

FOREWORD

INTRODUCTION

Dodecane-12-lactam

CAS N°: 947-04-6

SIDS Initial Assessment Report

For

SIAM 17

Arona, Italy, November 11 -14, 2003

- 1. Chemical Name:** Dodecane-12-lactam
- 2. CAS Number:** 947-04-6
- 3. Sponsor Country:** Germany
Contact Point:
BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit)
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- 4. Shared Partnership with:** Atofina SA: Dr. J. Bakès/Dr. J.-F. Régnier (France);
Ems Chemie: Dr. M. Matter (Switzerland);
UBE Industries Ltd.: Dr. E. Itoh/Mr. M. Harada (Japan);
- 5. Roles/Responsibilities of the Partners:**
 - Name of industry sponsor /consortium: Degussa AG, Germany
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 - Process used: see next page
- 6. Sponsorship History**
 - How was the chemical or category brought into the OECD HPV Chemicals Programme ? by ICCA initiative
- 7. Review Process Prior to the SIAM:** last literature search (update):
11 April 2003 (Ecotoxicology): databases CA, biosis; searchprofile CAS-No. and special search terms
1 April 2003 (Toxicology): databases medline, toxline; search-profile CAS-No. and special search terms
- 8. Quality check process:** As basis for the SIDS-Dossier the IUCLID was used.
All data have been checked and validated by BUA.
- 9. Date of Submission:** August 11, 2003

10. Date of last Update:**11. Comments:**

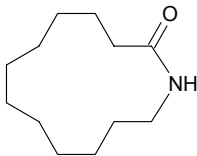
OECD/ICCA - The BUA ^{*} Peer Review Process

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), i.e. reliability not assignable)
- Review of 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.	947-04-6
Chemical Name	Dodecane-12-lactam
Structural Formula	
SUMMARY CONCLUSIONS OF THE SIAR	
<p>Human Health</p> <p>There is no information available on toxicokinetics and metabolism of dodecane-12-lactam. The acute oral LD₅₀ was 2,330 mg/kg bw (rat) with central nervous system stimulation (trembling, convulsive twitches, ataxia) as the main clinical sign appearing at about 1,580 mg/kg bw. The dermal LD₅₀ was greater than 2,000 mg/kg bw (rat). Decreased food consumption and stagnation of body weight development were noted. Valid acute inhalation studies are not available. Dodecane-12-lactam was not irritating to the rabbit skin or eye (OECD TG 404, 405). It was not sensitizing in a guinea pig maximization test (OECD TG 406; 1981).</p> <p>In a 90-day gavage study with rats, administration of dodecane-12-lactam at doses up to and including 25 mg/kg bw/day did not result in adverse effects (= NOAEL). At 125 mg/kg bw/day, blood examination revealed a slight increase in total serum protein and albumin levels in females and a moderate increase in potassium levels in males. Sodium excretion was also increased in males. In a few males treated with 25 or 125 mg/kg bw/day slight morphological changes in centrilobular hepatocytes (ground glass appearance) were noted, but this effect was reversible 4 weeks post-exposure, and in the absence of any other sign of liver toxicity was considered adaptive rather than adverse. No histopathological changes were found in the reproductive organs of these animals. In a subchronic study with dogs, administration of dodecane-12-lactam with the feed at a dose of 44 mg/kg bw/day (males) and 49 mg/kg bw/day (females), respectively, was not associated with adverse effects (= NOAEL), whilst a daily dose of 350 mg/kg bw (males) and 352 mg/kg bw (females), respectively, resulted in a significant increase in liver weight (up to +34% relative to the controls). The top dose of 969 mg/kg bw/day (males) and 989 mg/kg bw/day (females), respectively, severely affected the general health conditions of the animals and was lethal for one female.</p> <p>In all <i>in vitro</i> genotoxicity studies (Ames test according to OECD TG 471 (1981), HPRT test according to OECD TG 476 (1984); testing above limit of solubility neither required nor performed) and a chromosomal aberration test in human lymphocytes in compliance with OECD TG 473), dodecane-12-lactam showed negative results. Therefore it is expected that the chemical is not genotoxic <i>in vivo</i>.</p> <p>In a gavage study performed in accordance with OECD TG 414 (2001), dodecane-12-lactam had no adverse effects on the development of rats up to and including the highest tested dose level of 1,000 mg/kg bw/day. Doses of 250 and 1,000 mg/kg bw/day were maternally toxic as evidenced by reduced food consumption (-7%/-11%) and reduced body weight gain (-37%/-50%) and, at 1,000 mg/kg bw/day, poor general condition (NOAEL maternal toxicity: 50 mg/kg bw/day; NOAEL developmental toxicity: 1,000 mg/kg bw/day). No studies have been performed on the toxicity of dodecane-12-lactam to reproduction. Data from oral 90-day studies did not reveal any adverse effects on the reproductive organs in rats, whilst in dogs an impairment of sperm maturation, decreased testes and ovary weights, and atrophy of the prostate was found at a severely toxic dose level (about 1,000 mg/kg bw/day).</p> <p>Environment</p> <p>Dodecane-12-lactam has a melting point of 151.8 °C, a solubility in water of 0.3 g/l at 20 °C, and a vapour pressure</p>	

of 0.0012 Pa at 20 °C. The measured log K_{ow} is 2.92.

According to a Mackay Level I model calculation, the main target compartment for dodecane-12-lactam will be the hydrosphere (88.3 %), followed by sediment (5.9 %) and soil (5.8 %). The calculated Henry's law constant of 0.00079 Pa m³/mol indicates very low volatility from surface waters. With a calculated K_{oc} of 2258 l/kg, the sorption potential to soil or sediment organic matter is expected to be high.

In the atmosphere, dodecane-12-lactam is rapidly removed by reaction with hydroxyl radicals with a calculated half-life of 12 hrs. In water, it is not expected to hydrolyse at a significant rate under environmental conditions. Photolytical degradation in surface waters is expected to be of minor importance due to its chemical structure. Dodecane-12-lactam is readily biodegradable (OECD 301B: 83 % after 28 days). Thus in surface waters, the predominant removal mechanism is expected to be biodegradation. Experimentally determined BCF values below 2.6 l/kg (*Cyprinus carpio*) indicate a low bioaccumulation potential.

The lowest valid acute test results of aquatic testing determined for fish, invertebrates, and algae were as follows:

Leuciscus idus: 48-h-LC₅₀ = 50 mg/l

Daphnia magna: 24-h-EC₅₀ = 41 mg/l

Scenedesmus subspicatus: 72-h-EC₅₀ = 176 mg/l

From the lowest value among these, an aquatic PNEC of 0.041 mg/l is calculated using an assessment factor of 1000 according to the EU Technical Guidance Document.

Exposure

The production volume of dodecane-12-lactam is approximately 50,000 tonnes per year world wide. Production sites are in Germany, France and Japan. Dodecane-12-lactam is a chemical intermediate which is manufactured in closed systems, and which is used exclusively as a monomer for the polymerisation of polyamide. Releases into the environment may occur during production of dodecane-12-lactam as well as from its use as a monomer for polymer production. Furthermore, environmental releases are possible from residual contents of monomeric dodecane-12-lactam in the polymeric product during further processing of the polymer as well as during use and disposal of end products. Available information indicates that release from production is low. The residual monomer content in the polymer is approximately 0.2 % w/w, thus an amount of < 100 t/a may be released into the environment from formulation and from use and disposal of end products.

Dodecane-12-lactam is not used directly in consumer products. However, in Europe and the U.S. the chemical is authorized as a basic monomer for polymers to be used in food packaging materials, and residual monomers may come into contact with foodstuffs. In the EU, the specific migration limit for dodecane-12-lactam is 5 mg/kg foodstuff. Using this for a worst case estimate (uptake of 1 kg of foodstuff containing 5 mg dodecane-12-lactam every day), a 60 kg person could be exposed to a daily dose of 0.083 mg dodecane-12-lactam/kg bw/day. In the USA, no comparable migration limit has been set.

Workers could potentially be exposed during production and processing, with the main routes of exposure being the dermal and respiratory routes. There are no workplace measurements available. In the sponsor country, exposure to the chemical is controlled in occupational settings and considered to be very low due to its production and processing in closed systems.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

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

Environment:

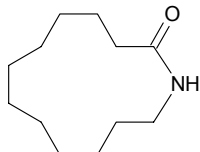
The chemical possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute aquatic toxicity which may become evident only at very high exposure levels they should nevertheless be noted by chemical safety professionals and users.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 947-04-6
IUPAC Name: Dodecane-12-lactam
Molecular Formula: C₁₂H₂₃NO
Structural Formula:



Molecular Weight: 197.32 g/mol
Synonyms: 1-Aza-2-cyclotridecanone
12-Aminododecanoic acid lactam
2-Oxododecamethylenimine
Azacyclotridecan-2-one
Cyclododecalactam
Dodecalactam
Dodecanoic acid, 12-amino-, lactam
Dodecanolactam
Dodecylactam
Laurin lactam
Lauro lactam
Lauryl lactam
omega-Dodecalactam

1.2 Purity/Impurities/Additives

Purity: ca. 99.9 % (w/w)
Impurities: ca. 0.01 % cyclododecanone (830-13-7)
Additives: none

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Physical state	solid	Ullmann, 1987
Melting point	151.8 °C	Ullmann, 1987
Boiling point	ca. 348 °C (1013 hPa)	Hüls AG, 1973
Relative density	0.973 g/cm ³ (20 °C)	Hüls AG, 1991c
Vapour pressure	0.0012 Pa (20 °C; extrapolated)	Chemische Werke Hüls, 1964
Water solubility	0.3 g/l (20 °C)	Ullmann, 1987
Partition coefficient n-octanol/water (log value)	2.92	CITI, 1992
Henry's law constant	0.00079 Pa m ³ /mol	Degussa AG, 2003

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The production of dodecane-12-lactam is estimated to be in the order of 50,000 tons per year worldwide. Production sites are in the EU (Germany, France) and in Japan (Degussa AG, 2002; Atofina, 2002; EMS-UBE Ltd., 2002). Dodecane-12-lactam is an intermediate which is manufactured in closed systems and used exclusively as a monomer for the polymerization of polyamide (Degussa AG, 2002; EMS-UBE Ltd., 2002). The substance is not recorded in the Swedish and Finnish product registers (Swedish Product Register, 2003, Finnish Product Register, 2003). In the Swiss product register 1 product intended for industrial use with a content of 100 % is listed (Swiss Product Register, 2001). In the Danish Product Register 3 products containing dodecane-12-lactam up to 2 % (total quantity of < 1 t/a) are recorded. Reported industry groups are "other printing works" and "maintenance and repair of motor vehicles" (Danish Product Register, 2002).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Releases into the environment may occur during production of dodecane-12-lactam as well as from its use as monomer for polymer production. Furthermore, environmental releases are possible from residual contents of monomeric dodecane-12-lactam in the polymeric product during further processing of the polymer as well as during use and disposal of end products.

Information on environmental releases from production is available for 3 sites:

France:

There is no aqueous effluent from the French production process. Solid wastes are incinerated. Release to air amounts to about 500 kg/year (Atofina, 2002).

Germany:

In the German production plant, process wastewater of approx. 12,000 m³/year containing approx. 0.3 kg/m³ dodecane-12-lactam (i.e. total amount of approx. 3,600 kg dodecane-12-lactam/year) is treated in a wastewater treatment plant. Approx. 500 t of solid waste are completely incinerated, the release to air amounts to approx. 15 kg/year (Degussa AG, 2002).

Japan:

Only negligible quantities of dodecane-12-lactam are released into a waste water treatment plant (effluent flow 0.01 m³/s) (further information not available) (EMS-UBE Ltd., 2002).

The residual monomer content in the polymer is approximately 0.2 % w/w, corresponding to 100 t/year for an annual world wide production of 50,000 t dodecane-12-lactam completely converted into polymer products. Only a minor fraction of this, which however cannot be quantified, is released to the environment during formulation, and release from the resulting products can be assumed to be low in view of the authorisation for food packaging materials (all state-of-the-art polyamide made from dodecane-12-lactam is of similar quality and thus may be used for the manufacture of food packaging articles meeting the authorisation requirements) (Degussa AG, 2002).

No further exposure information is available.

2.2.2 Photodegradation

In the atmosphere, dodecane-12-lactam is rapidly photodegraded by reaction with hydroxyl radicals with a calculated half-life of 12 hrs based on a tropospheric OH radical concentration of 5×10^5 molecules cm⁻³ (Degussa AG, 2003). Photolytical degradation in surface waters is expected to be of minor importance due to the chemical structure.

2.2.3 Stability in Water

In water, dodecane-12-lactam is not expected to hydrolyse at a significant rate under environmental conditions. With HYDROWIN v 1.67 a half-life of > 1 year can be estimated.

2.2.4 Transport between Environmental Compartments

Distribution modeling using Mackay, Level I (V 2.11) and based on the physico-chemical properties listed in Table 1 indicates that the main target compartment will be water with 88.3 %, followed by sediment (5.9 %) and soil (5.8 %) (Degussa AG, 2003).

Due to its (calculated) log K_{oc} of 3.354, it is expected to be highly adsorbed to soil and sediment, i.e. to have a high potential for geoaccumulation (Degussa AG, 2003).

The Henry's law constant governing the distribution of dodecane-12-lactam between aqueous solutions and air was calculated from water solubility and vapour pressure, see Table 1. A value of 0.00079 Pa m³/mol (Degussa AG, 2003) indicates very low volatility from aqueous solution according to the criteria of Thomas (1990).

2.2.5 Biodegradation

In a Modified Sturm test according to OECD Test Guideline 301 B with non-adapted, activated sludge, dodecane-12-lactam was readily biodegradable (83 % after 28 days) (Infracor, 2002a). Ready biodegradability was also observed in a BODIS Test (BOD of insoluble substances) according to ISO draft guideline 10708, where complete degradation already occurred after 21 days

(Hüls AG, 1989a). In a MITI-I-test comparable to OECD 301C no biodegradation was observed over the test period of 28 days. No explanation for this lack of biodegradation can be given. The available data on toxicity to microorganisms (see chapter 4.1) do not indicate an inhibition of the inoculum by the test substance.

Summarizing the available data on biodegradation, dodecane-12-lactam is readily biodegradable.

2.2.6 Bioaccumulation

In a study with *Cyprinus carpio*, the bioconcentration factor of dodecane-12-lactam was determined to be between 0.8 and 2.6 l/kg, indicating low potential for bioaccumulation (CITI, 1992).

2.2.7 Other Information on Environmental Fate

No information available.

2.3 Human Exposure

2.3.1 Occupational Exposure

There are no workplace measurements available. Workers could potentially be exposed during production and processing, with the main routes of exposure being the respiratory and dermal routes. In the sponsor country, exposure to the chemical is controlled in occupational settings and considered to be very low due to its production and processing in closed systems.

In the Swiss product register 1 product intended for industrial use with a content of 100 % is listed (Swiss Product Register, 2001). In the Danish Product Register 3 products containing dodecane-12-lactam up to 2 % are recorded. Reported industry groups are “other printing works” and “maintenance and repair of motor vehicles” (Danish Product Register, 2002). In “maintenance and repair of motor vehicles”, polyamide tubes are known to be handled at room temperature or slightly above. Exposure to dodecane-12-lactam through this use is considered to be negligible. No exposure information is available for “other printing works”.

2.3.2 Consumer Exposure

Dodecane-12-lactam is not used directly in consumer products (Degussa AG, 2002). The substance is not listed in the Finnish and Swedish Product Registers (2002), and the Swiss Product Register (2001) contains only one single product for industrial use. However, in Europe and the U.S. the chemical is authorized for use in food packaging materials, and residual monomers may occur in materials which come into contact with foodstuffs (EU: 2002/72/EC; USA: FDA, 21 CFR, § 177.1500). In the EU, the specific migration limit for dodecane-12-lactam is 5 mg/kg foodstuff. Assuming that a person weighing 60 kg consumes 1 kg of foodstuff contaminated with 5 mg dodecane-12-lactam each day, a worst case dose of 0.083 mg dodecane-12-lactam/kg bw/day is estimated. In the USA, no comparable migration limit has been set.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There is no information available on toxicokinetics, metabolism or distribution of dodecane-12-lactam.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

Valid acute inhalation studies are not available.

Dermal

In a limit test with rats, no mortality occurred after dermal treatment with 2,000 mg/kg bw for 24 hours under occlusive conditions. The treatment did not produce any adverse skin effects and clinical signs were limited to a slight decrease in food consumption and stagnation of body weight development, which also might have been caused by the constraints of the occlusive treatment. No abnormalities were observed at necropsy (Centre de Recherche et d'Élevage des Oncins, 1975).

Oral

After oral application the LD₅₀ for rats was found to be 2,330 mg/kg bw in a test performed according to OECD TG 401 (1981) at dose levels of 1,580, 1,990, 2,510 and 3,160 mg/kg bw. Clinical signs observed at doses \geq 1,580 mg/kg bw included prone position, convulsive twitches, tremor and impairment of breathing, followed by sedation and ataxia, salivation, hypothermia, staggering, crouched posture, and closed or small dark eyes. After 2 - 3 days, the animals showed an increase in motility and, in part, vocalization when being touched. Signs of toxicity disappeared after 11 days in the animals dosed with up to 2,510 mg/kg bw. Necropsy findings of animals that died during the study revealed hyperaemia of the gastric and intestinal mucosae, hyperaemia of the lungs, light-coloured spots on the liver and liver congestion. Hyperaemia of the gastric and intestinal mucosae were also found in some animals necropsied at the end of the study (Hüls AG, 1985a).

Studies in Humans

No information available.

Conclusion

The acute oral LD₅₀ was 2,330 mg/kg bw (rat) with central nervous system stimulation (trembling, convulsive twitches, ataxia) as the main clinical sign appearing at about 1,580 mg/kg bw. The dermal LD₅₀ was greater than 2,000 mg/kg bw (rat). Decreased food consumption and stagnation of body weight development were noted. Valid acute inhalation studies are not available.

3.1.3 Irritation

Studies in Animals

Skin Irritation

In a study performed according to OECD TG 404 under occlusive conditions, the chemical (moistened with paraffin oil) caused only very mild and transient effects on rabbit skin with average Draize scores of 0.44 for erythema and 0.17 for edema. Based on these results, dodecane-12-lactam cannot be considered as a skin irritant (Hüls AG, 1985b).

Eye Irritation

In an eye irritation study in rabbits following OECD TG 405, neat dodecane-12-lactam elicited only slight conjunctival effects that were most prominent at 48 hours after instillation and completely resolved within 6 days (average Draize scores 1.17 for redness and 0.56 for chemosis). 5 out of 6 animals showed a slight reddening of parts of the iris at 24 hours; this effect had completely subsided at 48 hours. Based on these results, dodecane-12-lactam cannot be considered as an eye irritant (Hüls AG, 1985c).

Conclusion

Dodecane-12-lactam was not irritating to the rabbit skin or eye (OECD TG 404, 405).

