level of 20 mg/kg bw until death. The cats died after 7, 21 and 40 doses. Marked reduction of body weight (up to 53% body weight loss) and pathological urine findings (proteinuria, erythrocytes in the urine) were recorded. Autopsy revealed a marked damage of the kidney (nephrosis) in the animal that died after 7 doses.
Test substance: Laromin C 260 (Dimethyldicykan)
Reliability: (3) invalid
Significant methodological deficiencies (only one dose level tested, low number of animals); does not meet the criteria of today's standard methods; documentation insufficient
13-DEC-2002 (37)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration: 4 - 5000 µg/plate; see freetext
Cytotoxic Concentration: >= 2500 µg/plate
Metabolic activation: with and without
Result: negative

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1975
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Standard plate test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats. Negative controls, solvent control treated with DMSO and positive controls treated with 2-aminoanthracene, N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylenediamine, and 9-aminoacridine were included. The test was carried out in two independent experiments following the same method.
Test concentrations:
1st experiment: 20, 100, 500, 2500, 5000 µg/plate (+/- S-9)
2nd experiment: 4, 20, 100, 500, 2500 µg/plate (+/- S-9)

No mutagenic effect (increase in the number of revertants) was noted with and without metabolic activation.
Bacteriotoxicity was observed at doses of 2500 µg/plate and above.
Test substance: Laromin C 260; according to the authors, purity was >99%
Reliability: (1) valid without restriction
Comparable to guideline study (meets OECD Guideline 471)
Flag: Critical study for SIDS endpoint
13-DEC-2002 (52)

Type: Cytogenetic assay
System of testing: Chinese hamster ovary cells (CHO-K1 BH4 cell line)
Concentration: 78.13 - 312.5 µg/ml (- S-9); 156.25 - 625 µg/ml (+ S-9); see freetext
Cytotoxic Concentration: = 312 µg/ml (- S-9); = 625 µg/ml (+ S-9)
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 473
Year: 1981
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: Chromosomal aberration assay with and without metabolic activation wit S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats. Negative controls treated with the vehicle (DMSO) and positive controls treated with mitomycin C (- S-9) and cyclophosphamide (+ S-9) were included.
Test concentrations:
0, 78.13, 156.25, 312.5 µg/ml (- S-9, 12-hour culture)
0, 156.25, 312.5, 625 µg/ml (+ S-9, 12-hour culture)
0, 156.25, 312.5, 625 µg/ml (+ S-9, 20-hour culture)

The test substance demonstrated no significant, dose-related increase in the frequency of cells with aberrations, either with or without S-9 mix.

Only in the highest concentration of 625 µg/ml (+ S-9), an increase in the frequency of polyploid cells was observed.

The pH of the culture medium containing S-9 mix and Dimethyldicykan at 0, 312.5 and 625 µg/ml was measured and values of 7.05, 7.45 and 7.55 were obtained. Although the pH value of 625 µg/ml does not appear to be excessive, it may have been sufficient to cause an increase in polyploid cells. Extreme pH values have been shown to cause various types of genotoxic damage in mammalian cells (Scott, D. et al., Mutat. Res. 257, 147-204 (1991)).
Dose-related increases in cytotoxicity were observed starting at 312 µg/ml without S-9 mix and 625 µg/ml with S-9 mix.
Test substance: Dimethyldicykan; according to the authors, purity was 99.9%
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
13-DEC-2002 (53)

Type: HGPRT assay

System of testing: Chinese Hamster V79 cells
Concentration: 0.03 - 1.2 mg/ml (- S-9); 0.1 - 2 mg/ml (+ S-9)
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 476
Year: 1984
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: Test on the induction of gene mutations on the HGPRT locus in Chinese hamster V79 cells. The study was performed in two independent experiments using identical procedures, both with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Wistar rats. Negative controls, solvent controls (DMSO) and positive controls treated with EMS - ethyl methane sulfonate (- S-9) and DMBA - 7,12-dimethylbenz[a]anthracene (+ S-9) were included.
The test substance was tested at the following concentrations:
Experiment 1:
0.10, 0.30, 0.80, 1.20, 2.00 (*), 3.00 (*) mg/ml (- S-9)
0.30, 1.00, 2.00, 3.00 (*), 4.00 (*), 5.00 (*) mg/ml (+ S-9)
Experiment 2:
0.03, 0.10, 0.30, 0.60 (*), 0.80 (*), 1.00 mg/ml (- S-9)
0.10, 0.30 (*), 0.60, 1.00, 1.50 (*), 2.00 mg/ml (+ S-9)
Concentrations marked with a (*) were not continued due to toxicity.
Up to the highest dose tested, no relevant increase in mutant colony numbers was obtained in both experiments.
Higher doses could not be tested due to severe cytotoxicity.
Test substance: 4,4'-Diamino-3,3'-dimethyldicyclohexylmethane; according to the authors, purity > 99% (GC)
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
13-DEC-2002 (54)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1537
Concentration: 31.5, 100, 315, 1000, 2000, 3000 µg/plate
Cytotoxic Concentration: > 1000 µg/plate (- S-9); > 3000 µg/plate (+ S-9)
Metabolic activation: with and without
Result: ambiguous

