FOREWORD INTRODUCTION

3-Aminomethyl-3,5,5-trimethylcyclohexylamine

CAS N°: 2855-13-2

SIDS Initial Assessment Report

For

SIAM 18

Paris, France, April 20–23, 2004

1. Chemical Name:	3-Aminomethyl-3,5,5-trimethylcyclohexylamine
2. CAS Number:	2855-13-2
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn-Bad Godesberg
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	3-Aminomethyl-3,5,5-trimethylcyclohexylamine Consortium Degussa AG, BASF AG, DuPont Chemical Solutions Enterprise
• 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): 22 October 2003 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 27 October 2003 (Ecotoxicology): databases CA, biosis; 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:	Deadline for circulation: 23 January 2004
10. Date of last Update:	

11. Comments:

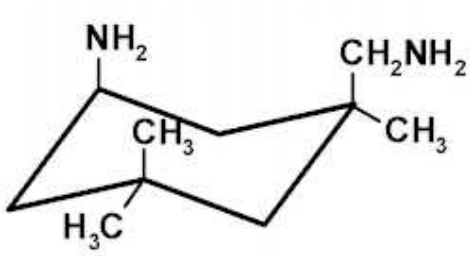
OECD/ICCA - The BUA* Peer Review Process

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.	2855-13-2
Chemical Name	3-Aminomethyl-3,5,5-trimethylcyclohexylamine
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There is no information available on toxicokinetics and metabolism of 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

There is only one valid but limited acute toxicity study of 3-aminomethyl-3,5,5-trimethylcyclohexylamine available. The LD_{50} after oral application to male rats is 1,030 mg/kg bw and the kidney is the potential target organ. Valid acute inhalation or dermal studies are not available.

Based on a limited skin irritation study with rabbits and rats, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is deemed to be a strong irritant (duration of the exposure not reported) and corrosive after repeated application. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is corrosive to the eyes of rabbits when tested according to OECD TG 405.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine was found to induce dermal sensitisation when tested according to OECD TG 406 in guinea pigs. From a number of publications there is evidence that frequent occupational exposure to 3-aminomethyl-3,5,5-trimethylcyclohexylamine may lead to the development of allergic contact dermatitis in humans. Since there is only one publication on possible airway effects of 3-aminomethyl-3,5,5-trimethylcyclohexylamine (describing a single human case) no definite conclusion can be drawn on respiratory sensitisation.

From two 14-day inhalative exposure studies with rats no NOAEL could be determined. At the first study's LOAEL of 18 mg/m^3, degeneration/necrosis in the olfactory epithelium of the nose were observed. Trachea, larynx and lungs were affected at 200 mg/m^3 and above (degeneration/necrosis, hyperplasia, squamous metaplasia). At the LOAEL of the follow-up study, i.e. at 2.2 mg/m^3, reversible minimal to mild degeneration of respiratory nasal mucosa in the anterior dorsal nose was observed. In a subchronic drinking water study according to OECD TG 408, the administration of 150 mg/kg bw/day led to reduced absolute and relative kidney weights in male and female rats (histopathology being indicative for tubular nephrosis), while 59 mg/kg bw/day (males) and 62 mg/kg bw/day (females) were determined as a NOAEL.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine was not mutagenic in bacteria and mammalian cell systems *in vitro* (Ames test according to Directive 84/449/EEC B.14 (1984) and HPRT test according to OECD TG 476 (1984)). It did not induce chromosomal aberrations in CHO cells *in vitro* in a test performed in accordance with OECD TG 473 (1981). *In vivo* mouse micronucleus tests (one performed according to OECD TG 474 (1983) for the induction of micronucleated polychromatic erythrocytes were clearly negative. From all *in vitro* and *in vivo* tests performed there is no evidence that 3-aminomethyl-3,5,5-trimethylcyclohexylamine has a mutagenic or clastogenic potential.

No studies have been performed on the toxicity of 3-aminomethyl-3,5,5-trimethylcyclohexylamine to reproduction.

Data from an oral 90-day study in rats according to OECD TG 408 did not reveal any adverse effects on the male and female reproductive organs.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine did not show any teratogenic or embryofetotoxic effects in a gavage study with rats performed in accordance with OECD TG 414 (2001) up to and including the highest tested dose level of 250 mg/kg bw/day. The NOAEL for maternal toxicity was 50 mg/kg bw/day, effects at 250 mg/kg bw/day were reduced food consumption and reduced body weight gain. The NOAEL for developmental toxicity is 250 mg/kg bw/day.