3.1.4 Sensitisation

Skin

In a Guinea pig maximization test according to OECD TG 406 (1981), sensitization was not observed in any of 20 animals treated with a 25 % preparation of dodecane-12-lactam in corn oil for both induction and challenge. Positive controls were not used in this study (Hüls AG, 1989b).

Conclusion

Dodecane-12-lactam was not sensitizing in a guinea pig maximization test (OECD TG 406, 1981).

3.1.5 Repeated Dose Toxicity

Oral

In a 90-day study performed in accordance with OECD TG 408 (1981), and in which a 30-day post exposure recovery period was included, Sprague Dawley rats (20 animals/low and mid dose/sex; 25 animals/control and high dose/sex) were orally gavaged with dodecane-12-lactam at 0, 5, 25 and 125 mg/kg bw/day. 5, and 25 mg/kg bw/day had no effects on the general condition and behavior of the animals, nor on body weight gain and food consumption.

At 125 mg/kg bw/day, dodecane-12-lactam had no adverse effects on hematological or urine parameters, organ weights or clinical signs. The clinical chemistry of the high dose group revealed a moderate increase in serum potassium levels and an increased sodium excretion in males, and a slight increase in total serum protein and albumin levels in females. Ground glass appearance of centrilobular hepatocytes was found in 4 males of the 25 mg/kg bw/day group, and in 4 males of the 125 mg/kg bw/day group. The change was shown to be reversible within 4 weeks in the 125 mg/kg bw/day group (reversibility was not investigated at 25 mg/kg bw/day but can be assumed based on the findings of the 125 mg/kg bw/day group). In the absence of any indications of liver toxicity in males (no changes in liver biochemistry, no changes in liver weight), the slight microscopic changes

were considered to be of an adaptive nature rather than adverse. All effects were reversible after the 4-week recovery period. No histopathological changes were found in the reproductive organs. The NOAEL was therefore established at 25 mg/kg bw/day (Sanofi Recherche, 1993).

In an oral feed study, Beagle dogs (4 males/females per group) were exposed to dodecane-12-lactam at 0, 44, 350, or 969 mg/kg bw/day (males) and 0, 49, 352, or 989 mg/kg bw/day (females). Exposure was for 13 (low/high dose groups) or 14 weeks (control/mid dose groups).

Dodecane-12-lactam did not cause effects in the low dose group. In the middle dose group, the activity of the alkaline phosphatase of the females was slightly elevated after 1.5 and 3 months. The absolute liver weight and the liver weight relative to the body weight were significantly increased in males (absolute: +34 %; relative: +40 %) and females (absolute: +25 %; relative: +38 %). In the high dose group, the general condition and behaviour were severely affected (apathy, ataxia, sialorrhoea, lateral decubitus, tonic clonic spasms, vomiting, diminished reaction to acoustic and visual stimuli). One female died at the end of week 5. Until the beginning of week 4, male dogs lost 25 %, females 20 % of their initial body weight. Until the end of week 13, they gained weight again, but did not reach their initial body weight (males: -20 %; females: -15 %). Food consumption was strongly reduced, a few dogs ate nothing for days. All dogs revealed a lowered leucocyte number (decrease in the number of neutrophilic granulocytes and lymphocytes) after 1.5 and 3 months. The absolute liver weight and the liver weight relative to the body weight were significantly increased in males (absolute: +35 %; relative: +76 %) and females (absolute: +59 %; relative: +90 %). The weights of the following organs were significantly decreased: testes (absolute: -39%; relative: -24 %), prostate (absolute: -67 %; relative: -58 %), and ovaries (absolute: -50 %; relative: -39 %). The histological examination of the testes revealed an impairment of the sperm maturation; the prostate was atrophic (INBIFO, 1974).

Conclusion

In a 90-day gavage study with rats, administration of dodecane-12-lactam at doses up to and including 25 mg/kg bw/day did not result in adverse effects (= NOAEL). At 125 mg/kg bw/day, blood examination revealed a slight increase in total serum protein and albumin levels in females and a moderate increase in potassium levels in males. Sodium excretion was also increased in males. In a few males treated with 25 or 125 mg/kg bw/day slight morphological changes in centrilobular hepatocytes (ground glass appearance) were noted, but this effect was reversible 4 weeks post-exposure, and in the absence of any other sign of liver toxicity was considered adaptive rather than adverse. No histopathological changes were found in the reproductive organs of these animals.

In a subchronic study with dogs, administration of dodecane-12-lactam with the feed at a dose of 44 mg/kg bw/day (males) and 49 mg/kg bw/day (females), respectively, was not associated with adverse effects (= NOAEL), whilst a daily dose of 350 mg/kg bw (males) and 352 mg/kg bw (females), respectively, resulted in a significant increase in liver weight (up to +34 % relative to the controls). The top dose of 969 mg/kg bw/day (males) and 989 mg/kg bw/day (females), respectively, severely affected the general health conditions of the animals and was lethal for one female.

3.1.6 Mutagenicity

In vitro Studies

In an Ames test performed according to OECD TG 471(1981) with *Salmonella typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100, test substance concentrations of up to 5,000 µg/plate

were employed in the presence and absence of Aroclor 1254-induced rat liver S9 mix. An increase in mutant frequency was not observed (Hüls AG, 1991a).

In a HPRT test with Chinese Hamster ovary (CHO) cells, dodecane-12-lactam concentrations of 8-80 mg/l (+/- S9 mix from Aroclor 1254 induced rat livers) did not increase the mutant frequency of treated cells. In accordance with OECD TG 476 (1984), the chemical was tested up to the limit of solubility under culture conditions, i.e. under culture conditions 80 mg/l was the highest concentration showing no precipitation. (The 1997 version of OECD TG 476 requires testing up to concentrations leading to visible precipitation.) Cytotoxicity was not observed at any of the concentrations tested (Hüls AG, 1991b).

In a cytogenetic assay with human lymphocytes (according to OECD TG 473), concentrations of 30 - 350 mg/l (+/-S9 mix from Aroclor 1254-induced rat livers) were employed. A significant increase in chromosomal aberrations was not observed even at cytotoxic concentrations (Hazleton, 1991).

In vivo Studies

No studies with respect to this endpoint have been performed.

Conclusion

In all *in vitro* genotoxicity studies (Ames test according to OECD TG 471 (1981), HPRT test according to OECD TG 476 (1984); testing above limit of solubility neither required nor performed) and a chromosomal aberration test in human lymphocytes in compliance with OECD TG 473), dodecane-12-lactam showed negative results. Therefore it is expected that the chemical is not genotoxic *in vivo*.

3.1.7 Carcinogenicity

No studies with respect to this endpoint have been performed.

3.1.8 Toxicity for Reproduction

Effects on Fertility

Studies on the toxicity of dodecane-12-lactam to reproduction have not been performed.

In a 90-day study performed in accordance with OECD TG 408(1981), Sprague Dawley rats (20 animals/low and mid dose/sex; 25 animals/control and high dose/sex) were orally gavaged with dodecane-12-lactam at 0, 5, 25 and 125 mg/kg bw/day. Treatment with up to 125 mg/kg bw/day had no effects on male or female genital organ weights (testes, prostate, seminal vesicles, uterus, ovaries). Likewise, histopathology of these organs of the top dose group did not detect any significant effects attributable to treatment with the test compound.

In a 90-day oral study with male and female beagle dogs (4 animals/dose/sex), administered with up to 989 mg/kg bw/day, the histological examination of the testes revealed an impairment of the sperm maturation and atrophy of the prostate at the highest exposure level (testes and prostate weights were also significantly decreased). This dose was clearly toxic to the animals as evidenced by a 25 % loss of body weight, and the effect can therefore be interpreted as secondary. Likewise, the reduction in ovary weights at the highest dose (absolute: -50 %; relative: -39 %) should be interpreted as a secondary effect, since the body weights of females were reduced by 15 %. Histopathological changes of the ovaries were not detected (INBIFO, 1974).

Developmental Toxicity

In a study performed in accordance with OECD TG 414(2001), pregnant Sprague Dawley rats were gavaged with doses of 50, 250 or 1,000 mg/kg bw/day on days 6 through 19 post-coitum inclusive (CIT, 2001).

In dams, slight to marked effects on food consumption and body weight gain were recorded in the 250 and 1,000 mg/kg bw/day groups:

Influence on:	Dose level (mg/kg bw/day)		
	50	250	1,000
Food consumption (compared to control)	±0 %	-7 %	-11 %
Net body weight gain* (compared to control)	-2 %	-37 %	-50 %

- net body weight gain = increase in body weight after day 6, corrected for weight of uterine content

Clinical signs of poor general condition were only recorded in a notable proportion of the animals given 1,000 mg/kg/day (resulting in the premature sacrifice of 2 animals). The NOAEL for maternal toxicity was 50 mg/kg bw/day.

Test substance-related adverse effects on the fetuses were not observed in any of the treatment groups. Parameters evaluated were body weight, pre- or post-implantation loss, sex ratio, external/skeletal/soft tissue malformations and variations.

Conclusion

In a gavage study performed in accordance with OECD TG 414 (2001), dodecane-12-lactam had no adverse effects on the development of rats up to and including the highest tested dose level of 1,000 mg/kg bw/day. Doses of 250 and 1,000 mg/kg bw/day were maternally toxic as evidenced by reduced food consumption (-7 %/-11 %) and reduced body weight gain (-37 %/-50 %) and, at 1,000 mg/kg bw/day, poor general condition (NOAEL maternal toxicity: 50 mg/kg bw/day; NOAEL developmental toxicity: 1,000 mg/kg bw/day).

No studies have been performed on the toxicity of dodecane-12-lactam to reproduction. Data from oral 90-day studies did not reveal any adverse effects on the reproductive organs in rats, whilst in dogs an impairment of sperm maturation, decreased testes and ovary weights, and atrophy of the prostate was found at a severely toxic dose level (about 1,000 mg/kg bw/day).

3.2 Initial Assessment for Human Health

There is no information available on toxicokinetics and metabolism of dodecane-12-lactam.

The acute oral LD₅₀ was 2,330 mg/kg bw (rat) with central nervous system stimulation (trembling, convulsive twitches, ataxia) as the main clinical sign appearing at about 1,580 mg/kg bw. The dermal LD₅₀ was greater than 2,000 mg/kg bw (rat). Decreased food consumption and stagnation of body weight development were noted. Valid acute inhalation studies are not available.

Dodecane-12-lactam was not irritating to the rabbit skin or eye (OECD TG 404, 405). It was not sensitizing in a guinea pig maximization test (OECD TG 406; 1981).

In a 90-day gavage study with rats, administration of dodecane-12-lactam at doses up to and including 25 mg/kg bw/day did not result in adverse effects (= NOAEL). At 125 mg/kg bw/day, blood examination revealed a slight increase in total serum protein and albumin levels in females

and a moderate increase in potassium levels in males. Sodium excretion was also increased in males. In a few males treated with 25 or 125 mg/kg bw/day slight morphological changes in centrilobular hepatocytes (ground glass appearance) were noted, but this effect was reversible 4 weeks post-exposure, and in the absence of any other sign of liver toxicity was considered adaptive rather than adverse. No histopathological changes were found in the reproductive organs of these animals.

In a subchronic study with dogs, administration of dodecane-12-lactam with the feed at a dose of 44 mg/kg bw/day (males) and 49 mg/kg bw/day (females), respectively, was not associated with adverse effects (= NOAEL), whilst a daily dose of 350 mg/kg bw (males) and 352 mg/kg bw (females), respectively, resulted in a significant increase in liver weight (up to +34 % relative to the controls). The top dose of 969 mg/kg bw/day (males) and 989 mg/kg bw/day (females), respectively, severely affected the general health conditions of the animals and was lethal for one female.

In all *in vitro* genotoxicity studies (Ames test according to OECD TG 471 (1981), HPRT test according to OECD TG 476 (1984); testing above limit of solubility neither required nor performed) and a chromosomal aberration test in human lymphocytes in compliance with OECD TG 473), dodecane-12-lactam showed negative results. Therefore it is expected that the chemical is not genotoxic *in vivo*.

In a gavage study performed in accordance with OECD TG 414 (2001), dodecane-12-lactam had no adverse effects on the development of rats up to and including the highest tested dose level of 1,000 mg/kg bw/day. Doses of 250 and 1,000 mg/kg bw/day were maternally toxic as evidenced by reduced food consumption (-7 %/-11 %) and reduced body weight gain (-37 %/-50 %) and, at 1,000 mg/kg bw/day, poor general condition (NOAEL maternal toxicity: 50 mg/kg bw/day; NOAEL developmental toxicity: 1,000 mg/kg bw/day).

No studies have been performed on the toxicity of dodecane-12-lactam to reproduction. Data from oral 90-day studies did not reveal any adverse effects on the reproductive organs in rats, whilst in dogs an impairment of sperm maturation, decreased testes and ovary weights, and atrophy of the prostate was found at a severely toxic dose level (about 1,000 mg/kg bw/day).

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

The following guideline studies for aquatic toxicity have been performed with dodecane-12-lactam:

<i>Cyprinus carpio</i> (OECD Guideline 203, semistatic):	LC ₅₀ (96 h): 63 mg/l (Infracor, 2002b)
<i>Daphnia magna</i> (OECD Guideline 202(I)):	EC ₅₀ (48 h): 59 mg/l (Infracor, 2002c)
<i>Scenedesmus subspicatus</i> (OECD Guideline 201):	EbC ₅₀ (72 h): 176 mg/l (Infracor, 2002d)
	ErC ₅₀ (72 h): 172 mg/l

Ecotoxicity testing performed in the late 1980s resulted in comparable effect concentrations:

<i>Leuciscus idus</i> (DIN 38412 part 15, static):	LC ₅₀ (48 h): 50 mg/l (Hüls AG, 1987)
--	--

Daphnia magna (DIN 38412 part 11): EC₅₀ (24 h): 41 mg/l (Hüls AG, 1988a)

An earlier test with *Scenedesmus subspicatus* with an EC₅₀ (72h) of 6.5 mg/l (Hüls AG, 1989c) was considered invalid, because of apparent difficulties with the analytical measurements. The stock solution, which was obtained by filtration after 16 hours of stirring, is reported to have had a concentration of 39.8 mg/l, which is far below the water solubility of about 300 mg/l.

From the lowest value among the valid studies, the EC₅₀ (24 h) for *Daphnia* of 41 mg/l, an aquatic PNEC of 0.041 mg/l is calculated using an assessment factor of 1000 according to the EU Technical Guidance Document.

Chronic Toxicity Test Results

There are no data available.

Toxicity to Microorganisms

A test of dodecane-12-lactam on *Pseudomonas putida* according to an inhouse procedure based on the inhibition of oxygen consumption gave an EC₅₀ (6 h) > 1700 mg/l (Hüls AG, 1988b).

4.2 Terrestrial Effects

There are no data on terrestrial effects available.

4.3 Other Environmental Effects

There are no data available.

4.4 Initial Assessment for the Environment

According to a Mackay Level I model calculation, the main target compartment for dodecane-12-lactam will be the hydrosphere (88.3 %), followed by sediment (5.9 %) and soil (5.8 %). The calculated Henry's law constant of 0.00079 Pa m³/mol indicates very low volatility from surface waters. With a calculated K_{oc} of 2258 l/kg, the sorption potential to soil or sediment organic matter is expected to be high.

In the atmosphere, dodecane-12-lactam is rapidly removed by reaction with hydroxyl radicals with a calculated half-life of 12 hrs. In water, it is not expected to hydrolyse at a significant rate under environmental conditions. Photolytical degradation in surface waters is expected to be of minor importance due to its chemical structure. Dodecane-12-lactam is readily biodegradable. Thus in surface waters, the predominant removal mechanism is expected to be biodegradation.

Experimentally determined BCF values below 2.6 l/kg indicate a low bioaccumulation potential.

The lowest valid acute test results of aquatic testing determined for fish, *Daphnia*, and algae were as following:

<i>Leuciscus idus</i> :	48-h-LC ₅₀ = 50 mg/l
<i>Daphnia magna</i> :	24-h-EC ₅₀ = 41 mg/l
<i>Scenedesmus subspicatus</i> :	72-h-EC ₅₀ = 176 mg/l

From the lowest value among these, an aquatic PNEC of 0.041 mg/l is calculated using an assessment factor of 1000 according to the EU Technical Guidance Document.

5 RECOMMENDATIONS

Human Health:

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

Environment:

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute aquatic toxicity which may become evident only at very high exposure levels they should nevertheless be noted by chemical safety professionals and users.