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1975
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Standard plate test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats. Solvent controls treated with DMSO and positive controls treated with benzo[a]pyrene, 2-aminoanthracene, 3-methylcholanthrene, benzo[a]pyrene-4,5-oxide, and N-methyl-N'-nitro-N-nitrosoguanidine were included. No increase in the number of revertants was observed in the

absence of S-9. A slight increase in the number of revertants was observed with tester strain TA100 (+ S-9); according to the authors, this may be attributed to a contaminant. Marked toxicity was observed in the absence of S-9 (1000 µg/plate and more). Precipitation of the test substance was observed at concentrations of 2000 µg/plate and more.
Test substance: Laromin C 260 "Kernfraktion" (79/56) (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane); according to the authors, purity was 99%
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
13-DEC-2002 (55)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1537
Concentration: 31.5, 100, 315, 1000, 3000 µg/plate (- S-9); 3.15, 10, 31.5, 100, 315, 1000, 3000 µg/plate (+ S-9)
Metabolic activation: with and without
Result: ambiguous

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1975
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Standard plate test with and without metabolic activation with S-9 mix prepared from liver homogenate of male Sprague-Dawley rats pretreated with Aroclor 1254, phenobarbital and beta-naphthoflavone. Solvent controls treated with DMSO and positive controls treated with benzo[a]pyrene, 2-aminoanthracene, 3-methylcholanthrene, benzo[a]pyrene-4,5-oxide, and N-methyl-N'-nitro-N-nitrosoguanidine were included. No increase in the number of revertants was observed in the absence of S-9. A slight increase in the number of revertants was observed with tester strain TA100 (+ S-9); according to the authors, this may be attributed to a contaminant. Increased number of revertants were observed at 1000 and 3000 µg/plate; however, pronounced precipitation of the test substance was observed at these concentrations.
Test substance: Laromin C 260 (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane); according to the authors, purity was 99%
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
13-DEC-2002 (56)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1537
Concentration: 31.5, 100, 315, 1000, 2000, 3000 µg/plate
Cytotoxic Concentration: = 315 µg/plate (- S-9); = 3000 µg/plate (+ S-9)
Metabolic activation: with and without
Result: ambiguous

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1975
GLP: no
Test substance: other TS: crude product (ca. 85% pure)

Remark: Standard plate test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats. Solvent controls treated with DMSO and positive controls treated with benzo[a]pyrene, 2-aminoanthracene, 3-methylcholanthrene, benzo[a]pyrene-4,5-oxide, and N-methyl-N'-nitro-N-nitrosoguanidine were included. No increase in the number of revertants was observed in the absence of S-9. A slight increase in the number of revertants was observed with tester strain TA100 (+ S-9); according to the authors, this may be attributed to a contaminant (purity ca. 85%) and to a cytotoxic effect of the compound. Marked toxicity was observed in the absence of S-9 (315 µg/plate and more); a marginal toxicity was noted at the highest concentration with metabolic activation. Precipitation of the test substance was observed at concentrations of 2000 µg/plate and more.
Test substance: Laromin C 260 "crude" (79/84) (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane); according to the authors, purity was ca. 85%
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
13-DEC-2002 (55)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1537
Concentration: 31.5, 100, 315, 1000, 2000, 3000 µg/plate
Cytotoxic Concentration: = 1000 µg/plate (- S-9); > 3000 g/plate (- S-9)
Metabolic activation: with and without
Result: ambiguous