Environment

3-Aminomethyl-3,5,5-trimethylcyclohexylamine has a melting point of 10 °C, is miscible with water and has a vapour pressure of 0.02 hPa at 20 °C. The measured log K_{ow} is 0.99 (23 °C). The pKa of approximately 10.4 characterises the substance as a moderate base.
According to a Mackay Level I model calculation, the main target compartment for 3-aminomethyl-3,5,5-trimethylcyclohexylamine will be water (99.8 %), followed by sediment and soil (both 0.08 %). It has to be considered that under environmental relevant pH conditions the substance is available as cation and therefore the prediction of the environmental distribution using the data for the uncharged molecule is not appropriate. The calculated Henry's law constant of 0.000446 Pa m^3/mol indicates very low volatility from surface waters. Dissociation in aqueous solution will further reduce the volatility. With a calculated K_{oc} of 340.4 l/kg, the sorption potential to soil or sediment organic matter is expected to be moderate. However, as in the environment the substance is available as cation, binding to the matrix of soils with high capacities for cation exchange (e.g. clay) cannot be excluded.

In the atmosphere, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is rapidly removed by reaction with hydroxyl radicals with a calculated half-life of 0.2 days. In water, it is expected to hydrolyse at a low rate under environmental conditions ($t_{1/2}$ > 1 year at 25°C). Photolytical degradation in surface waters is expected to be of minor importance due to the chemical structure. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is not readily biodegradable (OECD 301A: 8 % after 28 days). However, in a simulation test with activated, non-adapted sludge, a degradation of 42 % (including a minor, though not negligible contribution by adsorption to sludge) was measured after a contact time of 6 hrs. The log K_{ow} value of 0.99 indicates a low bioaccumulation potential.

The lowest valid acute test results of aquatic testing determined for fish, daphnids, and algae were as follows: *Leuciscus idus:* 96-h LC_{50} = 110 mg/l; *Daphnia magna:* 48-h EC_{50} = 23 mg/l; *Scenedesmus subspicatus:* 72-h ErC_{50}> 50 mg/l; 72-h E_bC_{50} = 37 mg/l

Long term aquatic toxicity data are available for two trophic levels: *Daphnia magna:* 21-d NOEC = 3.0 mg/l; *Scenedesmus subspicatus:* 72-h E_rC_{10} = 11 mg/l; 72-h E_bC_{10} = 3.0 mg/l

An assessment factor of 50 was applied to the lowest of two long-term results covering two trophic levels. The PNEC of 0.06 mg/l for aquatic organisms was calculated from the NOEC for *Daphnia* = 3.0 mg/l.

Exposure

The production volume of 3-aminomethyl-3,5,5-trimethylcyclohexylamine is approximately 35,000 t/year world wide. Production sites are in Germany and the U.S.A. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is used as a chemical intermediate to produce hardeners for epoxy resins and coatings, and is also directly used as a hardener. It has large applications in epoxy-based self-levelling and trowelable flooring systems, and various civil engineering applications such as paving, concrete protection and repair. Other applications include coatings for superior corrosion protection of metal, adhesives and anchoring compounds. It is further used in the production of non-crystalline speciality polyamides, as a chain extender in polyurethanes and as an intermediate in dyes.

Releases into the environment may occur during production of 3-aminomethyl-3,5,5-trimethylcyclohexylamine as well as from processing, formulation and use as an epoxy resin hardener. Available information indicates that in Germany release from production into waste water treatment plants is < 13,000 kg/year. The predicted environmental concentrations are of low toxicological significance.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine is used in a number of consumer products, mainly hardeners for paints, adhesives, and floor covering materials at various concentrations up to > 50%. Due to the low vapour pressure, exposure by inhalation is unlikely to occur.

Workplace measurements from the U.S. production site indicate a median concentration during 8-hr working shifts of <0.01 mg/m³ 3-aminomethyl-3,5,5-trimethylcyclohexylamine. No specific monitoring data for 3-aminomethyl-3,5,5-trimethylcyclohexylamine are available for the two German production sites. Exposure relevant operations are sampling, loading connections, cleaning operations, and leaks, all of which are low in duration and / or frequency. Exposure is controlled by measures like leak detection systems or exhaust ventilation as well as by personal protection equipment, which is depending on the job. No additional information is available on processing, formulation and use as an epoxy resin hardener.

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 possesses properties (sensitisation, corrosive effects) indicating a hazard for human health. In view of the magnitude of the potential for effects, consumer products are considered to be adequately labelled and occupational exposure is controlled sufficiently in the Sponsor country to ensure safe handling, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by Sponsor countries.