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I U C L I D

Data Set

Existing Chemical : ID: 947-04-6
CAS No. : 947-04-6
EINECS Name : dodecane-12-lactam
EC No. : 213-424-8
TSCA Name : Azacyclotridecan-2-one
Molecular Formula : C₁₂H₂₃NO

Producer related part
Company : Degussa AG
Creation date : 14.03.2001

Substance related part
Company : Degussa AG
Creation date : 14.03.2001

Status :
Memo :

Printing date : 02.12.2003
Revision date : 31.05.2003
Date of last update : 02.12.2003
Number of pages : 1

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, non confidential, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : cooperating company
Name : ATOFINA
Contact person : Dr. Jacqueline Bakès
Date : 13.06.2003
Street : 4-8, Cours Michelet
Town : 92091 Paris-la-Défense
Country : France
Phone : +33 1 4900 7121
Telefax : +33 1 4900 7214
Telex :
Cedex :
Email : jacqueline.bakes@atofina.com
Homepage : www.atofina.com

13.06.2003

Type : cooperating company
Name : Degussa AG
Contact person : Dr. Michael Weiss, Marl
Date : 01.03.2001
Street : Bennigsenplatz 1
Town : 40474 Duesseldorf
Country : Germany
Phone : +49 2365 49-4607
Telefax : +49 2365 49-7275
Telex :
Cedex :
Email : michael.weiss@degussa.com
Homepage : www.degussa.com

Remark : Contact point for any correspondence relating to the submission of this data set:

Degussa AG
 CF-CO-PM-Environment, Health & Safety
 Dr. Michael Weiss
 Bau 1137, PB 16
 D-45764 Marl

Reporting History

Year	Activity	Company
1994	Reporting	Huels AG
1997	Update	Huels AG
1998	None	Creanova Spezialchemie GmbH
2000	Update	Degussa-Huels AG
2002	Update extra	Degussa AG
2003	Update	Degussa AG

Type : cooperating company
Name : EMS-UBE Ltd.
Contact person : Mr. M. Furukawa, Mr. G. Castaldi
Date : 24.06.2002
Street : Kogushi 1978-10
Town : 755-8633 Ube

1. GENERAL INFORMATION

ID: 947-04-6

DATE: 02.12.2003

Country : Japan
Phone : +81 836 310 213
Telefax : +81 836 310 214
Telex :
Cedex :
Email : uems2k3@ube-ind.co.jp
Homepage :

(15)

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type : manufacturer
Name of plant : EMS-UBE Ltd.
Street : Kogushi 1978-10
Town : 755-8633 Ube
Country : Japan
Phone :
Telefax :
Telex :
Cedex :
Email : uems2k3@ube-ind.co.jp
Homepage :

(15)

Type : manufacturer
Name of plant : Degussa AG
Street : Paul-Baumann-Strasse 1
Town : 45764 Marl
Country : Germany
Phone : +49 2365 49-4607
Telefax : +49 2365 49-7275
Telex :
Cedex :
Email : michael.weiss@degussa.com
Homepage : www.degussa.com

03.06.2003

(10)

Type : manufacturer
Name of plant : ATOFINA - Mont
Street : BP3 - Argagnon
Town : 64300 Mont
Country : France
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Telefax : +33 1 4900 7214
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Cedex :
Email : jacqueline.bakes@atofina.com
Homepage : www.atofina.com

03.07.2003

(1)

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE**1.1.0 SUBSTANCE IDENTIFICATION****1.1.1 GENERAL SUBSTANCE INFORMATION**

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	solid
Purity	:	ca. 99.9 % w/w
Colour	:	
Odour	:	
Remark	:	Company (site): Degussa AG, Marl (Germany)

(10)

1.1.2 SPECTRA**1.2 SYNONYMS AND TRADENAMES****1-Aza-2-cyclotridecanone****12-Aminododecanoic acid lactam****12-Aminododecansaeurelactam (German)****2-Oxododecamethylenimine****Azacyclotridecan-2-one****Cyclododecalactam****Dodecalactam****Dodecan-12-lactam (German)****Dodecanoic acid, 12-amino-, lactam****Dodecanolactam****Dodecansaeure-omega-lactam (German)**

Dodecylactam**Laurin lactam****Laurinlactam****Lauro lactam****Lauryl lactam****omega-Dodecalactam****omega-Lauro lactam****1.3 IMPURITIES**

Purity : typical for marketed substance
CAS-No : 830-13-7
EC-No : 212-595-6
EINECS-Name : cyclododecanone
Molecular formula :
Value : ca. .01 % w/w

Remark : Company (site): Degussa AG, Marl (Germany)

1.4 ADDITIVES**1.5 TOTAL QUANTITY**

Quantity : ca. 50000 - tonnes produced in 2002

Remark : Worldwide annual production
Flag : Critical study for SIDS endpoint

1.6.1 LABELLING

Labelling : no labelling required (no dangerous properties)
Specific limits :

(11)

1.6.2 CLASSIFICATION

Classified : no classification required (no dangerous properties)
Class of danger :
R-Phrases :
Specific limits :

(11)

1.6.3 PACKAGING**1.7 USE PATTERN**

Type of use : type
Category : Non dispersive use

Remark : Company (site): Degussa AG, Marl (Germany)
 Predominantly closed system

(10)

Type of use : type
Category : Use in closed system

Remark : Company (site): EMS-UBE Ltd., Ube (Japan)

(15)

Type of use : industrial
Category : Chemical industry: used in synthesis

Remark : Company (site): Degussa AG, Marl (Germany)
 Company (site): EMS-UBE Ltd., Ube (Japan)

(10) (15)

Type of use : use
Category : Intermediates

Remark : Company (site): Degussa AG, Marl (Germany)
 Company (site): EMS-UBE Ltd., Ube (Japan)

(10) (15)

1.7.1 DETAILED USE PATTERN**1.7.2 METHODS OF MANUFACTURE**

Origin of substance : Synthesis
Type : Production

Method : Continuous process, water involved in process
Remark : Company (site): EMS-UBE Ltd., Ube (Japan)

(15)

1. GENERAL INFORMATION

ID: 947-04-6

DATE: 02.12.2003

Origin of substance : Synthesis
Type : Production

Method : The substance is produced by Beckmann rearrangement of lauryl oxime in concentrated sulfuric acid. The process is continuous, and water is involved in it.

Remark : Company (site): Degussa AG, Marl (Germany)

(10)

1.8 REGULATORY MEASURES**1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES**

Type of limit : MAK (DE)
Limit value :

Country : Germany
Result : MAK not established
03.06.2003

(13)

1.8.2 ACCEPTABLE RESIDUES LEVELS**1.8.3 WATER POLLUTION**

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 1 (weakly water polluting)

Country : Germany
Remark : No. 1199 in catalogue

(3)

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : no
No. in Seveso directive :

Country : Germany
Remark : Störfallverordnung 2000

(11)

1.8.5 AIR POLLUTION**1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES**

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS**1.9.2 COMPONENTS****1.10 SOURCE OF EXPOSURE**

Source of exposure : Environment: exposure from production
Exposure to the : Substance

Remark : Company (site): Degussa AG, Marl (Germany)
Result : - Release to air: approximately 15 kg/year
 - Release to waste water: ca. 0.3 kg/m³ x 1.5 m³/h x 8000
 h/year = ca. 3600 kg/year
 - Waste: ca. 500 t solid waste/year, all incinerated

(10)

Source of exposure : Environment: exposure from production
Exposure to the : Substance

Remark : Company (site): EMS-UBE Ltd., Ube (Japan)
Result : Release to surface water: negligible quantities to WWTP;
 effluent flow 0.01 m³/s

(15)

Source of exposure : Environment: exposure from production
Exposure to the : Substance

Remark : Company (site): Atofina (France)
Result : Air: Release to air amounts to about 500 kg/year.
 Water: There is no aqueous effluent from the French production process.
 Solid waste: Solid wastes are incinerated.

(1)

1.11 ADDITIONAL REMARKS**1.12 LAST LITERATURE SEARCH**

Type of search : External
Chapters covered : 3, 4
Date of search : 11.04.2003

21.10.2003

Type of search : External
Chapters covered : 5
Date of search : 01.04.2003

21.10.2003

Type of search : Internal and External
Chapters covered : 3, 4, 5
Date of search : 21.11.2001

21.10.2003

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 151.8 °C	
Sublimation	:		
Method	:	other: no data	
Year	:		
GLP	:	no data	
Test substance	:	no data	
Reliability	:	(2) valid with restrictions Data from peer reviewed handbook or collection of data	
Flag	:	Critical study for SIDS endpoint	
04.06.2003			(40)
Value	:	= 148 - 149 °C	
Sublimation	:		
Method	:	other: no data	
Year	:		
GLP	:	no data	
Test substance	:	other TS: self-made	
Reliability	:	(4) not assignable Documentation insufficient for assessment	
04.06.2003			(37)
Value	:	= 149 - 151 °C	
Sublimation	:		
Method	:	other: no data	
Year	:		
GLP	:	no data	
Test substance	:	no data	
Reliability	:	(4) not assignable Documentation insufficient for assessment	
04.11.2003			(9)
Value	:	= 150 °C	
Sublimation	:		
Method	:	other: no data	
Year	:		
GLP	:	no	
Test substance	:	other TS: self-made	
Reliability	:	(4) not assignable Documentation insufficient for assessment	
04.06.2003			(41)
Value	:	= 150 - 153 °C	
Sublimation	:		
Method	:	other: no data	
Year	:		
GLP	:	no data	
Test substance	:	no data	
Reliability	:	(4) not assignable Documentation insufficient for assessment	
04.06.2003			(5)

Value	: = 153 - 153.5 °C	
Decomposition	: no, at °C	
Sublimation	:	
Method	: other: no data	
Year	: 1949	
GLP	: no	
Test substance	: other TS	
Reliability	: (4) not assignable Documentation insufficient for assessment	
04.06.2003		(38)

2.2 BOILING POINT

Value	: ca. 348 °C at 1013 hPa	
Decomposition	:	
Method	: other: Part of a vapour pressure curve. Knowledge of the equipment available by the time of testing indicates performance comparable to OECD TG 104.	
Year	: 1973	
GLP	: no	
Test substance	: other TS: Most probably dodecane-12-lactam of Hüls AG, purity ca. 99.9 %	
Reliability	: (2) valid with restrictions Data from collection of data (not peer reviewed), supported by additional evidence: - Date and responsibility of the test are reported. - Test substance: Not documented but certainly of high purity - Method: Not documented but certainly comparable to OECD TG 104. - Dependence on temperature: The whole vapour pressure curve from the reference shows normal behaviour and good agreement within itself and with independently determined vapour pressure curves (see chapter 2.4 and additional data in the reference). - QSAR check: MpBpWin v1.40 from the EPIWIN software suite predicts a value of 361 °C, i.e. the magnitude of the value is reasonable.	
Flag	: Critical study for SIDS endpoint	
02.12.2003		(31)

2.3 DENSITY

Type	: density	
Value	: = .971 - .9747 g/cm ³ at 20 °C	
Method	: other: Pycnometer	
Year	: 1991	
GLP	: no	
Test substance	: other TS: Hüls AG, representative sample	
Result	: Mean density (3 digits) = 0.973 g/cm ³	
Test condition	: Two determinations in water	
Reliability	: (2) valid with restrictions Study not well documented, but sufficiently in view of its simplicity.	
Flag	: Critical study for SIDS endpoint	
22.10.2003		(29)
Type	: density	
Value	: = .968 - .9686 g/cm ³ at 50 °C	

Method : other: Pycnometer
Year : 1991
GLP : no
Test substance : other TS: Hüls AG, representative sample

Result : Mean density (3 digits) = 0.968 g/cm³
Test condition : Two determinations in water
Reliability : (2) valid with restrictions
 Study not well documented, but sufficiently in view of its simplicity.

22.10.2003 (29)

Type : density
Value : = .9617 - .9648 g/cm³ at 80 °C
Method : other: Pycnometer
Year : 1991
GLP : no
Test substance : other TS: Hüls AG, representative sample

Result : Individual results: 0.9626; 0.9648; 0.9617 g/cm³
 Mean density (3 digits) = 0.962 g/cm³
Test condition : Three determinations in water
Reliability : (2) valid with restrictions
 Study not well documented, but sufficiently in view of its simplicity.

22.10.2003 (29)

Type : density
Value : = .9063 - .9067 g/cm³ at 160 °C
Method : other: Pycnometer
Year : 1991
GLP : no
Test substance : other TS: Hüls AG, representative sample

Result : Mean density (3 digits) = 0.906 g/cm³
Test condition : Two determinations in liquid state
Reliability : (2) valid with restrictions
 Study not well documented, but sufficiently in view of its simplicity.

22.10.2003 (29)

Type : density
Value : = .9 g/cm³ at 160 °C
Method : other: no data
Year :
GLP : no data
Test substance : no data

Reliability : (2) valid with restrictions
 Data from handbook or collection of data
Flag : Critical study for SIDS endpoint

22.10.2003 (40)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : ca. .000012 hPa at 20 °C
Decomposition : no
Method : other (calculated): Extrapolation from measured data

Year	:		
GLP	:	no	
Test substance	:	as prescribed by 1.1 - 1.4	
Remark	:	Extrapolated from the experimentally determined vapour pressure curve in the source referenced: 220 degree C: 25.6 hPa 199 degree C: 10.9 hPa 180 degree C: 3.47 hPa 170.5 degree C: 2.73 hPa 159.6 degree C: 1.43 hPa 158 degree C: 1.08 hPa 148.3 degree C: 0.751 hPa 143 degree C: 0.448 hPa 139.5 degree C: 0.413 hPa 130.3 degree C: 0.203 hPa 119.8 degree C: 0.092 hPa 91.4 degree C: 0.015 hPa $\log(VP) = -4583 * (1/T) + 10.7071$ (T in K, VP in hPa) correlation coefficient: -0.9984	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
Flag	:	Critical study for SIDS endpoint	(6)
Value	:	ca. .00006 hPa at 20 °C	
Decomposition	:	no	
Method	:	other (calculated): Extrapolation from measured data	
Year	:		
GLP	:	no	
Test substance	:	as prescribed by 1.1 - 1.4	
Remark	:	Extrapolated from the experimentally determined vapour pressure curve in the source referenced: 348 degree C: 1013 hPa 318 degree C: 533 hPa 266 degree C: 133 hPa 237 degree C: 53 hPa 203 degree C: 13.3 hPa 189 degree C: 6.67 hPa 158 degree C: 1.33 hPa $\log(VP) = -4049 * (1/T) + 9.59082$ (T in K, VP in hPa)	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	(31)
Value	:	= .35 hPa at 180 °C	
Decomposition	:		
Method	:		
Year	:		
GLP	:	no data	
Test substance	:	no data	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	(40)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water	
Log pow	:	= 2.92 at °C	
pH value	:		
Method	:	other (measured)	
Year	:		
GLP	:	no data	
Test substance	:	no data	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
Flag	:	Critical study for SIDS endpoint	(9)
04.06.2003			
Partition coefficient	:	octanol-water	
Log pow	:	= 2.81 at 23 °C	
pH value	:		
Method	:	OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"	
Year	:	1981	
GLP	:	no	
Test substance	:	as prescribed by 1.1 - 1.4	
Reliability	:	(2) valid with restrictions Guideline study without detailed documentation	
04.06.2003			(27)
Partition coefficient	:	octanol-water	
Log pow	:	= 3.61 at °C	
pH value	:		
Method	:	other (calculated): SRC Logkow v1.54 Computer Program, Syracuse Research Corporation	
Year	:		
GLP	:		
Test substance	:		
Reliability	:	(2) valid with restrictions Accepted calculation method	
04.06.2003			(12)
Partition coefficient	:	octanol-water	
Log pow	:	= 1.72 at °C	
pH value	:		
Method	:	other (calculated)	
Year	:		
GLP	:		
Test substance	:		
Reliability	:	(4) not assignable Documentation insufficient for assessment	
04.06.2003			(14)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in Value	:	Water
pH value concentration	:	= .3 g/l at 20 °C
Temperature effects	:	at °C

Examine different pol.	:		
pKa	:	at 25 °C	
Description	:	moderately soluble (100-1000 mg/L)	
Stable	:		
Deg. product	:		
Method	:	other: no data	
Year	:		
GLP	:	no data	
Test substance	:	no data	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	
Flag	:	Critical study for SIDS endpoint	
04.06.2003			(40)
Solubility in Value	:	Water ca. .62 g/l at 22 °C	
pH value concentration	:	at °C	
Temperature effects	:		
Examine different pol.	:		
pKa	:	at 25 °C	
Description	:	moderately soluble (100-1000 mg/L)	
Stable	:		
Deg. product	:		
Method	:	other:	
Year	:	1957	
GLP	:	No	
Test substance	:	other TS	
Method	:	Pure substance in excess was kept in contact with water for 24 hours, a sample of the aqueous phase was taken, the water was removed by vacuum / heat treatment and the residue was weighed.	
Remark	:	The determination explicitly does not claim accuracy.	
Result	:	Solubility in other solvents at 22 degree C: 1,4-Dioxane: 28.4 g/l Benzene: 23.9 g/l Cyclohexane: 1.2 g/l	
Reliability	:	(3) invalid Significant methodological deficiencies	
04.06.2003			(17)
Solubility in Value	:	Water = .29 g/l at 25 °C	
pH value concentration	:	at °C	
Temperature effects	:		
Examine different pol.	:		
pKa	:	at 25 °C	
Description	:	moderately soluble (100-1000 mg/L)	
Stable	:		
Deg. product	:		
Method	:	other: no data	
Year	:		
GLP	:	no data	
Test substance	:	no data	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data	

04.06.2003

(9)

2.6.2 SURFACE TENSION**2.7 FLASH POINT**

Value : = 192 °C
Type : open cup
Method : other: DIN 51376
Year :
GLP : no data
Test substance : no data

Reliability : (2) valid with restrictions
Data from handbook or collection of data

(40)

2.8 AUTO FLAMMABILITY

Value : 320 - 330 °C at
Method : other: no data
Year :
GLP : no data
Test substance : no data

Reliability : (2) valid with restrictions
Data from handbook or collection of data

(40)

2.9 FLAMMABILITY**2.10 EXPLOSIVE PROPERTIES****2.11 OXIDIZING PROPERTIES****2.12 DISSOCIATION CONSTANT****2.13 VISCOSITY****2.14 ADDITIONAL REMARKS**

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm ³
Rate constant	:	= .0000000000331 cm ³ /(molecule*sec)
Degradation	:	= 50 % after .5 day(s)
Deg. product	:	
Method	:	other (calculated): AOP Computer Program, Vers. 1.53, Syracuse Research Center (based on method of Atkinson, see below)
Year	:	1994
GLP	:	
Test substance	:	
Method	:	Atkinson R (1987). A structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. Int J. Chem. Kinet. 19, 799-828
Remark	:	half-life refers to 24 hour-days
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint
05.06.2003		(12)

3.1.2 STABILITY IN WATER

Result	:	There are no experimental observations indicating significant hydrolysis under environmental conditions. Hydrolysis might be revealed during studies on water solubility and ecotoxicity. In particular, the homopolymers would break down rapidly in contact with water if the aliphatic amide function was liable to significant hydrolysis at room temperature. Polyamides are, however, used in textiles which are washed frequently even at elevated temperatures. With HYDROWIN v 1.67 a half-life of > 1 year can be estimated.
Reliability	:	(2) valid with restrictions Expert judgement
Flag	:	Critical study for SIDS endpoint
02.12.2003		(12)

3.1.3 STABILITY IN SOIL**3.2.1 MONITORING DATA****3.2.2 FIELD STUDIES**

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS**3.3.2 DISTRIBUTION**

Media	:	water - air	
Method	:	other (calculation): Vapour pressure x molecular weight / water solubility = 0.0012 Pa x 197.32 g/mol / (300 g/m ³)	
Year	:		
Result	:	Henry's Law Constant = 0.00079 Pa m ³ /mol	
Reliability	:	(2) valid with restrictions Accepted calculation method	
Flag	:	Critical study for SIDS endpoint	(12)
05.06.2003			
Media	:	water - soil	
Method	:	other (calculation): PCKowWin Version 1.66 as integrated in EpiWin Version 3.10 (first-order molecular connectivity index (1-MCI) method), Syracuse Research Center / U.S. EPA	
Year	:		
Result	:	Koc = 2258; log Koc = 3.354 "high" potential for geoaccumulation (Blume scale)	
Reliability	:	(2) valid with restrictions Accepted calculation method	
Flag	:	Critical study for SIDS endpoint	(12)
02.12.2003			
Media	:	air - biota - sediment(s) - soil - water	
Method	:	Calculation according Mackay, Level I	
Year	:		
Method	:	Level I V 2.11 Model with standard settings	
Result	:	Air: 0.0245 % Water: 88.2600 % Soil: 5.8048 % Sediment: 5.8692 % Susp. Sediment 0.0377 % Fish: 0.0037 % Aerosol: 1.16E-4 %	
Test condition	:	Data used: Molecular weight: 197.32 g/mol log Pow: 2.92 Vapour pressure: 0.0012 Pa Water solubility: 0.3 g/l Melting point: 151.8 degree C Temperature: 20 degree C	
		----- Volumes, densities, and organic carbon / fat concentration: Air: 6 000 000 000 m ³ , 1.206 kg/m ³ Water: 7 000 000 m ³ , 1000 kg/m ³ Soil: 45 000 m ³ , 1500 kg/m ³ , 2 % OC Sediment: 21 000 m ³ , 1300 kg/m ³ , 5 % OC Susp. sediment: 35 m ³ , 1500 kg/m ³ , 16.7 % OC Fish: 7 m ³ , 1000 kg/m ³ , 5 % fat Aerosol: 0.12 m ³ , 1500 kg/m ³	
Reliability	:	(2) valid with restrictions Accepted calculation method	