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1975
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Standard plate test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats. Solvent controls treated with DMSO and positive controls treated with benzo[a]pyrene, 2-aminoanthracene, 3-methylcholanthrene, benzo[a]pyrene-4,5-oxide, and N-methyl-N'-nitro-N-nitrosoguanidine were included. No increase in the number of revertants was observed in the absence of S-9. A slight increase in the number of revertants was observed with tester strain TA100 (+ S-9); according to the authors, this may be attributed to a contaminant. Marked toxicity was observed in the absence of S-9 (1000 µg/plate and more). Precipitation of the test substance was observed at concentrations of 2000 µg/plate and more.
Test substance: Laromin C 260 "commercial product" (79/57) (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane); according to the authors, purity was ca. 99%
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
13-DEC-2002 (55)

Type: Ames test

System of testing: Salmonella typhimurium TA98, TA100, TA1537
Concentration: ca. 29.7, 94.4, 297, 944, 1888, 2832 µg/plate (31.5, 100, 315, 1000, 2000, 3000 nl/plate)
Cytotoxic Concentration: > 3000 µg/plate
Metabolic activation: with and without
Result: negative

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1975
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Standard plate test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats. Solvent controls treated with DMSO and positive controls treated with benzo[a]pyrene, 2-aminoanthracene, 3-methylcholanthrene, benzo[a]pyrene-4,5-oxide, and N-methyl-N'-nitro-N-nitrosoguanidine were included. The test substance was added to the bacteria at concentrations of 31,5, 100, 315, 1000, 2000, and 3000 nl/plate (density = 0.944 g/ml). No increase in the number of revertants and no bacteriotoxicity was observed.
Test substance: Laromin C 260, "Dimethyldicykan Haerter I" (80/263), (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane); according to the authors, purity was >99%
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
13-DEC-2002 (57)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1537
Concentration: 31.5, 100, 315, 1000, 2000, 3000 µg/plate
Cytotoxic Concentration: = 1000 µg/plate (- S-9); > 3000 µg/plate (+ S-9)
Metabolic activation: with and without
Result: negative

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1975
GLP: no
Test substance: as prescribed by 1.1 - 1.4
Remark: Standard plate test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Dawley rats. Solvent controls treated with DMSO and positive controls treated with benzo[a]pyrene, 2-aminoanthracene, 3-methylcholanthrene, benzo[a]pyrene-4,5-oxide, and N-methyl-N'-nitro-N-nitrosoguanidine were included. No increase in the number of revertants was observed in any tester strain with and without S-9. Marked toxicity was observed in the absence of S-9 (1000 µg/plate and more). No precipitation of the test substance was observed.
Test substance: Laromin C 260 "Reinware" (79/296) (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane); according to the authors, purity was 99.8%
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
13-DEC-2002 (55)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1537
Concentration: ca. 29.7, 94.4, 297, 944, 1888, 2832 µg/plate (31.5, 100, 315, 1000, 2000, 3000 nl/plate)
Cytotoxic Concentration: > 2832 µg/plate
Metabolic activation: with and without
Result: negative

Method: other: according to Ames, B.N. et al.: Mutat. Res. 31, 347-364
Year: 1975
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Standard plate test with and without metabolic activation with S-9 mix prepared from liver homogenate of Aroclor 1254-pretreated male Sprague-Daweley rats. Solvent controls treated with DMSO and positive controls treated with benzo[a]pyrene, 2-aminoanthracene, 3-methylcholanthrene, benzo[a]pyrene-4,5-oxide, and N-methyl-N'-nitro-N-nitrosoguanidine were included. The test substance was added to the bacteria at concentrations of 31,5, 100, 315, 1000, 2000, and 3000 nl/plate (density = 0.944 g/ml). No increase in the number of revertants and no bacteriotoxicity was observed.
Test substance: Laromin C 260, "Dimethyldicykan Haerter II" (80/262), (3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane); according to the authors, purity was >99%
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
13-DEC-2002 (57)

5.6 Genetic Toxicity 'in Vivo'

5.7 Carcinogenicity

Species: rat **Sex:** female
Strain: no data
Route of administration: s.c.
Exposure period: single dose
Frequency of treatment: single dose
Post exposure period: 3 years
Doses: 142 mg/kg bw
Control Group: other: yes, concurrent no treatment and concurrent vehicle