Environment:

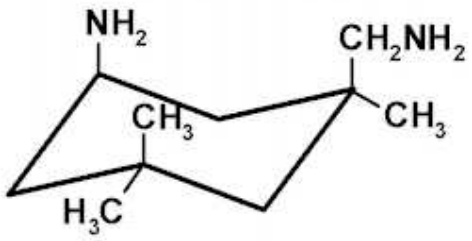
The chemical possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure levels, they should nevertheless be noted by chemical safety professionals and users.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 2855-13-2
IUPAC Name: 3-aminomethyl-3,5,5-trimethylcyclohexylamine
Molecular Formula: C10H22N2
Structural Formula:



Molecular Weight: 170.3
Synonyms: 1,3,3-Trimethyl-1-aminomethyl-5-aminocyclohexane
1-Amino-3,3,5-trimethyl-5-aminomethylcyclohexane
1-Amino-3-aminomethyl-3,3,5-trimethylcyclohexane
3-Aminomethyl-3,5,5-trimethylcyclohexylamin (German)
5-Amino-1,3,3-trimethylcyclohexanemethylamine
Cyclohexanemethanamine, 5-amino-1,3,3-trimethyl-
Degamin IPDA
Isophorondiamin (German)
Isophorone diamine
VESTAMIN IPD

1.2 Purity/Impurities/Additives

Purity: ≥ 99.7 % w/w

Impurities: ≤ 0.2 % w/w water

< 0.15 % w/w aminonitriles

< 0.15 % w/w secondary and tertiary amino compounds

Additives: none

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	
Physical state	Liquid	
Melting point	10°C	Hommel, 1998
Boiling point	247°C at 1,013 hPa	Hüls AG, 1992b
Relative density	0.92-0.925 g/cm³ at 20°C	Hüls AG, 1992b
Vapour pressure	ca. 0.02 hPa at 20°C	Hommel, 1998
Water solubility	Miscible	Hüls AG, 1992b
Partition coefficient n-octanol/water (log value)	0.99 at 23°C	Hüls Infracor, 1998
Henry's law constant	0.000446 Pa m^3/mol	Degussa AG, 2002a
K_{oc}	340.4 l/kg	Degussa AG, 2002a

The pKb of approximately 3.6 reported by VEBA-Chemie (1975) corresponds to a pKa of 14.0 - 3.6 = 10.4 and characterises the substance as a moderate base. It is in reasonable agreement with the QSAR result of 10.72 $\pm$ 0.20 obtained with the Solaris V4.67 software (STN, 2003). It should be noted that 3-aminomethyl-3,5,5-trimethylcyclohexylamine has two amine groups in asymmetric positions, which are thus expected to have slightly different basicities. The experimental pKa of approximately 10.4 reflects the overall basicity.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The world-wide production of 3-aminomethyl-3,5,5-trimethylcyclohexylamine is estimated to be in the order of 35,000 tons per year. Production sites are in Germany and the U.S.A. (BASF, 2002; Degussa, 2002b; E.I. DuPont de Nemours, 2004). 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is used as a chemical intermediate to produce hardeners for epoxy resins and coatings and is also directly used as a hardener. It has large applications in epoxy-based self-levelling and trowelable flooring systems, and various civil engineering applications such as paving, concrete protection and repair. Other applications include coatings for superior corrosion protection of metal, adhesives and anchoring compounds. It is further used in the production of non-crystalline specialty polyamides, as a chain extender in polyurethanes and as an intermediate in dyes (Degussa, 2002b). The most prominent substance produced from 3-aminomethyl-3,5,5-trimethylcyclohexylamine is the diisocyanate 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate, which is also predominantly used directly as a hardener or as an intermediate in the production of hardeners, particularly for coatings (Degussa, 2003).

In the Swedish Product Register (Feb. 2002), 247 products containing 3-aminomethyl-3,5,5-trimethylcyclohexylamine are listed, 36 of which are consumer products. "Hardeners for paints, adhesives and plastics, floor covering materials, paints, anti-corrosive paints" are given as the main uses.

In the Swiss Product Register (Dec. 2001), a total of 595 products containing 3-aminomethyl-3,5,5-trimethylcyclohexylamine are listed, 21 of which are consumer products. The majority of the

consumer products containing 3-aminomethyl-3,5,5-trimethylcyclohexylamine are hardeners (18/21), while professional use is focussed on hardeners (363/574), adhesives, putty and fillers (77/574) and paints and varnishes (72/574).