Flag : Critical study for SIDS endpoint
04.06.2003 (12)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, domestic, non-adapted
Concentration : 20.9 mg/l related to Test substance
 15.3 mg/l related to DOC (Dissolved Organic Carbon)
Contact time :
Degradation : = 83 (±) % after 28 day(s)
Result : readily biodegradable
Kinetic of testsubst. : 5 day(s) = 2 - 5 %
 9 day(s) = 10 - 39 %
 12 day(s) = 56 - 61 %
 14 day(s) = 65 - 70 %
 19 day(s) = 71 - 84 %
Control substance : Benzoic acid, sodium salt
Kinetic : 2 day(s) = 36 %
 9 day(s) = 79 %
Deg. product :
Method : OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO₂ evolution)"
Year : 1992
GLP : yes
Test substance : other TS: Degussa AG,
 Batch No. 3347/24418, 24 March 2000
 Sample No. 1863/011001, ID No. 0649/82141
 purity 99.86 % (GC)
Method : Directive 92/69/EEC, C.4-C
Test condition : INOCULUM/TEST ORGANISM
 - Source: Municipal STP Marl-Ost, sampled 08 Jan 2002
 - Initial cell concentration: 20 ml/test vessel, 114E+04 CFU/ml
 TEST SYSTEM
 - Culturing apparatus: ca. 5000 ml Woulff Flask with standard ground joints
 - Number of culture flasks per concentration:
 test substance 2, control substance 1, inoculum only 2
 - Aeration device: aeration with CO₂-free air
 - Measuring equipment: Shimadzu carbon analyzer
 METHOD OF PREPARATION OF TEST SOLUTION: preparation of 20 l of mineral medium, aeration overnight, 2400 ml into each test vessel, addition of inoculum, complete to 3 l.
 DURATION OF THE TEST: 29 days (acidification on day 28)
 ANALYTICAL PARAMETER: TIC (total inorganic carbon) analysis of bound carbon dioxide
 SAMPLING: after 0, 2, 5, 9, 12, 14, 19, 23, 28 and 29 days
 TEST CONDITIONS
 - Test temperature: 20.8-22.1 (mean 21.3) degree C
 - pH value: 7.4 (day 28)
 - Concentration of suspended solids: 27.7 mg/l
 REFERENCE SUBSTANCE: concentration 25.0 mg/l
Reliability : (1) valid without restriction

	Guideline study	
Flag	: Critical study for SIDS endpoint	
04.11.2003		(33)
Type	: aerobic	
Inoculum	: activated sludge, non-adapted	
Concentration	: 51 mg/l related to Test substance related to	
Contact time	:	
Degradation	: = 90 (±) % after 14 day(s)	
Result	: readily biodegradable	
Kinetic of testsubst.	: 7 day(s) = 1 % 14 day(s) = 90 % 21 day(s) > 100 % 28 day(s) > 100 % %	
Control substance	: Diethylene glycol	
Kinetic	: 14 day(s) = 55 % 21 day(s) = 84 %	
Deg. product	: not measured	
Method	: other: BODIS Test (ISO 10708, in preparation)	
Year	: 1989	
GLP	: no	
Test substance	: as prescribed by 1.1 - 1.4	
Result	: Reported degrees of degradation of test substance: 7 days: 1 % (individual replicate results: 1 %; 0 %; 2 %) 14 days: 90 % (89 %; 91 %; 91 %) 21 days: 105 % (103 %; 105 %; 107 %) 28 days: 108 % (106 %; 110 %; 109 %) Linear interpolation of the degrees of degradation between days 7 and 14 indicates passage of the 10 % level after ... days and 60 % degradation within 4.7 days: $(90 - 1) \% \text{ in } 7 \text{ days} = 12.7 \% / \text{day}$ $12.7 \% / \text{day} = (10 - 1) \% / 0.71 \text{ days} = 60 \% / 4.7 \text{ days}$	
Test condition	: INOCULUM/TEST ORGANISM - Type of sludge: activated sludge from predominantly domestic sewage treatment plant - Sampling site: STP Marl-West - Pretreatment: stabilization for one week under conditions of testing laboratory TEST SYSTEM - Culturing apparatus: glass bottles, 200 ml test solution, 91 ml air - Number of culture flasks per concentration: 3 - Aeration device: continuous shaking - Closed vessels used: yes INITIAL TEST SUBSTANCE CONCENTRATION: 10.2 mg/200 ml DURATION OF THE TEST: 28 days ANALYTICAL PARAMETER: BOD = Oxygen SAMPLING: weekly CONTROLS: blank, reference substance REFERENCE SUBSTANCE: diethylene glycol	
Reliability	: (2) valid with restrictions Comparable to guideline study with acceptable restrictions	
11.07.2003		(25)
Type	: aerobic	
Inoculum	: activated sludge	
Concentration	: 100 mg/l related to Test substance related to	

3. ENVIRONMENTAL FATE AND PATHWAYS

ID: 947-04-6

DATE: 02.12.2003

Contact time :
Degradation : = 0 (±) % after 28 day(s)
Result : under test conditions no biodegradation observed
Deg. product :
Method : other: Comparable to OECD Test Guideline 301C, Modified MITI Test (I) (1981)

Year : 1992
GLP : no data
Test substance : no data

Test condition : 30 mg/l activated sludge
300 ml test solution at 25 degree C
Reliability : (2) valid with restrictions
Comparable to guideline study with acceptable restrictions
30.07.2003 (9)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : Cyprinus carpio (Fish, fresh water)
Exposure period : 42 day(s) at 25 °C
Concentration : .5 mg/l
BCF : = .8 - 1.2
Elimination : no data
Method : other: corresponding to OECD guideline 305 C (1981)
Year : 1992
GLP : no data
Test substance : no data

Result : BCF at 0.05 mg/l exposure level < 2.6
Test condition : Flow-through system;
O2 6-8 mg/l;
15-20 fish/level, average lipid content 4.8 %;
Analysis by gas chromatography
Reliability : (2) valid with restrictions
Test procedure according to guideline without detailed documentation
Flag : Critical study for SIDS endpoint
05.06.2003 (9)

Species : other: QSAR estimate
Exposure period : at °C
Concentration :
BCF : = 35.35
Elimination :
Method : other: calculation with BCFWIN v2.14 as integrated in EPIWIN v3.10,
Syracuse Research Center / U.S. EPA
Year :
GLP :
Test substance :

Test condition : log Kow used: 2.92
Reliability : (2) valid with restrictions
Accepted calculation method
02.12.2003 (12)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	: semistatic
Species	: Cyprinus carpio (Fish, fresh water)
Exposure period	: 96 hour(s)
Unit	: mg/l
LC0	: = 48
LC50	: = 63
LC100	: = 84
Limit test	: no
Analytical monitoring	: yes
Method	: Directive 84/449/EEC, C.1 "Acute toxicity for fish"
Year	: 1992
GLP	: yes
Test substance	: other TS: Degussa AG Batch No. 3347/24418, 24 March 2000 Sample No. 1863/011001, ID No. 0649/82141 purity 99.86 % (GC)
Method	: OECD Test Guideline 203 (1992)
Result	: - Nominal/measured concentrations: Concentrations of stock solutions were determined analytically; concentrations of test solutions were calculated from concentrations of stock solutions. - Stability control: 13; 27; 76; 245 mg/l nominal 15; 30; 79; 248 mg/l; stock: 272 mg/l (measured at 0 h) 15; 31; 79; 258 mg/l; stock: 295 mg/l (measured at 24 h) - Effect data (Mortality): no mortalities at concentrations <= 48 mg/l 100 % mortality at concentrations >= 84 mg/l within 24 h
Test condition	: TEST ORGANISMS - Supplier: Di Mamma, Brakel (The Netherlands) - Age/size/weight/loading: length 3-5 cm, weight ca. 0.52 g - Feeding: ca. 2 % of body weight daily - Pretreatment: 14 days quarantine - Feeding during test: no STOCK AND TEST SOLUTION AND THEIR PREPARATION - Other procedures: 1 g test substance was stirred for ca. 18 hours in water and filtered. Test solutions were prepared daily. STABILITY OF THE TEST CHEMICAL SOLUTIONS: confirmed in pilot study: analytical determination after 0 and 24 hours of concentration series 13; 27; 76; 245 mg/l nominal DILUTION WATER - Source: synthetic fresh water CaCl ₂ x 2 H ₂ O: 294 mg/l MgSO ₄ x 6 H ₂ O: 114 mg/l NaHCO ₃ : 65 mg/l KCl: 6 mg/l - Ca/Mg ratio: 4:1 - Na/K ratio: 10:1 - Aeration: continuous - Hardness: 14 degree dH = 250 mg CaCO ₃ /l - pH: 8.1 - Oxygen content: 8.6 mg/l TEST SYSTEM - Concentrations: 28; 48; 84; 146; 253 mg/l

	- Renewal of test solution: daily
	- Exposure vessel type: volume 20 l, water content 10 l
	- Number of replicates, fish per replicate: 1 replicate with 10 fish
	- Test temperature: 20.0 (19.2-20.6) degree C
	- Dissolved oxygen: 94-100 % saturation
	- pH: 7.8-8.1
	- Adjustment of pH: no
	- Photoperiod: 16 / 8 hours
	DURATION OF THE TEST: 96 hours
	MONITORING OF TEST SUBSTANCE CONCENTRATION: DOC determination
Reliability	: (1) valid without restriction
	Guideline study
Flag	: Critical study for SIDS endpoint
04.11.2003	
	(34)
Type	: static
Species	: Leuciscus idus (Fish, fresh water)
Exposure period	: 48 hour(s)
Unit	: mg/l
LC0	: = 40
LC50	: = 50
LC100	: = 60
Limit test	: no
Analytical monitoring	: no
Method	: other: DIN 38412 part 15
Year	: 1987
GLP	: no
Test substance	: as prescribed by 1.1 - 1.4
Result	: RESULTS: - Effect data (Mortality): Dead fish after 48 hours ----- 40 mg/l 0 50 mg/l 3 60 mg/l 10 ----- 95 % confidence interval of LC50: 37 - 68 mg/l
Test condition	: TEST ORGANISMS - Strain: Leuciscus idus melanotus HECKEL - Supplier: Eggers, Hohenwestedt (Germany) - Wild caught: no - Feeding: daily 3 % of body weight TetraMin - Pretreatment: single treatment with Zephirol 1:50,000 for 1 hour followed by 14 days under quarantine - Feeding during test: no STOCK AND TEST SOLUTION AND THEIR PREPARATION - Concentration of vehicle / solvent: Solubilizer ethanol (CAS No. 64-17-5), concentration not reported; concentration of test substance 100 g/l TEST SYSTEM - Test type: static - Concentrations: 40 / 50 / 60 mg/l - Renewal of test solution: no - Exposure vessel type: 10 l solution in 18 l aquarium - Number of replicates, fish per replicate: 1, 10 - Test temperature: 20 +/- 1 degree C - Dissolved oxygen: 7.9-9.0 mg/l - pH: 7.3-8.1 - Adjustment of pH: no

	DURATION OF THE TEST: 48 hours	
	TEST PARAMETER: mortality	
Reliability	: (2) valid with restrictions	
	Including additional raw data, the study is well documented, meets generally accepted scientific principles, acceptable for assessment	
Flag	: Critical study for SIDS endpoint	
11.07.2003		(21)
Type	:	
Species	: Oryzias latipes (Fish, fresh water)	
Exposure period	: 48 hour(s)	
Unit	: mg/l	
LC50	: = 68.4	
Limit test	: no	
Analytical monitoring	: no data	
Method	: other: JIS K 0102-1986-71 (Japanese Industrial Standard)	
Year	: 1992	
GLP	: no data	
Test substance	: no data	
Test condition	: TEST ORGANISMS	
	- Supplier: Nakashima fish farm, Kuamoto 869-01, Japan	
	- Wild caught: no	
	- Pretreatment: external disinfection with Elbarju and sodium chloride; acclimatization; HgCl ₂ test	
	DILUTION WATER	
	- Source: Underground water pumped up from the ground of Kurume Research Laboratories.	
	- Various parameters were determined but not reported.	
	TEST SYSTEM	
	- Test type: static or semistatic	
	- Renewal of test solution: every 6-8 hours in case of semi-static	
	- Exposure vessel type: round glass vessel, 4 l / level	
	- Number of replicates, fish per replicate: 10 fish / level	
	- Test temperature: 25 +/- 2 degree C	
	- Various parameters were determined but not reported.	
	STATISTICAL METHODS: Doudoroff method or Probit method	
Reliability	: (2) valid with restrictions	
	Test procedure in accordance with national standard methods with acceptable restrictions (documentation incomplete)	
05.06.2003		(9)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	: static
Species	: Daphnia magna (Crustacea)
Exposure period	: 48 hour(s)
Unit	: mg/l
EC0	: = 23
EC50	: = 59
EC100	: = 245
Limit Test	: no
Analytical monitoring	: yes
Method	: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year	: 1992
GLP	: yes

Test substance	: other TS: Degussa AG Batch No. 3347/24418, 24 March 2000 Sample No. 1863/011001, ID No. 0649/82141 purity 99.86 % (GC)
Method	: OECD Test Guideline 202(I) (1984)
Result	: RESULTS: EXPOSED - Nominal/measured concentrations: Concentrations of stock solutions were determined analytically; concentrations of test solutions were calculated from concentrations of stock solutions. Results of nominal vs analytical and stability control: 13; 27; 75; 245 mg/l (nominal) 15; 30; 79; 248 mg/l, 272 mg/l (stock) measured (0 hours) 14; 30; 80; 251 mg/l, 298 mg/l (stock) measured (48 hours) - Effect data (Immobilisation): 13; 23; 42; 76; 136; 245 mg/l 0; 0; 0; 11; 13; 20 immobile after 24 hours 0; 0; 3; 17; 19; 20 immobile after 48 hours - 24 h EC50 = 72 (42-76) mg/l (graphically) 48 h EC50 = 59 (48-73) mg/l (probit analysis) RESULTS CONTROL: 0 immobile after 24 h, 1 immobile after 48 h RESULTS: TEST WITH REFERENCE SUBSTANCE - Concentrations: 1.0 mg/l; 2.0 mg/l - Results: 45 % immobilisation; 100 % immobilisation (24 h)
Test condition	: TEST ORGANISMS - Strain: Daphnia magna Straus, clone 5 - Source/supplier: inhouse - Breeding method: Females are maintained in M4 medium in 1 l beakers. At 2-3 day intervals, the exuviae are syphoned off and the water is changed. In the course of this, the offspring is removed from the breeding vessels. Juveniles are isolated for further breeding each ca. 4 weeks - Age: < 24 hours - Feeding: Scenedesmus subspicatus, as much as consumed - Pretreatment: Filtration of adults 24 h prior to testing - Feeding during test: no - Control group: yes STOCK AND TEST SOLUTION AND THEIR PREPARATION - Other procedures: 1 g test substance was stirred for ca. 18 hours in synthetic fresh water and filtered. STABILITY OF THE TEST CHEMICAL SOLUTIONS: confirmed in pilot study: analytical determination after 0 and 48 hours of concentration series 13; 27; 76; 245 mg/l nominal and stock solution REFERENCE SUBSTANCE: potassium dichromate, CAS RN 7778-50-9 DILUTION WATER - Source: Synthetic: CaCl ₂ x 2 H ₂ O: 294 mg/l MgSO ₄ x 6 H ₂ O: 114 mg/l NaHCO ₃ : 65 mg/l KCl: 6 mg/l - Ca/Mg ratio: 4:1 - Na/K ratio: 10:1 TEST SYSTEM - Concentrations: 13; 23; 42; 76; 136; 245 mg/l - Exposure vessel type: round-bottom test tubes calibrated to 10 ml - Number of replicates, individuals per replicate: 4 replicates with 5 individuals each - Test temperature: 20 +/- 1 degree C

		- Dissolved oxygen: \geq 7.3 mg/l by end of test - Photoperiod: dark DURATION OF THE TEST: 48 hours TEST PARAMETER: immobilisation MONITORING OF TEST SUBSTANCE CONCENTRATION: DOC measurement	
Reliability	:	(1) valid without restriction Guideline study	
Flag 21.10.2003	:	Critical study for SIDS endpoint	(36)
Type	:	static	
Species	:	Daphnia magna (Crustacea)	
Exposure period	:	24 hour(s)	
Unit	:	mg/l	
EC50	:	= 41	
EC100	:	> 73	
Limit Test	:	no	
Analytical monitoring	:	no	
Method	:	other: DIN 38412 part 11	
Year	:	1988	
GLP	:	no	
Test substance	:	as prescribed by 1.1 - 1.4	
Result	:	RESULTS: EXPOSED, CONTROL - Effect data (Immobilisation): No. of immobile daphnia Control: 1 (24 h) 13.5 mg/l: 2 (24 h) 19.0 mg/l: 2 (24 h) 27.1 mg/l: 3 (24 h) 37.9 mg/l: 8 (24 h) 54.2 mg/l: 12 (24 h) 73.1 mg/l: 19 (24 h) EC50, 95 % confidence interval: 34.7-48.6 mg/l (24 hours) RESULTS: TEST WITH REFERENCE SUBSTANCE - Concentrations: 0.9 mg/l / 1.9 mg/l - Results: 0 % immobile / 55 % immobile (24 hours)	
Test condition	:	TEST ORGANISMS - Strain: Daphnia magna, Ircha - Source/supplier: Hüls AG (inhouse) - Control group: 2 reference substance controls, one blank STOCK AND TEST SOLUTION AND THEIR PREPARATION - Concentration: Saturated solution, concentration 198 mg DOC/l = 271 mg test substance/l. REFERENCE SUBSTANCE: potassium dichromate, CAS RN 7778-50-9 TEST SYSTEM - Concentrations: 13.5; 19.0; 27.1; 37.9; 54.2; 73.1 mg/l (nominal) - Number of replicates, individuals per replicate: 4 replicates with 5 individuals each - Test temperature: 20 +/- 1 degree C DURATION OF THE TEST: 24 hours TEST PARAMETER: immobilisation STATISTICAL METHODS: probit analysis	
Reliability	:	(2) valid with restrictions Including additional raw data, the study is well documented, meets generally accepted scientific principles, acceptable for assessment	
Flag 11.07.2003	:	Critical study for SIDS endpoint	(22)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Scenedesmus subspicatus (Algae)
Endpoint : biomass
Exposure period : 72 hour(s)
Unit : mg/l
NOEC : = 135
EC10 : = 137
EC50 : = 176
Limit test :
Analytical monitoring : yes
Method : Directive 87/302/EEC, part C, p. 89 "Algal inhibition test"
Year : 1992
GLP : yes
Test substance : other TS: Degussa AG
Batch No. 3347/24418, 24 March 2000
Sample No. 1863/011001, ID No. 0649/82141
purity 99.86 % (GC)

Method : OECD Test Guideline 201 (1984)
Result : RESULTS: EXPOSED
- Nominal/measured concentrations:
Analyses were performed only for the stability control:
13; 78; 249 mg/l nominal,
15; 89; 257 mg/l measured (0 hours)
15; 87; 250 mg/l measured (72 hours)
- Effect data/Element values: based on nominal concentrations
EC10 (growth rate) = 141 mg/l
EC50 (growth rate) = 172 mg/l
- Cell density data: (cells/ml)
control: 2E+04 (0 h); 55E+04 (72 h)
13 mg/l: 2E+04 (0 h); 68E+04 (72 h)
23 mg/l: 2E+04 (0 h); 86E+04 (72 h)
42 mg/l: 2E+04 (0 h); 156E+04 (72 h)
76 mg/l: 2E+04 (0 h); 147E+04 (72 h)
135 mg/l: 2E+04 (0 h); 53E+04 (72 h)
243 mg/l: 2E+04 (0 h); 1E+04 (72 h)
- Note the stimulatory (hormetic) effect at low concentrations.