Method: other: BASF-Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: The carcinogenicity of the test substance was studied in female rats (body weight ca. 100 g). Fifteen rats were given a single subcutaneous injection of 0.2 ml of a 7.5% solution of the test substance in Lutrol (= 150 µl/kg bw = ca. 142 mg/kg bw). The animals were observed for about 3 years (until natural death). Another 15 rats were injected with the vehicle (vehicle control group); and 30 rats remained untreated (untreated control group). Skin neoplasms at the application site were observed in the test and vehicle

control group. According to the authors, these neoplasms were attributed to the route of administration. There were no local tumors observed. Neoplastic changes of different organs were observed occasionally. Total tumor incidence (benign/malignant) was:
Test group: 4/2 in 15 animals
Vehicle control group: 4/2 in 15 animals
Untreated control group: 8/7 in 30 animals
A urinalysis was conducted on 5 test animals after 6 months and revealed no lesions of the kidneys or urinary bladder.

Test substance: Laromin C 260 (Dimethyldicykan)

Reliability: (3) invalid
Significant methodological deficiencies (only one dose level tested, only single administration of the test substance, low number of animals); does not meet the criteria of today's standard methods

13-DEC-2002 (40) (58)

5.8.1 Toxicity to Fertility

Type: other: effect on the gonads
Species: rat
Sex: male/female
Strain: Wistar
Route of administration: inhalation
Exposure Period: 3 months
Frequency of treatment: 6 hours each working day
Premating Exposure Period
male: no mating
female: no mating
Duration of test: 3 months
Doses: 2, 12, 48 µg/l
Control Group: yes

Method: other: OECD Guide-line 413
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: A subchronic inhalation toxicity study was conducted. Extensive histopathological examination of the testes, ovaries and uterus was included. No effects on the gonads at doses causing no severe body weight retardation were observed in either study.
See chapter 5.4 for details.

Test substance: Laromin C 260; according to the authors, purity was >99.5%

Reliability: (1) valid without restriction
GLP guideline study

Flag: Critical study for SIDS endpoint

11-DEC-2002 (59)

Type: other: effect on the gonads
Species: rat
Sex: male/female
Strain: Wistar
Route of administration: gavage
Exposure Period: 3 months
Frequency of treatment: each working day (5 d/w)
Premating Exposure Period
male: no mating

female: no mating
Duration of test: 3 months
Doses: 2.5, 12, 60 mg/kg bw/d
Control Group: yes

Method: other: OECD Guide-line 408
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: A subchronic oral toxicity study was conducted. Extensive histopathological examination of the testes, ovaries and uterus was included. No effects on the gonads at doses causing no severe body weight retardation were observed in either study.
See chapter 5.4 for details.
Test substance: Laromin C 260; according to the authors, purity was >99 %
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
11-DEC-2002 (44)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat **Sex:**
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: days 6-19 p.c.
Frequency of treatment: daily
Duration of test: until day 20 p.c.
Doses: 5, 15 or 45 mg/kg/day
Control Group: other: vehicle (0.5% aqueous carboxymethylcellulose)
NOAEL Maternal Toxity: = 5 mg/kg bw
NOAEL Teratogenicity: = 45 mg/kg bw
NOAEL Fetotoxicity : = 15 mg/kg bw

Method: OECD Guide-line 414 "Teratogenicity"
Year: 2000
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: OECD Draft Method of June 2000: pregnant female Sprague-Dawley rats were treated with the test substance or the vehicle from day 6 post-coitum to one day prior the expected day of parturition (day 19 post-coitum). Clinical signs and mortality were checked daily. Body weight and food consumption were recorded at designated intervals.
On day 20 post-coitum, the dams were sacrificed and subjected to a macroscopic examination. The fetuses were removed by hysterectomy. The following litter parameters were recorded: weight of gravid uterus of the pregnant females (to allow the calculation of the corrected body weight gain), number of corpora lutea, implantation sites, early and late resorptions, dead and live fetuses. The fetuses were weighed, sexed and submitted to external examination. Half of the fetuses were subjected to a detailed examination of the soft tissue (serial sections after fixation in Harrison's fluid) and the other half of the fetuses were subjected to a detailed examination of the skeleton and cartilage (following staining with alizarin red

and alcian blue).

Remark: Dose selection:
The doses used in this study were selected based on the results of a preliminary range finding maternal toxicity study. Groups of 10 mated female Sprague-Dawley rats received the test substance in 0.5% aqueous carboxymethylcellulose at dose levels of 0 (vehicle control group), 50, 100, and 200 mg/kg bw/d. The test substance was administered by gavage on days 6 through 19 of gestation inclusive. The animals were sacrificed on day 20 of gestation, with exception of the high dose dams; these rats were sacrificed on day 10 post coitum due to marked toxicity.