The product registers of Denmark (Feb. 2002) and Finland (Year of reference 2001) list 407 and 157 products, respectively, containing 3-aminomethyl-3,5,5-trimethylcyclohexylamine at various concentrations up to 100 %. The total annual quantities of 3-aminomethyl-3,5,5-trimethylcyclohexylamine are 193 tons in Denmark and 983 tons in Finland, respectively. Use patterns are similar to those in the Swedish and Swiss product registers. No information is reported on how many of these products are for private users or consumers (Danish Product Register, 2002; Finnish Product Register, 2002).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Releases into the environment may occur during production, processing, formulation and direct use of 3-aminomethyl-3,5,5-trimethylcyclohexylamine. The following exposure information for the single production sites is available:

Germany:

In the BASF production plant, exhaust gases go to a flare. Release to the industrial waste water treatment plant from the continuously operated process is reported to < 5,000 kg/year (receiving water: river Rhine, flow rate 734 m³/s; BASF, 2002). The maximum local concentration at low flow after complete mixing is: maximum load per hour (5,000 kg/year / 365 d/year / 24 h/d) / water flow per hour at low flow conditions (734 m^3/s x 3,600 s/h) = 0.22 µg/l. This concentration may be lower due to possible elimination in sewage treatment plant.
In the Degussa production plant, offgas is quantitatively combusted. Process wastewater of approx. 8,000 m³/year (1 m^3/hour at 8000 h/year) contains approx. 993 g/m³ 3-aminomethyl-3,5,5-trimethylcyclohexylamine (i.e. total amount of 7,940 kg 3-aminomethyl-3,5,5-trimethylcyclohexylamine/year) and is treated in a wastewater treatment plant. Other waste is transferred in liquid state to complete incineration (Degussa, 2002b). The low flow rate of the receiving water is 8.13 m^3/s (Emschergenossenschaft, 2003). The local concentration at low flow after complete mixing is: load per hour (7,940 kg / 8,000 h) / water flow per hour at low flow conditions (8.13 m^3/s x 3,600 s/h) = 34 µg/l. Also this concentration may be lower due to possible elimination in sewage treatment plant. A pipeline leading the effluent directly to the river Rhine is in preparation (Degussa, 2002b).

U.S.A.:

At the DuPont production site, approximately 1000 kg/year of 3-aminomethyl-3,5,5-trimethylcyclohexylamine is released to the air, primarily as fugitive emissions. There are no releases of process wastewater to any receiving surface waters. Process wastewater of approximately 7000 m^3/year from this unit is disposed of by deepwell injection after treatment in a series of carbon adsorption units. The concentration of 3-aminomethyl-3,5,5-trimethylcyclohexylamine in the process waste water disposed of by deepwell injection is typically below 100 ppm. Approximately 2000 m^3/year of other process waste, containing approximately 20 m^3/year 3-aminomethyl-3,5,5-trimethylcyclohexylamine is transferred in liquid state to an on-site energy recovery unit where 3-aminomethyl-3,5,5-trimethylcyclohexylamine is completely destroyed (E.I. DuPont de Nemours, 2004).

For the German production sites, taking into account complete mixing with the receiving rivers, PECs of ≤ 34 µg/l (Emscher) and ≤ 0.22 µg/l (Rhine) were calculated.

Additional releases to the environment are expected to arise from the processing, formulation and use of the substance. These quantities may be higher than those from production. However, quantitative information is not available. Degussa (2002b) has shared some information on residual monomer contents in polymeric reaction products and on releases from these products: The residual monomer content cannot be determined directly by routine analytical methods because the reaction products are insoluble polymers. Also, it is expected to vary significantly with the identities and the absolute and relative concentrations of the monomers used. An indirect determination is usually made by differential scanning calorimetry (DSC): The reaction enthalpy of the residual reaction is compared to the reaction enthalpy of the total reaction. In order to achieve satisfactory technical properties of the resulting polymers, a conversion of about 90 % is required. 3-aminomethyl-3,5,5-trimethylcyclohexylamine has four protons which can react in the hardening reaction. Assuming independent reactions of these four protons, a conversion rate of 90 % leaves 0.1 x 0.1 x 0.1 x 0.1 = 0.01 % of the initial 3-aminomethyl-3,5,5-trimethylcyclohexylamine unreacted. The concentration of 3-aminomethyl-3,5,5-trimethylcyclohexylamine in the reaction mixture is normally between 2 and 20 %, i.e. its maximum concentration in the final product would be 20 ppm. Differences in reactivity will lead to a preferred reaction of the most reactive proton with the polymer and consequently to a more rapid decrease in residual monomeric 3-aminomethyl-3,5,5-trimethylcyclo-hexylamine. Migration tests were done to check compliance of a certain polymer product with German standards for drinking water pipes. The result of 2.3 [µg/dm^2*d]; was well below the limit value of < 7.5 [µg/dm^2*d]. However, it should be noted that this test was done on a product designed to show very low migration. Migration from other products may be higher but will be limited by the availability of residual monomers (see above). The crosslinking reaction will proceed slowly during the lifetime of the final article.