Test condition : TEST ORGANISMS
- Strain: CHODAT (86.81 SAG)
- Source/supplier: origin: University of Göttingen (Germany)
- Laboratory culture: From a stock culture, a preculture is seeded three days before begin of test. Test cultures are seeded from the latter.
- Method of cultivation: Erlenmeyer flasks under light benches on a rotary shaker at 100 rpm (12 x 15 minutes/day)
- Controls: yes
- Initial cell concentration: approximately 20,000 cells/ml
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Concentration of vehicle/ solvent: 1 g/l stirred in deionized water for about 18 h and filtered off: 270 mg/l
STABILITY OF THE TEST CHEMICAL SOLUTIONS: series of test substance solutions (13; 78; 249 mg/l nominal) without test organism, otherwise same conditions
GROWTH/TEST MEDIUM CHEMISTRY: as described in methods
TEST SYSTEM
- Concentrations: 13; 23; 42; 76; 135; 243 mg/l
- Renewal of test solution: no
- Exposure vessel type: Erlenmeyer flasks under light benches on a rotary shaker at 100 rpm (12 x 15 minutes/day =

	every 2 hours)	
	- Number of replicates: 5 (test substance) resp. 10 (control)	
	- Test temperature: 24.3-24.5 degree C	
	- pH: beginning of test: 7.6-8.0; end of test: 8.0-10.1	
	- Intensity of irradiation: approximately 6,000-10,000 lux, white	
	MONITORING OF TEST SUBSTANCE CONCENTRATION: determination of dissolved organic carbon	
Reliability	: (1) valid without restriction	
	Guideline study	
Flag	: Critical study for SIDS endpoint	
04.11.2003		(35)
Species	: <i>Scenedesmus subspicatus</i> (Algae)	
Endpoint	: growth rate	
Exposure period	: 72 hour(s)	
Unit	: mg/l	
EC10	: = .9	
EC50	: = 6.5	
EC90	: = 44.6	
Limit test	: no	
Analytical monitoring	: no	
Method	: other: German Umweltbundesamt draft procedure	
Year	: 1984	
GLP	: no	
Test substance	: as prescribed by 1.1 - 1.4	
Remark	: The result is in conflict with the GLP study, which was performed later because the present study was considered to be insufficiently documented. According to information from the production plant operator, the purity of the product has not changed significantly since the sample for the present study was taken. Particularly the highly toxic substance hydroxyl ammonium sulfate, which is used in the synthesis of dodecane-12-lactam, is not expected to have occurred in the final product. Thus the most probable source of error is the analytical equipment, which determined a concentration of the stock solution far below water solubility.	
Result	: RESULTS: EXPOSED AND CONTROL - Cell density data: Cells/ml after 0; 24; 48; 72 hours (mean)	

	Control: 1; 4.3; 10.0; 19.9 (x 10,000)	
	1.2 mg/l: 1; 5.1; 9.0; 16.3 (x 10,000)	
	2.4 mg/l: 1; 5.3; 8.8; 15.0 (x 10,000)	
	4.0 mg/l: 1; 5.1; 8.9; 14.1 (x 10,000)	
	7.2 mg/l: 1; 4.6; 7.3; 10.6 (x 10,000)	
	11.9 mg/l: 1; 3.5; 4.9; 5.7 (x 10,000)	
	19.9 mg/l: 1; 2.9; 3.4; 3.5 (x 10,000)	
Test condition	: TEST ORGANISMS - Strain: CHODAT (86.81 SAG) - Source/supplier: Origin: Institut fuer Wasser-, Boden- und Lufthygiene, Berlin, further bred inhouse - Laboratory culture: From a stock culture, a preculture is seeded three days before begin of test. Test cultures are seeded from the latter. - Controls: yes - Initial cell concentration: ca. 10,000 cells/ml	
	STOCK AND TEST SOLUTION AND THEIR PREPARATION - Concentration of vehicle/ solvent: Test substance stirred in water for 16 hours and filtered, no vehicle or solvent. Resulting concentration 39.8 mg/l	
	TEST SYSTEM	

- Concentrations:
0 / 1.2 / 2.4 / 4.0 / 7.2 / 11.9 / 19.9 mg/l
- Renewal of test solution: no
- Number of replicates: 4
STATISTICAL METHODS: Probit analysis
Reliability : (3) invalid
Observations with water solubility in conflict with other studies, test concentration data not reliable.
14.07.2003 (24)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : Pseudomonas putida (Bacteria)
Exposure period : 6 hour(s)
Unit : mg/l
EC10 : > 1700
Analytical monitoring Method : no
: other: Test for inhibition of oxygen consumption by Pseudomonas putida (Hüls Method)
Year : 1988
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : Test concentration (mg/l): 0 85.9 431.7 842.5 1717
Decrease in O2 (HgCl2): - +0.01 -0.20 -0.16 -0.08
Decrease in O2 (Test): 4.98 5.02 4.82 4.85 4.86
Percent effect := 0 -0.8 3.2 2.6 2.4

Test condition : STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Concentration of vehicle/ solvent: Nonyl phenol, ethoxylated (10 EO), propoxylated (5 PO) was used as solubilizer.
REFERENCE SUBSTANCE: HgCl2 was added to a parallel test series resulting in complete inhibition of oxygen consumption
TEST SYSTEM
- Test type: static
- Concentrations: 85.9; 431.7; 842.5; 1717 mg/l
- Renewal of test solution: no
- Number of replicates: 1
DURATION OF THE TEST: 5-6 hours
TEST PARAMETER: oxygen consumption

Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment

Flag : Critical study for SIDS endpoint

16.07.2003 (23)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

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 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 2330 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	5
Vehicle	:	other: fatty alcohol ethoxylate (Cremophor EL)
Doses	:	
Method	:	other: OECD Guideline 401 "Acute Oral Toxicity" (1981)
Year	:	1985
GLP	:	no
Test substance	:	other TS: purity > 99.9 %; main impurity cyclododecanone ca. 100 ppm
Result	:	<p>MORTALITY:</p> <p>1580 mg/kg: none</p> <p>1990 mg/kg: 3 males, 1 female, within 24 hours</p> <p>2510 mg/kg: 1 male, 5 females, within 24 hours</p> <p>3160 mg/kg: 8 males, 7 females, within 72 hours</p> <p>CLINICAL SIGNS: observed in all dosed animals: About 10 to 15 minutes after administration, the animals took a prone position and showed convulsive twitches, tremor and Straub's phenomenon. After half an hour, the animals took a lateral position, had a ruffled fur and continued to show convulsive twitches and impairment of breathing. Later on, moderate to severe sedation and ataxia, salivation, hypothermia, staggering, crouched posture, closed or small dark eyes and, in some animals, diarrhea were observed. After 2-3 days, the animals showed a ruffled fur, increase in motility and, in part, vocalisation when being touched. Signs of toxicity had disappeared after 11 days in the animals of the three lower dose groups, while the animals of the highest dose group (3160 mg/kg) showed signs of toxicity during the 14-day observation period.</p> <p>BODY WEIGHT: not affected by treatment.</p> <p>NECROPSY FINDINGS: Post-mortem dissection revealed hyperaemia of the gastric and intestinal mucosae, hyperaemia of the lungs, light-coloured spots on the liver and liver congestion. Dissection at the end of the experiment also revealed hyperaemia of the gastric and intestinal mucosae in some animals.</p>
Test condition	:	<p>TEST ORGANISMS:</p> <ul style="list-style-type: none"> - Strain: Wistar (Bor: WISW (SPF TNO)) - Source: Winkelmann, Borchon (Germany) - Weight at study initiation: <ul style="list-style-type: none"> females 117 g, males 126 g (mean) - Controls: no - Number: 5 males + 5 females, twice as many at highest dose <p>ADMINISTRATION:</p> <ul style="list-style-type: none"> - Test substance preparation: the test substance was finely ground in a mortar, mixed with cremophor EL, stirred in an Ultra-Turrax and then heated to 40 deg C. - Doses: 1580 / 1990 / 2510 / 3160 mg/kg bw (gavage), selected after screening test with small number of animals - Single dose after 16 h of fasting

		- Volume administered or concentration: 20 ml/kg - Post dose observation period: 14 days	
		EXAMINATIONS:	
		- body weight: before and on days 1, 7, 14 after treatment - clinical signs: up to 6 hours after treatment, then daily - gross pathology - statistical methods: Litchfield and Wilcoxon (1949), J. Pharmacol. Exp. Ther. 96, 99	
Reliability	:	(1) valid without restriction Guideline study	
Flag 04.07.2003	:	Critical study for SIDS endpoint	(18)
Type	:	LD50	
Value	:	= 2600 mg/kg bw	
Species	:	rat	
Strain	:	Sprague-Dawley	
Sex	:	male/female	
Number of animals	:		
Vehicle	:	CMC	
Doses	:		
Method	:	other: see Test Condition	
Year	:	1975	
GLP	:	no	
Test substance	:	other TS: lauryl lactam supplied by Elf Atochem, purity not stated	
Result	:	MORTALITY: - Time of death: 8 hours - 4 days after dosing - Number of deaths at each dose: dose males (time) females (time) 1000 0/5 1/5 (2d) 2000 2/10 (8h, 2d) 5/10 (8h (2), 1d, 2d, 3d) 3000 2/5 (1d, 2d) 4/5 (1d (2), 2d, 3d) confidence interval 1814 - 3727 mg/kg CLINICAL SIGNS: not reported.	
Test condition	:	TEST ORGANISMS: - Number of animals: low and high dose groups: 5 per group and sex medium dose group: 10 per sex - Weight at study initiation: males mean 180, 170, 160 g for low, mid and high dose groups females mean 230, 170, 200 g for low, mid and high dose groups (no further details reported) - Animals were fasted for 15 to 20 hours before administration of the test substance. - Controls: none reported ADMINISTRATION: - Route: Oral gavage - Doses: 1000 / 2000 / 3000 mg/kg - Doses per time period: no data - Volume administered or concentration: volume 10 / 20 / 20 ml/kg, concn. 10 / 10 / 15 % - Post dose observation period: 14 days EXAMINATIONS: none reported STATISTICAL METHOD: Litchfield and Wilcoxon	
Reliability	:	(2) valid with restrictions limited documentation	(4)
Type	:	LD50	
Value	:	> 1000 mg/kg bw	

Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	10
Vehicle	:	other: aqueous tragacanth suspension
Doses	:	
Method	:	other
Year	:	1964
GLP	:	no
Test substance	:	other TS: lauryl lactame "technically pure", no further data
Result	:	<p>MORTALITY:</p> <ul style="list-style-type: none"> - Time of death: within 24 hours - Number of deaths at each dose: only 1 at highest dose <p>CLINICAL SIGNS:</p> <ul style="list-style-type: none"> 100, 250 mg/kg bw: none observed 500, 1000 mg/kg bw: 10/10 animals in each group showed impairment of breathing, slight muscle tremor, sedative effects, reduced general condition, beginning 2 hours after dosing and reversible within 24 hours.
Test condition	:	<p>TEST ORGANISMS:</p> <ul style="list-style-type: none"> - Controls: no data <p>ADMINISTRATION:</p> <ul style="list-style-type: none"> - Doses: 100 / 250 / 500 / 1000 mg/kg bw (by single gavage) - Volume administered or concentration: 1 / 2.5 / 5 / 10 % - Post dose observation period: 7 days
Reliability	:	<p>(2) valid with restrictions limited documentation, short post dose observation period</p>
		(2)
Type	:	LD50
Value	:	> 1000 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	10
Vehicle	:	other: aqueous tragacanth suspension
Doses	:	
Method	:	other
Year	:	1964
GLP	:	no
Test substance	:	other TS: lauryl lactam "technically pure" (no further details)
Result	:	<p>MORTALITY:</p> <ul style="list-style-type: none"> - Time of death: within 24 hours - Number of deaths at each dose: 2 at highest dose <p>CLINICAL SIGNS:</p> <ul style="list-style-type: none"> 500 mg/kg bw: none observed 1000 mg/kg bw: 10/10 animals showed signs similar to those observed in rats, i.e. impairment of breathing, slight impairment of breathing, slight muscle tremor, sedative effects, reduced general condition, beginning 2 hours after dosing and reversible within 24 hours.
Test condition	:	<p>TEST ORGANISMS:</p> <ul style="list-style-type: none"> - 10 animals / dose (gender not specified) <p>ADMINISTRATION:</p> <ul style="list-style-type: none"> - Doses: 500 / 1000 mg/kg bw (as single gavage) - Volume administered or concentration: 5 / 10 % - Post dose observation period: 7 days
Reliability	:	<p>(2) valid with restrictions limited documentation; short post dose observation period</p>

(2)

Type : LD50
Value : > 1000 mg/kg bw
Species : rabbit
Strain :
Sex :
Number of animals : 2
Vehicle : other: aqueous tragacanth suspension
Doses :
Method : other
Year : 1964
GLP : no
Test substance : other TS: lauryl lactam "technically pure", no further details

Result : MORTALITY:
 - Number of deaths at each dose: no mortality occurred
 CLINICAL SIGNS: none

Test condition : TEST ORGANISMS:
 - Controls: no data
 ADMINISTRATION:
 - Doses: 1000 mg/kg bw (as single gavage)
 - Volume administered or concentration: 10 %
 - Post dose observation period: 7 days

Reliability : (2) valid with restrictions
 limited documentation; short post dose observation period, small number of animals

(2)

Type : LD50
Value : ca. 250 mg/kg bw
Species : cat
Strain :
Sex :
Number of animals : 2
Vehicle : other: aqueous tragacanth suspension
Doses :
Method : other
Year : 1964
GLP : no
Test substance : other TS: lauryl lactam ("technically pure"), no further details

Result : MORTALITY:
 - Time of death: within 24 hours
 - Number of deaths at each dose: 1 at medium, 2 at high dose
 CLINICAL SIGNS:
 similar to those observed in rats and mice (i.e. impairment of breathing, slight muscle tremor, sedative effects, reduced general condition, beginning 2 hours after dosing and reversible within 24 hours)

Test condition : TEST ORGANISMS:
 - 2 animals / dose
 ADMINISTRATION:
 - Doses: 100 / 250 / 500 mg/kg bw (as single dose per gavage)
 - Volume administered or concentration: 1 / 2.5 / 5 %
 - Post dose observation period: 7 days

Reliability : (2) valid with restrictions
 limited documentation; short post dose observation period, small number of animals; not a standard species

(2)

Type : LD50
Value : > 1000 mg/kg bw
Species : guinea pig
Strain :
Sex :
Number of animals : 2
Vehicle : other: aqueous tragacanth suspension
Doses :
Method : other
Year : 1964
GLP : no
Test substance : other TS: lauryl lactam, "technically pure" (no further details)

Result : MORTALITY: no mortality occurred
 CLINICAL SIGNS: none

Test condition : TEST ORGANISMS:
 - Controls: no data
 ADMINISTRATION:
 - Doses: 1000 mg/kg bw (gavage)
 - Doses per time period: single dose
 - Volume administered or concentration: 10 %
 - Post dose observation period: 7 days

Reliability : (2) valid with restrictions
 limited documentation; short post dose observation period, small number of animals

(2)

Type : other: Liver function impairment
Value : >= 1000 mg/kg bw
Species : rabbit
Strain :
Sex :
Number of animals : 2
Vehicle : other: 25 % aqueous tragacanth suspension
Doses : 1000 mg/kg bw
Method : other
Year : 1964
GLP : no
Test substance : other TS: lauryl lactame "technically pure", no further data

Result : No impairment of liver function was observed.

Test condition : 2 rabbits were given a single dose of 1,000 mg/kg bw of the test substance as 25 % aqueous tragacanth suspension by gavage.
 Liver function tests were performed after 1 hour, 24 hours, and 7 days:
 Bromophthalein test (Hofmann-Oestel); SGPT; SDH

Reliability : (2) valid with restrictions
 limited documentation

(2)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC0
Value :
Species : other: 20 mice, 10 rats, 2 guinea pigs, 1 rabbit
Strain :
Sex :
Number of animals :
Vehicle :

Doses	:	
Exposure time	:	
Method	:	other
Year	:	1964
GLP	:	no
Test substance	:	other TS: lauryl lactam "technically pure", no further details
Result	:	Except for minor signs of irritancy of the mucosa of nose, throat, and eyes, no signs of intoxication were observed.
Test condition	:	ADMINISTRATION: - Animals were exposed in a 400 l room to the vapors of the test substance that were generated by heating as follows: Test 1: 10 g heated at 170 degree C for 4 hours; loss 9.6 g Test 2: 40 g heated at 180 degree C for 4 hours; loss 15.1 g Test 3: 40 g heated at 200 degree C for 5 hours; loss 26.4 g - Post exposure observation period: 14 days
Reliability	:	(3) invalid methodological deficiencies: no analytical monitoring

(2)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	5
Vehicle	:	CMC
Doses	:	
Method	:	other: see reference for details
Year	:	1975
GLP	:	no
Test substance	:	other TS: lauryl lactam supplied by Elf Atochem, purity not stated
Result	:	MORTALITY: no mortalities CLINICAL SIGNS: slight decrease in food consumption (no quantitative data presented) and a stagnation of body weight development (356, 352, 354 g mean body weight for males at d1, d7 and d14, respectively; 237, 236, 240 g mean body weight for females at d1, d7 and d14, respectively). IRRITATION: no skin effects at all were noted. NECROPSY FINDINGS: none
Test condition	:	TEST ORGANISMS: - Weight at study initiation: - 5 male and 5 female rats, supplied from IFFA-CREDO 325-375 g, mean 356 g (males) 220-270 g, mean 236 g (females) - Controls: untreated. No details reported. ADMINISTRATION: - test substance preparation: the test substance was ground to fine powder and suspended in 1% aqueous carboxy methyl cellulose - to the shaved back of the animals - Occlusion: yes, for 24 hours - Vehicle: 1 % carboxy methylcellulose (CMC) aqueous suspension - Concentration in vehicle: 40 % - Total volume applied: 5 ml/kg bw