Conclusions of the dose-finding study:
The test substance produced slight maternotoxic effects when administered to pregnant rats (days 6 to 19 post coitum) at a dose level of 50 mg/kg bw/d. At 100 mg/kg bw/d, marked maternotoxicity was recorded, with forestomach, stomach and liver as target organs. The 200 mg/kg bw/d dose level was dramatically toxic to the pregnant rats. All surviving dams were sacrificed in a moribund condition before schedule on day 10 post coitum.

Result: Test group 4 (45 mg/kg/day):
. no substance-related effects on clinical signs or mortality,
. reduction in food consumption (-7%) and body weight gain (-13% for gross gain, -44% for corrected gain) during the period of treatment,
. several macroscopic findings in the liver (i.e. paleness, accentuated lobular pattern and/or whitish areas),
. no substance-related effects on gestational parameters,
. no substance-related effects at external or soft tissue examination of the fetuses. For skeltal effects see text below.

Test group 3 (15 mg/kg/day):
. no substance-related effects on clinical signs or mortality,
. reduction in body weight gain (-8% for gross gain, -23% for corrected gain) during the period of treatment,
. no substance-related effects on gestational parameters,
. no substance-related effects at external, soft tissue or skeletal examination of the fetuses.

Test group 2 (5 mg/kg/day):
. no substance-related effects on dams, gestational parameters or fetuses.

It should be noted that there were some fluctuations with respect to incomplete ossification between the control and the high dose group which might be influenced by the higher number of fetuses/litter (12.6 control, 13.7 in the high dose), however fetal weights were not different from the control group. The number of fetuses/litter were 12.6, 13.4, 12.7, 13.7). When taking the number of affected fetuses/litter into account, a statistically significant increase of incomplete ossification at the high dose was noted for the interparietal (29.1% versus 7.0% in the control, historical control: 1.5 - 19.1%) and parietal bones

(16.2% versus 1.6% in the control, historical control: 0 - 6.9%), whereas incomplete ossification of supraoccipital bones was significantly increased but was within the range of historical control values. Incomplete ossification of frontal bones was slightly higher than historical control values in the control group and twice as high in the 45 mg/kg group (not significant).

On the other hand, incomplete ossification of thoracic vertebra(e) was statistically significantly higher in the control (5.1 versus 0.6 in the high dose). This also holds for incomplete ossification of 5th sternebra (69.3% versus 45.3% in the high dose). If the summary of skeletal variations is taken into consideration the number of affected fetuses/litter is comparable between all test groups (94.2% control, 94.6% low dose, 91.2% mid dose and 92.8% high dose).

Under the conditions of the study, the NOAEL for maternal toxicity was 5 mg/kg bw/d; the NOAEL for fetotoxicity was 15 g/kg bw/d; and the NOAEL for teratogenicity was 45 mg/kg bw/d (the highest dose tested).

Test substance: 3,3'-Dimethyl-4,4'-diaminodicyclohexylmethane; according to the authors, purity was 99.7% (confirmed by analysis)

Reliability: (1) valid without restriction
GLP guideline study

Flag: Critical study for SIDS endpoint

22-AUG-2003 (60)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

5.11 Additional Remarks

6.1 Methods Handling and Storing

Safe Handling: Ensure thorough ventilation of stores and work areas. Avoid aerosol formation.

Fire/Exp. Prot.: Prevent electrostatic charge - sources of ignition should be kept well clear - fire extinguishers should be kept handy

Storage Req.: Segregate from acids and acid forming substances. Containers should be stored tightly sealed in a dry place.

Add. Information: Storage duration: 24 months

Remark: PERSONAL PROTECTIVE EQUIPMENT

Respiratory protection:
Wear respiratory protection if ventilation is inadequate.

Hand protection:
Suitable chemical resistant safety gloves (EN 374) also with prolonged, direct contact (Recommended: Protective index 6, corresponding >480 minutes of permeation time according to EN 374): E.g. nitrile rubber (0.4 mm), chloroprene rubber (0.5 mm), polyvinylchloride (0.7 mm) and other.
Manufacturer's directions for the use should be observed because of great diversity of types.