	- Dose: 2000 mg/kg bw	
	- Removal of test substance: yes, washed off with lukewarm water 24 hours after administration.	
	EXAMINATIONS:	
	- clinical observations after end of exposure, repeated during next hours, and repeated daily for 14 days	
	- autopsy after 14 days observation period.	
Reliability	: (2) valid with restrictions limited documentation	
Flag	: Critical study for SIDS endpoint	(4)
Type	: LD50	
Value	: > 1000 mg/kg bw	
Species	: rat	
Strain	:	
Sex	:	
Number of animals	: 5	
Vehicle	: other: aqueous tragacanth suspension	
Doses	:	
Method	: other	
Year	: 1964	
GLP	: no	
Test substance	: other TS: lauryl lactam "technically pure", no further details	
Test condition	: ADMINISTRATION: - Type of exposure: rats were fixed lying on their backs. The test preparation was applied to the abdominal skin, which had been shaved on the preceding day. The test substance preparation was removed with soap and water four hours after application. - Concentrations: 25 % in vehicle; only one dose group - Post exposure period: 7 days	
Reliability	: (2) valid with restrictions limited documentation	(2)
Type	: LD50	
Value	: > 1000 mg/kg bw	
Species	: rat	
Strain	:	
Sex	: male	
Number of animals	: 5	
Vehicle	: other: aqueous tragacanth suspension	
Doses	: 1000 mg/kg bw	
Method	: other	
Year	: 1964	
GLP	: no	
Test substance	: other TS: lauryl lactam "technically pure", no further details	
Result	: MORTALITY: no mortalities	
Test condition	: ADMINISTRATION: - Type of exposure: The test preparation was applied to the dorsal skin, which had been shaved on the preceding day. The test substance preparation was not washed off the skin during the experiment. The animals wore cardboard collars to avoid licking the test substance preparation. - Concentrations: 25 % in vehicle; only one dose group - Post exposure observation period: 7 days	
Reliability	: (2) valid with restrictions	

limited documentation, short post dose observation period

(2)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Value : = 410 mg/kg bw
Species : rat
Strain :
Sex :
Number of animals : 10
Vehicle : other: aqueous tragacanth suspension
Doses :
Route of admin. : i.p.
Exposure time :
Method : other
Year : 1964
GLP : no
Test substance : other TS: lauryl lactam "technically pure", no further details

Result : MORTALITY:
 - Time of death: within 24 hours
 - Number of deaths at each dose:
 50 mg/kg: 0
 100 mg/kg: 2
 250 mg/kg: 2
 500 mg/kg: 5
 600 mg/kg: 7
 750 mg/kg: 9
 1000 mg/kg: 10
 CLINICAL SIGNS: (similar to) impairment of breathing, slight muscle tremor, sedative effects, reduced general condition, beginning 1/2 hour after dosing and reversible within 24 hours, observed in all dose levels except lowest

Test condition : TEST ORGANISMS:
 - Controls: no data
 ADMINISTRATION:
 - Doses: 50 / 100 / 250 / 500 / 600 / 750 / 1000 mg/kg bw (gavage)
 - Doses per time period: single dose
 - Volume administered or concentration: 0.5 / 1 / 2.5 / 5 / 6 / 7.5 / 10 %
 - Post dose observation period: 7 days
 - statistical methods: Litchfield and Wilcoxon

Reliability : (2) valid with restrictions
 limited documentation

(2)

Type : LD50
Value : = 500 - 750 mg/kg bw
Species : mouse
Strain :
Sex : male/female
Number of animals : 3
Vehicle : other
Doses :
Route of admin. : i.p.
Exposure time :
Method : other: see Test Condition

Year : 1971
GLP : no
Test substance : no data

Result : CLINICAL SIGNS:
5/6 side position at 500 mg/kg bw
6/6 trembling at 500 mg/kg bw

Test condition : TEST ORGANISMS:
- Weight at study initiation: 17-27 g
- Controls: saline injections
ADMINISTRATION:
- Doses: logarithmic like 30 / 100 / 300 / 1000 etc. mg/kg bw
administered as 2 % suspension in 5 % acacia solution
- Volume administered or concentration: max. 1 ml
- Post dose observation period: 2 days
EXAMINATIONS: CNS stimulant activity, mortality

Reliability : (4) not assignable
Documentation insufficient for assessment

(14)

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration :
Exposure : Occlusive
Exposure time : 4 hour(s)
Number of animals : 3
Vehicle :
PDII :
Result : not irritating
Classification : not irritating
Method : other: OECD Guideline 404 "Acute Dermal Irritation/Corrosion" (1981)
Year : 1985
GLP : no
Test substance : other TS: purity > 99.9 %; main impurity cyclododecanone ca. 100 ppm

Result : Only 1/6 animal showed very slight edema (grade 1) at 1 hour. At 24 hours erythema (grades 1 and 2) were seen in 3/6 animals, one animal showed grade 1 edema. At 48 and 72 hours, still one animal had erythema (grade 2) and edema (grade 1). All effects were completely reversible within 6 days (AVERAGE SCORE
- Erythema: 0.44
- Edema: 0.17
- Irritation index: 0.5/8)
REVERSIBILITY: yes

Test condition : TEST ANIMALS:
- Strain: Small white Russian, Chbb-SPF
- Sex: male and female
- Source: Dr. Karl Thomae GmbH, Biberach
- Weight at study initiation: 2.0-2.5 kg
- Number of animals: 3 males, 3 females
ADMINISTRATION/EXPOSURE
- Preparation of test substance: 0.5 g, ground in mortar, wetted with paraffin oil
- Area of exposure: 6 cm²
- Occlusion: mull patch, polyethylene film, elastic dressing
- Vehicle: paraffin oil

		- Post exposure observation period: 8 days	
		- Removal of test substance: washing with warm water	
		EXAMINATIONS	
		- Scoring system: according to Draize	
		- Observations at 1, 24, 48, 72 hours, 6 and 8 days after administration of the test substance	
Reliability	:	(2) valid with restrictions	
		In deviation from OECD TG 404 occlusive dressing was used.	
Flag	:	Critical study for SIDS endpoint	
04.07.2003			(20)
Species	:	rabbit	
Concentration	:	undiluted	
Exposure	:	Occlusive	
Exposure time	:	23 hour(s)	
Number of animals	:	6	
Vehicle	:		
PDII	:		
Result	:	not irritating	
Classification	:		
Method	:	other: Official Journal 21 April 1971 / 05 June 1973	
Year	:	1975	
GLP	:	no	
Test substance	:	no data	
Result	:	AVERAGE SCORE index: 0.04/8	
		- Erythema: score 1 for 2 animals on scarified flank at 24 hrs, scores of "0" for edema and erythema were observed for all other animals and flanks	
		REVERSIBILITY: yes	
Test condition	:	TEST ANIMALS:	
		- Strain: New Zealand	
		- Sex: male	
		- Weight at study initiation: 2.5 - 3.5 kg	
		- Controls: not reported	
		ADMINISTRATION/EXPOSURE	
		- test substance preparation: not reported	
		- Area of exposure: ca. 14 cm x 14 cm shaved, scarified on right flank (no bleeding)	
		- Total volume applied:	
		0.5 g per application,	
		1 application on each flank of each test animal	
		- Post exposure observation period: 48 hours	
		EXAMINATIONS	
		- Scoring system:	
		max. 4 scores each for erythema and edema (Draize scores)	
		- Examination time points:	
		1 hour after removal of the patch (i.e. at 24 hours after application of the test substance, and after additional 48 hours	
Reliability	:	(2) valid with restrictions	
		limited documentation	
04.07.2003			(4)
Species	:	rabbit	
Concentration	:		
Exposure	:		
Exposure time	:		
Number of animals	:		
Vehicle	:		
PDII	:		
Result	:	not irritating	
Classification	:		

Method	:	other: see Test Condition	
Year	:	1964	
GLP	:	no	
Test substance	:	other TS: lauryl lactam "technically pure", no further data	
Method	:	The substance was applied either neat or moistened with water or oil on small cotton swabs to the inner side of rabbit ears for 24 hours.	
Reliability	:	(3) invalid application site inappropriate	(2)
Species	:	human	
Concentration	:		
Exposure	:		
Exposure time	:		
Number of animals	:		
Vehicle	:		
PDII	:		
Result	:		
Classification	:		
Method	:	other	
Year	:	1964	
GLP	:	no	
Test substance	:	other TS: lauryl lactam "technically pure", no further data	
Method	:	The substance was applied either dry or moistened with oil or water on small cotton swabs to the upper arms of 7 male volunteers for 8 hours. No details are reported with regard to quantity and as to whether the exposure was under occlusive, open or semi-occlusive conditions.	
Result	:	Minor and transient signs of irritation (redness) were observed (no further details reported).	
Reliability	:	(4) not assignable Documentation insufficient for assessment	(2)

5.2.2 EYE IRRITATION

Species	:	rabbit	
Concentration	:	undiluted	
Dose	:	.1 other: gram	
Exposure time	:		
Comment	:	not rinsed	
Number of animals	:	3	
Vehicle	:		
Result	:	not irritating	
Classification	:	not irritating	
Method	:	other: OECD Guideline 405 "Acute Eye Irritation/Corrosion" (1981)	
Year	:	1985	
GLP	:	no	
Test substance	:	other TS: purity > 99.9 %; main impurity cyclododecanone ca. 100 ppm	
Result	:	A slight corneal opacity was noted in one female at 24 hrs, that diminished in severity at 48 hrs already, and was completely reversible at 72 hours. 5/6 animals showed a slight reddening of parts of the iris at 24 hours; this effect was completely resolved at 48 hours. Very slight to slight conjunctival redness started at 1 hour after instillation, and was most prominent at 24 hours (grades 1-3 for redness, 0-2 for swelling), diminished in severity by 48 hours (grades 0-2 for redness, 0-1 for swelling) and was only seen in 2/6 animals at 72 hours (grade 1 redness, no swelling). Conjunctival effects	

		were completely reversible within 6 days. (AVERAGE SCORE	
		- Cornea: 0.11	
		- Iris: 0.28	
		- Conjunctivae (Redness): 1.17	
		- Conjunctivae (Chemosis): 0.56	
		- Overall irritation score: 7.17/110)	
		REVERSIBILITY: yes	
Test condition	:	TEST ANIMALS:	
		- Strain: Small white Russian, Chbb-SPF	
		- Sex: male and female	
		- Source: Dr. Karl Thomae GmbH, Biberach	
		- Weight at study initiation: 2.1-2.4 kg	
		- Number of animals: 3 males, 3 females	
		- Controls: left eye	
		ADMINISTRATION/EXPOSURE	
		- Preparation of test substance: finely ground in a mortar	
		- Amount of substance instilled: 0.1 g	
		- Vehicle: none	
		- Postexposure observation period: 3 weeks	
		EXAMINATIONS	
		- Ophthalmoscopic examination: 1, 24, 48, 72 hours, 6 days after treatment	
		- Scoring system: Draize (1959); Appendix VI of 79/831/EEC	
		- Tool used to assess score: Na fluorescein / ophthalmic lamp / visual inspections	
Reliability	:	(1) valid without restriction	
		Guideline study	
Flag	:	Critical study for SIDS endpoint	
04.07.2003			(19)
Species	:	rabbit	
Concentration	:		
Dose	:	100 other: mg	
Exposure time	:		
Comment	:	not rinsed	
Number of animals	:	6	
Vehicle	:		
Result	:	not irritating	
Classification	:		
Method	:	other: similar to OECD TG 405 (1981), for details see Test conditions	
Year	:	1975	
GLP	:	no	
Test substance	:	no data	
Result	:	No corneal effects were noted at any observation. 1 hour after instillation, slight conjunctival redness (Draize grades 1 and 2) was noted in 5/6 animals, that subsided completely within 24 hours. 1 hour after instillation one animal showed iritis (grade 1), that resolved within 1 days.	
		REVERSIBILITY: effects were completely reversible within 2 days	
Test condition	:	TEST ANIMALS:	
		- Strain: New Zealand	
		- Sex: male	
		- Weight at study initiation: ca. 2.5 kg	
		- Controls: right eye	
		ADMINISTRATION/EXPOSURE	
		- Vehicle: dispersed in non-irritating solvent, unspecified	
		- Postexposure observation period: 7 days	
		EXAMINATIONS	

	- Ophthalmoscopic examination: after 1 hour, 24 hours, 2, 3, 4, and 7 days	
	- Scoring system: according to Draize	
	- Tool used to assess score: ophthalmoscope, retinograph, visual inspection	
Reliability	: (2) valid with restrictions limited documentation (vehicle not specified)	(4)
Species	: rabbit	
Concentration	: undiluted	
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	: other	
Year	: 1964	
GLP	: no	
Test substance	: other TS: lauryl lactam "technically pure", no further details	
Method	: The powdered test substance was applied to the conjunctival sac of one rabbit.	
Result	: Minor signs of transient mucosal irritation (no details reported) No effect on cornea was observed.	
Reliability	: (4) not assignable Documentation insufficient for assessment	(2)

5.3 SENSITIZATION

Type	: Guinea pig maximization test	
Species	: guinea pig	
Concentration	: 1 st : Induction 1 % intracutaneous 2 nd : Induction 25 % occlusive epicutaneous 3 rd : Challenge 25 % occlusive epicutaneous	
Number of animals	: 20	
Vehicle	: other: corn oil	
Result	: not sensitizing	
Classification	: not sensitizing	
Method	: other: OECD Guideline 406 "Skin Sensitization" (1981)	
Year	: 1989	
GLP	: no	
Test substance	: other TS: purity ca. 99.9 %; main impurity cyclododecanone ca. 100 ppm	
Result	: RESULTS OF TEST - Sensitization reaction: 0/20 (none of the animals showed a positive reaction at 24 and 48 hrs) - Irritation: No reaction was caused by the corn oil patch. - Clinical signs: 10-16 days after the begin of the study, considerable losses of weight as well as signs of paralysis were observed in a high fraction of the animals. Slow recovery was observed after treatment with vitamin C from day 14 onwards. No findings were obtained in a bacteriological examination of the organs after the end of the study. - After intracutaneous application, the places of injections showed intense erythema and edema as well as necroses in	

Test condition	: case of treatment with Freund's Complete Adjuvant (FCA), distinct erythema and edema in case of treatment with 1 % test substance, and slight erythema in case of treatment with corn oil. - After removal of the first patch (i.e. 2nd induction treatment), severe inflammation, severe erythema and edema of all animals treated with FCA (treatment and control groups) were observed in the area of injections.
Reliability	: TEST ANIMALS: - Strain: Dunkin-Hartley (Bor: DHPW) - Sex: male - Source: F. Winkelmann, Borchon - Weight at study initiation: test group mean 325 g; control group mean 324 g - Number of animals: 20 - Controls: 9 animals; treatment: vehicle ADMINISTRATION/EXPOSURE - Preparation of test substance for induction: The test substance was ground to a fine powder and dissolved in the vehicle (corn oil) at elevated temperature. After cooling down, the resulting suspension was thoroughly mixed. - Induction schedule: single intracutaneous treatment, 1 week later dermal induction; slight to medium inflammation caused (10 % SDS in vaseline) before application of patch; patch removed after 48 h - Challenge schedule: after 2 further weeks, occlusive epicutaneous, removal of patch after 24 h, readings after further 24 and 48 hours. EXAMINATIONS - Grading system: 0 % of animals positive: no sensitisation 1 - 8 % of animals positive: very slight sensitisation 9 - 28 % of animals positive: slight sensitisation 29 - 64 % of animals positive: distinct sensitisation 65 - 80 % of animals positive: severe sensitisation 81 -100 % of animals positive: extreme sensitisation
Flag	: (2) valid with restrictions No positive control (not required by 1981 version of Test Guideline)
16.07.2003	: Critical study for SIDS endpoint

(26)

5.4 REPEATED DOSE TOXICITY

Type	: Sub-chronic
Species	: rat
Sex	: male/female
Strain	: Sprague-Dawley
Route of admin.	: gavage
Exposure period	: 90 days
Frequency of treatm.	: 7 days/week
Post exposure period	: yes (5 m/5 f of the control and high dose group for 30 days)
Doses	: 0, 5, 25, or 125 mg/kg bw d
Control group	: yes, concurrent vehicle
NOAEL	: = 25 mg/kg bw
LOAEL	: = 125 mg/kg
Method	: other: OECD Guideline 408 "Subchronic Oral Toxicity - Rodent: 90-day study" (1981)
Year	: 1992
GLP	: yes
Test substance	: other TS: Elf Atochem Batch 9611, Purity >= 99.5 % (NMR)

Result	: TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: <ul style="list-style-type: none">- Mortality and time to death:<ul style="list-style-type: none">0 mg/kg: 1 female, day 83, esophageal perforation5 mg/kg: 1 male, day 25, aspiration pneumonia25 mg/kg: no mortalities125 mg/kg 1 male, 1 female, days 56, 63, cause for mortality not obvious: Animals showed no specific signs accounting for death (stress changes and agonal pulmonary edema). Ground glass appearance of centrilobular hepatocytes (the female), although imputable to treatment, could not be considered as a cause.- Clinical signs: no abnormality detected- Body weight gain: no abnormality detected- Food/water consumption: no abnormality detected- Ophthalmoscopic examination: no abnormality detected- Clinical chemistry: high dose group: moderate increase in potassium (males), no longer statistically significant by end of reversibility period (day 121); slight increase (females only) in total proteins (78.4 vs 75.1 g/l) and albumin (39.3 vs 37.3 g/l)- Haematology: no abnormality detected- Urinalysis:<ul style="list-style-type: none">day 45: moderate increase in potassium excretion of medium / high dose males (2728 / 2426 vs 1774 mc.moles); moderate increase in sodium concentration and excretion of high dose males (40 vs 23 mM; 802 vs 370 mc.moles);day 85: no abnormality detected- Organ weights: no abnormality detected- Gross pathology: no abnormality detected- Histopathology: ground glass appearance of centrilobular hepatocytes in 4 males each of mid and high dose groups <p>Target organ: liver All observed effects returned to normal values after a recovery period of 30 days.</p>
Test condition	: TEST ORGANISMS <ul style="list-style-type: none">- Supplier: Charles River France- Age: about 7 weeks- Weight at study initiation: 270 g (male) / 200 g (female)- Number of animals:<ul style="list-style-type: none">20 male and 20 female (low and mid-dose group);25 male and 25 female (control and high dose group), 5 per sex and group of these in reversibility study ADMINISTRATION / EXPOSURE <ul style="list-style-type: none">- Duration of test/exposure:<ul style="list-style-type: none">96 days for reversibility study; 90 days for other animals- Post exposure period: days 97 - 126 (reversibility study)- Vehicle: gum arabic solution supplemented with 0.5 % Tween 80- Concentration in vehicle: 10 % (aqueous suspension)- Total volume applied: 5 ml/kg- Doses: 0; 5; 25; 125 mg/kg bw d CLINICAL OBSERVATIONS AND FREQUENCY: <ul style="list-style-type: none">- Clinical signs: daily- Mortality: daily- Body weight: twice weekly- Food consumption: weekly- Ophthalmoscopic examination: days 83/84- Haematology:<ul style="list-style-type: none">days 85/86: erythrocytes, hemoglobin, packed cell volume, Wintrobe's indices (mean corpuscular volume, hemoglobin, and hemoglobin concentration = MCV, MCH, MCHC), reticulocytes (percentage and absolute; only 10 last animals per sex and group), leukocytes, differential

	leukocyte count (percentage and absolute), thrombocytes. coagulation day 97: prothrombin time, activated partial thromboplastin time, fibrinogen level
	- Biochemistry: days 90/91-121: glucose, urea, creatinine, total proteins, albumin, globulins, albumin/globulin ratio, triglycerides, cholesterol, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatases, gamma-glutamyl transpeptidase, sodium, potassium, chloride, calcium, inorganic phosphate
	- Urinalysis: first 5 animals/sex/group, days 45, 85: volume, pH, proteins, ketone bodies, bilirubins, urobilinogen, specific gravity, glucose, leukocytes, blood, nitrite, erythrocytes, leukocytes, epithelial cells, renal cells, casts, ammonium magnesium phosphate crystals, oxalate crystals, bacteria, parasites
	ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
	- Macroscopic: skin and subcutaneous tissues, mammary tissue, liver, spleen, kidneys, thymus, heart, lungs, tracheobronchial lymph nodes, urinary bladder, ovaries, uterine tubes, uterine cervix, vagina, testes, epididymides, seminal vesicles, prostate, aorta, sciatic nerve, popliteal lymph nodes, femur and bone marrow, crural muscle, pancreas, esophagus, forestomach, glandular area (stomach), duodenum, jejunum, ileum, cecum, colon, rectum, mesenteric lymph nodes, salivary glands, thyroid glands, parathyroid glands, larynx, tongue, eyes, harderian glands, brain, pituitary, inner ear, femoral bone marrow
	- Microscopic: same as macroscopic except for femur and bone marrow, tongue, and inner ear
	STATISTICAL METHODS:
	- parametric methods for statistical distributions; Levene test followed by 1-ANOVA and/or Student t test; Bonferroni's method or Scheffe's method for multiple comparisons
	- non-parametric methods: Kruskal Wallis test
Reliability	: (1) valid without restriction Guideline study
Flag 04.07.2003	: Critical study for SIDS endpoint
	(39)
Type	: Sub-chronic
Species	: dog
Sex	: male/female
Strain	: Beagle
Route of admin.	: oral feed
Exposure period	: 13 weeks (low and high dose groups); 14 weeks (mid dose and control groups)
Frequency of treatm.	: 6 days/week
Post exposure period	: none
Doses	: m: 44, 350, or 969 mg/kg bw/day; f: 49, 352, or 989 mg/kg bw/day
Control group	: yes
NOAEL	: = 49 mg/kg
LOAEL	: = 350 mg/kg
Method	: other: see Test Condition
Year	: 1974
GLP	: no
Test substance	: other TS: white, caked material with intensive smell, ground before application. No data on composition or origin.
Result	: TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: LOW dose group: NOAEL