Supplementary note: The specifications are based on own tests, literature data and information of glove manufacturers or are derived from similar substances by analogy. Due to many conditions (e.g. temperature) it must be considered, that the practical usage of a chemical-protective glove in practice may be much shorter than the permission time determined in accordance to EN 374.

Eye protection:
Tightly fitting safety goggles (splash goggles) (EN 166)

Body protection:
Body protection must be chosen on activity and possible exposure, e.g. apron, protecting boots, chemical-protection-suit (according to DIN-EN 465).

General safety and hygiene measures:
Avoid contact with skin, eyes and clothing. Do not breathe vapour/spray.

TRANSPORT INFORMATION

Land transport

ADR	Class	8
	Packaging group	I
	UN-number	2922
	Designation of goods	CORROSIVE LIQUID,

TOXIC, N.O.S. (Contains:
3.3'-DIMETHYL-4.4'-DIAMINODICYCLOHEXYLMETHANE)

RID	Class	8
	Packaging group	I

	UN-number	2922
	Designation of goods	CORROSIVE LIQUID, TOXIC, N.O.S. (Contains: 3.3'-DIMETHYL-4.4'-DIAMINODICYCLOHEXYLMETHANE)

Inland waterway transport

ADNR	Class	8
	Item/letter	76a)
	Packaging group	I
	UN-number	2922
	Designation of goods	CORROSIVE LIQUID, TOXIC, N.O.S. (Contains: 3.3'-DIMETHYL-4.4'-DIAMINODICYCLOHEXYLMETHANE)

Sea transport

IMDG/GGVSee	Class	8
	Packaging group	I
	UN-number	2922
	Marine pollutant	YES
	Exact technical name	CORROSIVE LIQUID, TOXIC, N.O.S. (Contains: 3.3'-DIMETHYL-4.4'-DIAMINODICYCLOHEXYLMETHANE)

Air transport

ICAO/IATA	Class	8
	Packaging group	I
	UN-number	2922
	Designation of goods	CORROSIVE LIQUID, TOXIC, N.O.S. (Contains: 3.3'-DIMETHYL-4.4'-DIAMINODICYCLOHEXYLMETHANE

Flag: non confidential, Critical study for SIDS endpoint
11-MAR-2004 (4)

6.2 Fire Guidance

Prot. Equipment: wear self.contained breathing apparatus and chemical-protective clothing.
Ext. Medium: water, dry extinguishing media, foam, carbon dioxide
Add. Information: Collect separately contaminated extinguishing water, do not allow to reach sewage of effluent systems

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (4)

6.3 Emergency Measures

Type: other: General advice

Remark: Immediately remove contaminated clothing.
If danger of loss of consciousness, place patient in recovery position and transport accordingly. Apply artificial respiration if necessary.
First-aiders should pay attention to their own safety.
Flag: non confidential, Critical study for SIDS endpoint
11-MAR-2004 (4)

Type: injury to persons (inhalation)

Remark: Keep patient calm, remove to fresh air, seek medical attention
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (4)

Type: injury to persons (skin)

Remark: Immediately wash thoroughly with plenty of water, apply sterile dressings, consult a skin specialist.
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (4)

Type: injury to persons (eye)

Remark: Immediately wash affected eyes for at least 15 minutes under running water with eyelids held open, consult an eye specialist.
Flag: non confidential, Critical study for SIDS endpoint
26-FEB-2001 (4)

Type: injury to persons (oral)

Remark: Immediately rinse mouth and then drink plenty of water, seek medical attention.
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (1)

Type: other: Note to physician

Remark: Treat according to symptoms (decontamination, vital functions), no known specific antidote.
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (4)

Type: accidental spillage

Remark: Personal precautions:
Breathing protection required. Avoid contact with the skin, eyes and clothing.

Environmental precautions:
Do not empty into drains.

Methods for cleaning up or taking up:
For large amounts: Pump off product
For residues: Pick up with suitable absorbent material (e.g. sand, saw dust, general-purpose binder, kieselguhr). Dispose of absorbed material in accordance with regulations.
Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (4)

6.4 Possib. of Rendering Subst. Harmless

6.5 Waste Management

Memo: other: Incinerate in siutable incineration plant, observing local authority regulations.

Flag: non confidential, Critical study for SIDS endpoint
10-JAN-2003 (4)

6.6 Side-effects Detection

6.7 Substance Registered as Dangerous for Ground Water

6.8 Reactivity Towards Container Material

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