For the MIDDLE dosage group it is reported that the activity of the alkaline phosphatase in the serum of the females was slightly elevated after 1.5 and after 3 months. The liver weight was remarkably high (males 34 % absolute, 40 % relative; females 25 % absolute, 38 % relative)

The following observations are reported for the HIGH dosage group:

- Mortality and time to death: 1 female died after 5 weeks. On the last days before this death lateral positioning, extremely high respiratory frequency, tonic spasms and tremors were observed.

- Clinical signs: The general condition and behavior were severely affected. This was principally expressed as apathy, ataxia, sialorrhea, lateral positioning and tonoclonic spasms; the reaction to acoustic and visual stimuli was diminished. The feces had a mixed formed/unformed consistency and were interspersed with tiny, pinhead-sized, white particles which appeared to be the test substance. Vomiting appeared at times.

- Body weight gain: The dogs lost an average of 25 % (male) or 20 % (female) of their initial body weight until the beginning of the 4th week. Until the end of the application period they gained weight again, but did not reach their initial body weights (final body weights of males -20 %, females -15 %).

- Food/water consumption: The food consumption was strongly reduced; a few dogs ate nothing for days. Food consumption (g/kg bw/day, mean 1st to 13th week, mean 1st to 14th week; n.d. = not determined; [only control and mid dose groups were exposed for 14 weeks]):

Males:

Negative control: 43.9, 43.7;

low dose: 44.0, n.d.;

mid dose: 50.0; 50.0;

high dose: 31.3; n.d. (range: from 17.3 in week 2 to 42.6 in week 13);

Females:

Negative control: 42.4, 42.4;

low dose: 48.7, n.d.;

mid dose: 50.2; 50.3;

high dose: 38.4; n.d. (range: from 21.6 in week 3 to 50.0 in week 13);

From week 3 onwards additional food (200 g per animal and day) was offered to the high dose male and female animals; this food was completely eaten by females, whilst only 72% of it (144 g/day) were consumed by the male animals.

- Ophthalmoscopic examination: No indications of an effect

- Clinical chemistry: The clinical-chemical examinations of the blood, serum, or plasma showed a slight elevation of the SGPT-activity and a distinct elevation of the SAP-activity after 1.5 and after 3 months.

- Haematology: The hematological examinations with 1 male dog at the study time point 3 months showed slightly lowered values for the erythrocyte number, the hemoglobin concentration in the blood and the hematocrit. With 1 female dog the reticulocyte number was distinctly elevated at the same time. The leucocyte number was lowered with all dogs of the high dosage group after 1.5 and after 3 months; this reduction is shown by the decrease in the number of neutrophilic granulocytes and lymphocytes.

- Urinalysis: No indications of an effect

- Organ weights: The liver weight showed an increase (males 35 % absolute, 75 % relative; females 59 % absolute, 90 % relative) whereas a decrease was observed in the testes (-39 % absolute, -24 % relative), prostate (-67 % absolute, -58% relative), and ovaries (-50 % absolute, -39 %

Test condition

relative).
- Gross pathology: No indications of an effect
- Histopathology: The histological examination of the testes revealed an impairment of the sperm maturation; the prostate was atrophic. Atrophy was found in the uterus of the dog which died. Fibrosis of the endometrial stroma was observed in 1 dog.
- Other: No indications of an effect resulted from the examinations of the sternal marrow smears as well as from the liver function test and the kidney function test.

: TEST ORGANISMS

- Supplier: Asta Werke (Austria): 18 dogs; Graeflich Degenberg-Schonburgsches Rentamt (Germany): 7 dogs; inhouse: 15 dogs
- Age: 26 weeks (mean)
- Weight at study initiation: males 11.8 kg, females 9.2 kg (mean)
- Number of animals: 4 males + 4 females per group

ADMINISTRATION / EXPOSURE

- Type of exposure: in the diet (low and mid dose), gelatine capsules (high dose)
- Post exposure period: none
- Vehicle: gelatine capsules (high dose), dispensed daily in 2 equally large doses in an interval of approx. 4.5 hours
- Concentration in food: 0.1 and 0.7 % (w/w) (low / mid dose)

SATELLITE GROUPS AND REASONS THEY WERE ADDED: positive control substance caprolactam applied in food (7 % w/w) to one further group

CLINICAL OBSERVATIONS AND FREQUENCY:

- Clinical signs: at least daily, during working time practically continuously
- Mortality: at least daily
- Body weight: at the beginning and weekly
- Food consumption: daily
- Ophthalmoscopic examination: before beginning and after 1.5 and 3 months
- Haematology:

Peripheral blood, before beginning and after 1.5 and 3 months: Counting of erythrocytes, reticulocytes, normoblasts, HEINZ' bodies, leucocytes, thrombocytes. Determination of hematocrit, hemoglobin, erythrocyte volume, leucocyte formula. Calculation of erythrocyte volume (MCV), hemoglobin content per erythrocyte (MCH), hemoglobin concentration in the erythrocyte (MCHC).

Bone marrow, at dissection: Cell formula, granulopoietic-erythropoietic quotient

- Biochemistry:

before beginning and after 1.5 and 3 months: Glucose, thromboplastin time, total protein and protein fractions, albumin-globulin quotient, sedimentation rate of erythrocytes, activity of GPT, GOT, AP; bilirubin, cholesterol, urea, creatinine, sodium, potassium

- Urinalysis:

before beginning and after 1.5 and 3 months: color quality and intensity, pH, albumin, glucose, ketone bodies, occult blood, bilirubin, urobilinogen, organic and non-organic sediment constituents.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):

- Macroscopic: general condition, rigor mortis, hair coat, skin, eyes, nose, oral cavity, ears, preputium, vulva, anus,

testes with epididymides, mammary glands, subcutaneous tissue
 - blood vessels and blood - and skeletal muscles, nerves,
 thyroid, parathyroid, abdominal cavity (peritoneum,
 contents), diaphragm, spleen mesentery lymph nodes,
 pancreas, mandibular gland, parotid gland, lymph nodes
 (retrophar., mandib., cerv. superf. and axillar.), tongue,
 pharynx, larynx, thoracic cavity (pleura, contents), thymus,
 trachea, lungs, mediastinum, pericardium, epicardium, heart,
 aorta, pulmonary artery, ureters, urinary bladder, urethra
 prostate, ovaries, oviducts, uterus, vagina, esophagus,
 stomach, small intestine, colon, caecum rectum, adrenals,
 kidneys, liver, gall bladder, hypophysis, brain
 - Microscopic: heart, lungs, esophagus, stomach (large
 curvature, small curvature, pylorus region), small intestine
 (duodenum, jejunum, ileum), caecum, colon, liver, pancreas,
 kidney, urinary bladder, testes (right and left), epididymes
 (right and left), ovaries (right and left), prostate,
 uterus, thyroid with parathyroid, adrenals (right and left),
 cerebrum, cerebellum, periph. nerve, spleen, lymph nodes,
 bone marrow
 OTHER EXAMINATIONS:
 - Liver function test: before beginning and after 1.5 and 3 months: 2-Dye-
 test according to Zimmer
 - Kidney function test: before beginning and after 1.5 and 3
 months: Phenol-red test

Reliability : (2) valid with restrictions
 limited documentation (test substance)

Flag : Critical study for SIDS endpoint
 04.11.2003 (32)

Type :
Species : rat
Sex : male
Strain :
Route of admin. : gavage
Exposure period : 12 weeks
Frequency of treatm. : 5 days/week
Post exposure period : no
Doses : 500; 250; 120; 60 mg/kg bw/day
Control group : yes, concurrent vehicle
NOAEL : = 500 mg/kg bw
Method : other: see Test Condition
Year : 1964
GLP : no
Test substance : other TS: lauryl lactam "technically pure", no further data

Result : - No mortalities,
 - no effects on blood or urine parameters,
 - no macroscopic changes in organs inspected,
 - no effect on organ weights, and
 - no effect on body weight development were observed

Test condition : TEST ORGANISMS
 - Number of animals: 10 male animals were used per group
 ADMINISTRATION / EXPOSURE
 - Vehicle: aqueous tragacanth suspension
 CLINICAL OBSERVATIONS AND FREQUENCY:
 - Mortality: yes
 - Body weight: weekly
 - Blood and urine parameters were studied (no further details available)
 ORGANS EXAMINED AT NECROPSY: not reported
 - Weights determined: liver, kidney, spleen, suprarenal

Reliability	:	gland, thyroid gland (2) valid with restrictions limited documentation	(2)
Type	:		
Species	:	other: 20 mice, 10 rats, 2 guinea pigs, 1 rabbit, 1 cat	
Sex	:		
Strain	:		
Route of admin.	:	inhalation	
Exposure period	:	5 days	
Frequency of treatm.	:	4 hours/day	
Post exposure period	:	14 days	
Doses	:		
Control group	:	no	
Method	:	other: see Test Condition	
Year	:	1964	
GLP	:	no	
Test substance	:	other TS: lauryl lactam "technically pure", no further details	
Result	:	Except for minor signs of irritancy of the mucosa of nose, throat, and eyes, no signs of intoxication were observed.	
Test condition	:	ADMINISTRATION: - Type of exposure: Animals were exposed in a 400 l room to the vapours of the test substance that were generated by heating 20 g of test substance at 160 degree C. The average loss of test substance during the daily exposure was 11.4 g.	
Reliability	:	(3) invalid No analytical monitoring; significant methodological deficiencies	(2)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration	:	8, 40, 200, 1,000, 5000 ug/plate (main test), and 125, 250, 500, 1,000, 2,000 ug/plate (pre-incubation test)
Cycotoxic concentr.	:	1000, 2000, and 5000 ug/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	Directive 84/449/EEC, B.14
Year	:	1991
GLP	:	yes
Test substance	:	other TS: Purity > 99.5 %; manufactured by Hüls AG on 29 Nov. 1990; Sample ID 3630/81273
Result	:	The test chemical was not mutagenic both with and without metabolic activation, even at cytotoxic concentrations. Precipitation of the test substance occurred at concentrations > 1000 ug/plate. The positive controls were functional.
Test condition	:	In accordance with OECD TG 471 (1981) SYSTEM OF TESTING - Metabolic activation system: Arochlor induced S9 fraction (Wistar rat liver), activity checked on TA 100 with aminoanthracene ADMINISTRATION: - Dosing: preincubation test: 40 g/l in dimethyl sulfoxide

	125; 250; 500; 1000; 2000 ug/plate main test: 50 g/l in dimethyl sulfoxide 8; 40; 200, 1000; 5000 ug/plate - Number of replicates: 3 - Positive controls: TA 98, TA 1538: nitrofluorene (2.5 ug/plate) TA 100, TA 1535: sodium azide (2.5 ug/plate) TA 1537: aminoacridine (50 ug/plate) Enzymatic activity: TA 100 / aminoanthracene (10 ug/plate) - Negative control: solvent (dimethyl sulfoxide); untreated - Pre-incubation time: 30 minutes (30 degree C) EVALUATION CRITERIA: According to Ames (1975): Mutagenic effect at 5000 ug/plate or less (no details reported)
Reliability	: (1) valid without restriction Guideline study
Flag 04.07.2003	: Critical study for SIDS endpoint (28)
Type	: Cytogenetic assay
System of testing	: Human Lymphocytes
Test concentration	: 30 - 350 mg/l
Cycotoxic concentr.	:
Metabolic activation	: with and without
Result	: negative
Method	: other: OECD Guideline 473 (1983)
Year	: 1991
GLP	: yes
Test substance	: other TS: Atochem SA, batch no. 9611, purity determined by NMR: no impurities > 0.5 % detectable
Result	: Treatment of cultures with lauryl lactam in both the absence and presence of S-9 resulted in frequencies of aberrant cells which were similar to and not significantly different from those observed in concurrent negative controls. Proportions of aberrant cells in all treated cultures fell within historical negative control ranges. The positive controls were functional. PRECIPITATION CONCENTRATION: 355 mg/l CYTOTOXIC CONCENTRATION: - With metabolic activation: 46 % mitotic inhibition at 350 mg/l - Without metabolic activation: 61 % mitotic inhibition at 280 mg/l
Test condition	: SYSTEM OF TESTING - Species/cell type: lymphocyte cultures from a single male donor, duplicate cultures - Metabolic activation system: male Sprague-Dawley rat liver post-mitochondrial fraction (S-9) from Aroclor 1254 induced animals - No. of metaphases analyzed: 100 from each culture if possible, i.e. 200 metaphases / dose group ADMINISTRATION: - Dosing: 30.06; 37.58; 46.98; 58.72; 73.40; 91.75; 114.7; 143.4; 179.2; 224.0; 280.0; 350.0 mg/l - Number of replicates: 2 - Application: with S-9: 3 hours treatment + 17 or 41 h recovery period without S-9: 20 or 44 h treatment - Solvent: dimethyl sulfoxide (DMSO) - Positive and negative control groups and treatment: negative: solvent positive with S-9: cyclophosphamide (25 ug/ml) positive without S-9: methyl methanesulfonate (50 ug/ml)

	Chromosome aberrations were analysed in cells sampled 20 hours after the start of treatment at 3 consecutive dose levels. The highest concentrations chosen for analysis at this time, 280 and 350 ug/ml, induced approximately 61% and 46% mitotic inhibition in the absence and presence of S-9, respectively.	
	CRITERIA FOR EVALUATING RESULTS: The proportions of cells with structural aberrations excluding gaps for each treatment condition were compared with the proportion in negative controls using Fisher's exact test, $p \leq 0.05$	
Reliability	: (1) valid without restriction Guideline study	
Flag 04.07.2003	: Critical study for SIDS endpoint	(16)
Type	: HGPRT assay	
System of testing	: Chinese hamster ovary (CHO) K1 cells	
Test concentration	: 0; 8; 20; 40; 60; 80 mg/l	
Cytotoxic concentr.	: not observed below solubility limit (80 mg/l)	
Metabolic activation	: with and without	
Result	: negative	
Method	: other: OECD Guideline 476 (1984)	
Year	: 1991	
GLP	: yes	
Test substance	: other TS: Purity approximately 99.5 %; manufactured by Hüls AG on 29 Nov. 1990; Sample ID 3630/81273	
Result	: The test substance was not mutagenic at the hypoxanthine-guanine phosphoribosyl-transferase (HPRT) locus in CHO cells both with and without metabolic activation. The positive controls were functional. Cytotoxicity was not observed.	
Test condition	: SYSTEM OF TESTING - Species/cell type: CHO-K1 cells (Salvage Laboratories, Meckenheim, Germany) - Metabolic activation system: from Aroclor 1254 induced Wistar rat liver (Cytotest Cell Research, Rossdorf, Germany) ADMINISTRATION: - Number of replicates: 2 - Application: $2E+05$ cells/25 ml flask; exposure time 4 h - Positive and negative control groups and treatment: positive, no metabolic activation: Ethyl methane sulfonate positive, metabolic activation: 3-Methylcholanthrene negative, no metab. activ.: HO medium with 0.4 % ethanol negative, metab. activ.: HO medium plus S9 mix with 0.4 % ethanol - Vehicle: ethanol, dimethyl sulfoxide (1%) CRITERIA FOR EVALUATING RESULTS: statistically significant, dose related increase in mutant frequency at concentrations of the test substance resulting in > 10 % cell survival. Mean frequency > maximum spontaneous frequency Statistical method: t-test	
Reliability	: (2) valid with restrictions No testing beyond the limit of solubility under the test conditions, i.e. at concentrations resulting in visible precipitation (not required by 1984 version of guideline)	
Flag 11.07.2003	: Critical study for SIDS endpoint	(30)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type : other: subchronic toxicity
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 90 days
Frequency of treatm. : 7 days/week
Premating exposure period
 Male :
 Female :
Duration of test :
No. of generation studies : 0
Doses : 0, 5, 25, or 125 mg/kg bw/day
Control group : yes, concurrent vehicle
NOAEL parental : = 25 mg/kg bw
Method : other: OECD Guideline 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year : 1981
GLP : yes
Test substance : other TS: Elf Atochem Batch 9611, Purity >= 99.5 % (NMR)

Result : TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death:
0 mg/kg: 1 female, day 83, esophagal perforation
5 mg/kg: 1 male, day 25, aspiration pneumonia
25 mg/kg: no mortalities
125 mg/kg 1 male, 1 female, days 56, 63, cause for mortality not obvious:
Animals showed no specific signs accounting for death (stress changes and agonal pulmonary edema). Ground glass appearance of centrilobular hepatocytes (the female), although imputable to treatment, could not be considered as a cause.
- Clinical signs: no abnormality detected
- Body weight gain: no abnormality detected
- Food/water consumption: no abnormality detected
- Ophthalmoscopic examination: no abnormality detected
- Clinical chemistry: high dose group: moderate increase in potassium (males), no longer statistically significant by end of reversibility period (day 121); slight increase (females only) in total proteins (78.4 vs 75.1 g/l) and albumin (39.3 vs 37.3 g/l)
- Haematology: no abnormality detected
- Urinalysis:
day 45: moderate increase in potassium excretion of medium / high dose males (2728 / 2426 vs 1774 mc.moles);
moderate increase in sodium concentration and excretion of high dose males (40 vs 23 mM; 802 vs 370 mc.moles);
day 85: no abnormality detected
- Organ weights: no abnormality detected
- Gross pathology: no abnormality detected
- Histopathology: ground glass appearance of centrilobular hepatocytes in

4 males each of mid and high dose groups

Test condition

Target organ: liver

All observed effects returned to normal values after a recovery period of 30 days.

: TEST ORGANISMS

- Supplier: Charles River France

- Age: about 7 weeks

- Weight at study initiation: 270 g (male) / 200 g (female)

- Number of animals:

20 male and 20 female (low and mid-dose group);

25 male and 25 female (control and high dose group), 5 per sex and group of these in reversibility study

ADMINISTRATION / EXPOSURE

- Duration of test/exposure:

96 days for reversibility study; 90 days for other animals

- Post exposure period: days 97 - 126 (reversibility study)

- Vehicle: gum arabic solution supplemented with 0.5 % Tween 80

- Concentration in vehicle: 10 % (aqueous suspension)

- Total volume applied: 5 ml/kg

- Doses: 0; 5; 25; 125 mg/kg bw d

CLINICAL OBSERVATIONS AND FREQUENCY:

- Clinical signs: daily

- Mortality: daily

- Body weight: twice weekly

- Food consumption: weekly

- Ophthalmoscopic examination: days 83/84

- Haematology:

days 85/86: erythrocytes, hemoglobin, packed cell volume, Wintrobe's indices (mean corpuscular volume, hemoglobin, and hemoglobin concentration = MCV, MCH, MCHC), reticulocytes (percentage and absolute; only 10 last animals per sex and group), leukocytes, differential leukocyte count (percentage and absolute), thrombocytes.

coagulation day 97: prothrombin time, activated partial thromboplastin time, fibrinogen level

- Biochemistry:

days 90/91-121: glucose, urea, creatinine, total proteins, albumin, globulins, albumin/globulin ratio, triglycerides, cholesterol, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatases, gamma-glutamyl transpeptidase, sodium, potassium, chloride, calcium, inorganic phosphate

- Urinalysis:

first 5 animals/sex/group, days 45, 85: volume, pH, proteins, ketone bodies, bilirubins, urobilinogen, specific gravity, glucose, leukocytes, blood, nitrite, erythrocytes, leukocytes, epithelial cells, renal cells, casts, ammonium magnesium phosphate crystals, oxalate crystals, bacteria, parasites

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):

- Macroscopic: skin and subcutaneous tissues, mammary tissue, liver, spleen, kidneys, thymus, heart, lungs, tracheobronchial lymph nodes, urinary bladder, ovaries, uterine tubes, uterine cervix, vagina, testes, epididymides, seminal vesicles, prostate, aorta, sciatic nerve, popliteal lymph nodes, femur and bone marrow, crural muscle, pancreas, esophagus, forestomach, glandular area (stomach), duodenum, jejunum, ileum, cecum, colon, rectum, mesenteric lymph nodes, salivary glands, thyroid glands, parathyroid glands, larynx, tongue, eyes, harderian glands, brain, pituitary, inner ear, femoral bone marrow

	- Microscopic: same as macroscopic except for femur and bone marrow, tongue, and inner ear
	STATISTICAL METHODS:
	- parametric methods for statistical distributions; Levene test followed by 1-ANOVA and/or Student t test; Bonferroni's method or Scheffe's method for multiple comparisons
	- non-parametric methods: Kruskal Wallis test
Reliability	: (1) valid without restriction
	Guideline study
Flag	: Critical study for SIDS endpoint
	(39)
Type	: other: subchronic toxicity
Species	: dog
Sex	: male/female
Strain	: Beagle
Route of admin.	: oral feed
Exposure period	: 13 weeks (low and high dose groups); 14 weeks (mid dose and control groups)
Frequency of treatm.	: 6 days/week
Premating exposure period	
	Male :
	Female :
Duration of test	:
No. of generation studies	: 0
Doses	: m: 44, 350, or 969 mg/kg bw/day; f: 49, 352, or 989 mg/kg bw/day
Control group	: yes
NOAEL parental	: = 49 mg/kg bw
Method	: other: see Test Conditions
Year	: 1974
GLP	: no
Test substance	: other TS: white, caked material with intensive smell, ground before application. No data on composition or origin.
Result	: TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: LOW and MIDDLE dose groups: No effects on male or female genital organ weights (testes, prostate, seminal vesicles, ovaries).
	The following observations are reported for the HIGH dosage group:
	- Mortality and time to death: 1 female died after 5 weeks.
	- Clinical signs: The general condition and behavior were severely affected. This was principally expressed as apathy, ataxia, sialorrhoea, lateral positioning and tonic spasms; the reaction to acoustic and visual stimuli was diminished.
	- Body weight gain: The dogs lost an average of 25 % (male) or 20 % (female) of their initial body weight until the beginning of the 4th week. Until the end of the application period they gained weight again, but did not reach their initial body weights (final body weights of males -20 %, females -15 %).
	- Food/water consumption: The food consumption was strongly reduced; a few dogs ate nothing for days. Food consumption (g/kg bw/day, mean 1st to 13th week, mean 1st to 14th week; n.d. = not determined):
	Males:
	Negative control: 43.9, 43.7;
	low dose: 44.0, n.d.;
	mid dose: 50.0; 50.0;
	high dose: 31.3; n.d. (range: from 17.3 in week 2 to 42.6 in week 13);
	Females:
	Negative control: 42.4, 42.4;

Test condition

- low dose: 48.7, n.d.;
mid dose: 50.2; 50.3;
high dose: 38.4; n.d. (range: from 21.6 in week 3 to 50.0 in week 13);
From week 3 onwards additional food (200 g per animal and day) was offered to the high dose male and female animals; this food was completely eaten by females, whilst only 72% of it (144 g/day) were consumed by the male animals.
- Organ weights: A decrease was observed in the testes (-39 % absolute, -24 % relative), prostate (-67 % absolute, -58% relative), and ovaries (-50 % absolute, -39 % relative).
 - Gross pathology: No indications of an effect
 - Histopathology: The histological examination of the testes revealed an impairment of the sperm maturation; the prostate was atrophic. Atrophy was found in the uterus of the dog which died. Fibrosis of the endometrial stroma was observed in 1 dog.
- : TEST ORGANISMS
- Supplier: Asta Werke (Austria): 18 dogs; Graeflich Degenberg-Schonburgsches Rentamt (Germany): 7 dogs; inhouse: 15 dogs
 - Age: 26 weeks (mean)
 - Weight at study initiation: males 11.8 kg, females 9.2 kg (mean)
 - Number of animals: 4 males + 4 females per group
- ADMINISTRATION / EXPOSURE
- Type of exposure: in the diet (low and mid dose), gelatine capsules (high dose)
 - Post exposure period: none
 - Vehicle: gelatine capsules (high dose), dispensed daily in 2 equally large doses in an interval of approx. 4.5 hours
 - Concentration in food: 0.1 and 0.7 % (w/w) (low / mid dose)
- SATELLITE GROUPS AND REASONS THEY WERE ADDED: positive control substance caprolactam applied in food (7 % w/w) to one further group
- CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: at least daily, during working time practically continuously
 - Mortality: at least daily
 - Body weight: at the beginning and weekly
 - Food consumption: daily
 - Ophthalmoscopic examination: before beginning and after 1.5 and 3 months
 - Haematology:
Peripheral blood, before beginning and after 1.5 and 3 months: Counting of erythrocytes, reticulocytes, normoblasts, HEINZ' bodies, leucocytes, thrombocytes. Determination of hematocrit, hemoglobin, erythrocyte volume, leucocyte formula. Calculation of erythrocyte volume (MCV), hemoglobin content per erythrocyte (MCH), hemoglobin concentration in the erythrocyte (MCHC).
Bone marrow, at dissection: Cell formula, granulopoietic-erythropoietic quotient
 - Biochemistry:
before beginning and after 1.5 and 3 months: Glucose, thromboplastin time, total protein and protein fractions, albumin-globulin quotient, sedimentation rate of erythrocytes, activity of GPT, GOT, AP; bilirubin, cholesterol, urea, creatinine, sodium, potassium
 - Urinalysis:
before beginning and after 1.5 and 3 months: color quality and intensity, pH, albumin, glucose, ketone bodies, occult blood, bilirubin, urobilinogen,

orgasmic and non-orgasmic sediment constituents.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):

- Macroscopic: general condition, rigor mortis, hair coat, skin, eyes, nose, oral cavity, ears, preputium, vulva, anus, testes with epididymides, mammary glands, subcutaneous tissue
- blood vessels and blood - and skeletal muscles, nerves, thyroid, parathyroid, abdominal cavity (peritoneum, contents), diaphragm, spleen mesentery lymph nodes, pancreas, mandibular gland, parotid gland, lymph nodes (retrophar., mandib., cerv. superf. and axillar.), tongue, pharynx, larynx, thoracic cavity (pleura, contents), thymus, trachea, lungs, mediastinum, pericardium, epicardium, heart, aorta, pulmonary artery, ureters, urinary bladder, urethra prostate, ovaries, oviducts, uterus, vagina, esophagus, stomach, small intestine, colon, caecum rectum, adrenals, kidneys, liver, gall bladder, hypophysis, brain
- Microscopic: heart, lungs, esophagus, stomach (large curvature, small curvature, pylorus region), small intestine (duodenum, jejunum, ileum), caecum, colon, liver, pancreas, kidney, urinary bladder, testes (right and left), epididymes (right and left), ovaries (right and left), prostate, uterus, thyroid with parathyroid, adrenals (right and left), cerebrum, cerebellum, periph. nerve, spleen, lymph nodes, bone marrow

OTHER EXAMINATIONS:

- Liver function test: before beginning and after 1.5 and 3 months: 2-Dye-test according to Zimmer
- Kidney function test: before beginning and after 1.5 and 3 months: Phenol-red test

Reliability : (2) valid with restrictions
limited documentation (test substance)
Flag : Critical study for SIDS endpoint

20.10.2003

(32)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : day 6 through day 19 post-coitum inclusive
Frequency of treatm. : daily
Duration of test : 20 days
Doses : 50, 250, or 1000 mg/kg bw/day
Control group : yes, concurrent vehicle
NOAEL maternal tox. : = 50 mg/kg bw
NOAEL teratogen. : >= 1000 mg/kg bw
Method : OECD Guide-line 414 "Teratogenicity"
Year : 2001
GLP : yes
Test substance : other TS: Degussa AG, batch Nos. 3347/24936 (GC purity 99.95 %) and 3347/24977 (GC purity 99.93 %)

Result : **MATERNAL TOXIC EFFECTS BY DOSE LEVEL:**
- Mortality and day of death: There were no treatment-related deaths at the 50 and 250 mg/kg bw/day dose

levels. At the 1000 mg/kg/day dose level, two females which presented poor clinical condition were prematurely sacrificed on day 8 post-coitum.

- Number aborting: no abortions
- Number of resorptions: no total resorptions
- Body weight: Slight to marked effects in mid- and high-dose groups:
 - 50 mg/kg bw/day: gross 3 % above, net 2 % below control
 - 250 mg/kg bw/day: gross 15 %, net 37 % below control
 - 1000 mg/kg bw/day: gross 26 %, net 50 % below control (gross = days 6 to 20; net = from day 6, corrected for weight of uterine content)
- Food/water consumption: Slight to marked effects in mid- and high-dose groups:
 - 50 mg/kg bw/day: not affected
 - 250 mg/kg bw/day: food consumption 7 % below control
 - 1000 mg/kg bw/day: food consumption 11 % below control
- Description, severity, time of onset and duration of clinical signs:
 - 50 mg/kg bw/day, 250 mg/kg bw/day: no clinical signs that were related to the treatment with the test substance
 - 1000 mg/kg bw/day: Severe clinical signs of poor clinical condition in a notable proportion of the animals: piloerection, round back, sedation, dyspnea and/or hypokinesia in 14/24 females, generally from the beginning until the end of the treatment.
- Gross pathology incidence and severity: There was no macroscopic finding that was attributed to the treatment with the test substance in any group.

FETAL DATA:

- Litter size and weights: No treatment-related effects were observed on the pre- and the post-implantation losses, and the sex ratio. The minimally lower fetal weight recoded at 250 and 1000 mg/kg/day was not statistically significant and considered to be secondary to the lower maternal body weight gain, and thus did not represent a direct adverse effect on the embryofetal development. Mean fetal weights:
 - 50 mg/kg bw/day: 4.04 +/- 0.21 g
 - 250 mg/kg bw/day: 3.89 +/- 0.30 g
 - 1000 mg/kg bw/day: 3.87 +/- 0.26 g
 - control: 3.93 +/- 0.25 g
- Number viable: no treatment-related effect
- Sex ratio: no treatment-related effect
- External abnormalities: No treatment-related fetal external malformations or variations were noted in any group.
- Soft tissue abnormalities: No fetal soft tissue malformations or variations that were ascribed to the treatment with the test substance were recorded in any group.
- Skeletal abnormalities: No fetal skeletal malformations or variations that were ascribed to the treatment with the test substance were recorded in any group.

Test condition : TEST ORGANISMS

- Source: Charles River Laboratories, L'Arbresle (France)
- Strain: CrI CD (SD) IGS BR
- Age: 10-11 weeks
- Weight at study initiation: 190-332 (mean 263) g
- Number of animals: 24 per group; only the first 20 pregnant females were taken into consideration for fetal examinations.

ADMINISTRATION / EXPOSURE

- Treatment: doses based on preliminary study (CIT/Study No. 20870 RSR)

	<ul style="list-style-type: none"> - Vehicle: mixture of gum Arabic (10%) and tween 80 (0.5%) in purified water - Concentration in vehicle: 10, 50, or 200 mg/ml (suspensions; homogeneity verified by analysis) - Total volume applied: 5 ml/kg bw/day - Type or preparation of particles: Daily. The test substance was ground to fine powder using a mortar and pestle, suspended in the vehicle in order to achieve the desired concentrations, and then homogenized using a magnetic stirrer. <p>MATING PROCEDURES: Females were mated at breeder's facilities. Mating was confirmed by detection of a vaginal plug (day 0). 5 days acclimatization period to the conditions of the study followed.</p> <p>PARAMETERS ASSESSED DURING STUDY:</p> <ul style="list-style-type: none"> - Body weight gain: days 2, 6, 9, 12, 15, 18, 20 - Food consumption: intervals days 2-6, 6-9, 9-12, 12-15, 15-18, 18-20 - Clinical observations: at least once a day - Examination of uterine content: number of corpora lutea, implantation sites, early and late resorptions, dead and live fetuses - Examination of fetuses: body weight, sex, external examination (all); detailed examination of the soft tissue (one half) or detailed examination of the skeleton (bone and cartilage, other half).
Conclusion	<p>: The test substance was not maternotoxic at 50 mg/kg bw/day. At dose-levels of 250 and 1000 mg/kg bw/day, the test substance produced slight to marked maternotoxicity resulting in reduction in food consumption and body weight gain. In addition, some mortality and clinical signs of toxicity were recorded at 1000 mg/kg/day.</p> <p>No embryo- and fetotoxicity was recorded at any dose-levels, and no teratogenic effects were found. Consequently, the No Observed Effect Level for maternal toxicity is 50 mg/kg/day and the No Observed Effect Level for developmental toxicity is greater than 1000 mg/kg/day.</p>
Reliability	<p>: (1) valid without restriction Guideline study</p>
Flag 21.10.2003	<p>: Critical study for SIDS endpoint</p>
Species	: rat
Sex	: female
Strain	: Sprague-Dawley
Route of admin.	: gavage
Exposure period	: day 6 through day 19 post-coitum inclusive
Frequency of treatm.	: daily
Duration of test	: 20 days
Doses	: 100, 300, or 1000 mg/kg bw d
Control group	: yes, concurrent vehicle
NOAEL teratogen.	: = 1000 - mg/kg bw
Method	: other
Year	:
GLP	: yes
Test substance	: other TS: Degussa AG Batch No. 3347/24936, purity > 99 %
Result	<p>: MATERNAL TOXIC EFFECTS BY DOSE LEVEL:</p> <ul style="list-style-type: none"> - Mortality and day of death: no mortality in any group - Number aborting: no abortions - Number of resorptions: no total resorptions

(8)

- Body weight: Minor to marked decrease in all treated groups
 - Food/water consumption: Minor to marked decrease in all treated groups
 - Description, severity, time of onset and duration of clinical signs: There were no clinical signs that were related to the treatment with the test substance in any group. Ptyalism was recorded in all females of the high dose-level group, but this sign was considered to be of no toxicological significance.
 - Gross pathology incidence and severity: There was no macroscopic finding that was attributed to the treatment with the test substance in any group.
- FETAL DATA:
- Litter size and weights: higher litter size and slightly lower fetal body weight in the treated groups when compared to the control were considered to be secondary effects.
 - Number viable: no treatment-related effect
 - Sex ratio: no treatment-related effect
 - External abnormalities: No treatment-related external malformations or variations were noted in any group.
- Test condition** : TEST ORGANISMS
- Source: Charles River Laboratories, L'Arbresle (France)
 - Age: 10-11 weeks
 - Weight at study initiation: 224-270 (mean 246) g
 - Number of animals: 7 per group
- ADMINISTRATION / EXPOSURE
- Treatment: doses based on 14-day range-finding study
 - Control group and treatment: vehicle
 - Vehicle: mixture of gum Arabic (10%) and tween 80 (0.5%)
 - Concentration in vehicle: 20, 60, or 200 mg/ml
 - Total volume applied: 5 ml/kg bw d
 - Type or preparation of particles: Daily. The test substance was ground to fine powder using a mortar and pestle, suspended in the vehicle in order to achieve the desired concentrations, and then homogenized using a magnetic stirrer.
- MATING PROCEDURES: Females were mated at breeder's facilities. Mating was confirmed by detection of a vaginal plug (day 0). 5 days acclimation period to the conditions of the study followed.
- PARAMETERS ASSESSED DURING STUDY:
- Body weight gain: days 2, 6, 8, 11, 14, 16, 18, 20
 - Food consumption: intervals days 2-6, 6-8, 8-11, 11-14, 14-16, 16-18, 18-20
 - Clinical observations: daily
 - Examination of uterine content: number of corpora lutea, implantation sites, early and late resorptions, dead and live fetuses
 - Examination of fetuses: body weight, sex, external examination
- Conclusion** : Minimal to slight maternotoxic effect (decrease in food consumption and body weight);
No evidence of embryo- and fetotoxicity or external malformations at any dose-level.
- Reliability** : (2) valid with restrictions
preliminary study; small number of animals

(7)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

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