2.2.2 Photodegradation

In the atmosphere, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is rapidly photodegraded by reaction with hydroxyl radicals. According to the method of Atkinson (1987), i.e. using the AOP computer program (Syracuse Research Center), the reaction rate with OH-radicals is 8.47 x 10^{-11} cm^3 x molecule^{-1} x s^{-1}. Based on a tropospheric OH-radical concentration of 500,000 molecules x cm^{-3} the corresponding half-life is calculated to 0.2 days. In view of the absence of chromophores in the structure, one will expect that photolytical degradation in surface waters will be of minor importance.

2.2.3 Stability in Water

Stability in water was determined according to OECD 111 (Infracor, 2002a). In a preliminary test less than 10 % degradation was observed after 5 days at 50 °C and pH 4, 7, and 9, corresponding to a $t_{1/2}$ of > 1 year at 25 °C. A main test was therefore not required.

2.2.4 Transport between Environmental Compartments

The distribution of 3-aminomethyl-3,5,5-trimethylcyclohexylamine in a “unit world” was calculated according to the Mackay fugacity model level I (V. 2.11) (Degussa, 2002a), based on the physico-chemical properties listed in section 1. The main target compartment estimated was water (99.8 %), whereas soil and sediments (both 0.08 %) are expected to be of minor importance. It has to be considered, that under environmental relevant pH conditions, the substance is available as a cation and thus the prediction of the environmental distribution using the values for the uncharged molecule is not appropriate.

Due to its (calculated) log K_{oc} of 2.532 (K_{oc} = 340.4 l/kg), it is expected to be moderately adsorbed to soil and sediment, i.e. to have a moderate potential for geoaccumulation (Degussa AG, 2002a).

As under environmental pH conditions the substance is available as cation, binding to the matrix of soils with high capacities for cation exchange (e.g. clay) cannot be excluded.

The Henry's law constant governing the distribution of 3-aminomethyl-3,5,5-trimethylcyclohexylamine between aqueous solutions and air was calculated using a QSAR computer programme, see Table 1. A value of 0.000446 Pa m^3/mol (Degussa AG, 2002a) indicates very low volatility from aqueous solution according to the criteria of Thomas (1990).

2.2.5 Biodegradation

In a DOC-Die Away Test (similar to OECD 301 A) using 3-aminomethyl-3,5,5-trimethylcyclohexylamine as test substance 8 % degradation was determined after 28 days incubation (Hüls AG, 1993d). Activated sludge from a biological treatment plant receiving primarily municipal sewage was used as inoculum. Based on this test, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is not readily biodegradable.

In a simulation test with activated, non-adapted sludge (similar to OECD 303 A), a degradation of 42 % was measured after a contact time of 6 hrs (Hüls AG, 1992a). These 42 % elimination are the result of biodegradation plus adsorption to the sludge, which was renewed daily. The moderate adsorption potential of 3-aminomethyl-3,5,5-trimethylcyclohexylamine (see chapter 2.2.4) suggests that the contribution of adsorption is of minor, though not negligible importance.

2.2.6 Bioaccumulation

No studies with respect to this endpoint have been performed. Due to the low log K_{ow} of 0.99 the bioaccumulation potential is considered to be low.

2.2.7 Other Information on Environmental Fate

No information available.

2.3 Human Exposure

2.3.1 Occupational Exposure

260 personal air sampler determinations taken during the period 1996-2000 in the U.S. production plant gave concentrations during 8-hr working shifts from not detectable to 0.043 (median 0.0057) mg 3-aminomethyl-3,5,5-trimethylcyclohexylamine/m^3. Exposure relevant operations are sampling, loading connections, and leaks. Exposure is controlled by a leak detection system and a Deluge system as well as by personal protection equipment, which is depending on the job: Butyl gloves, goggles, Tychem SL coverall, Level A Chemsuit, respirator w/canister, and / or air-line respirator (E.I. DuPont De Nemours, 2004).

No monitoring data for 3-aminomethyl-3,5,5-trimethylcyclohexylamine are available for the two German production sites. In the BASF plant, only one person per shift, i.e. two persons per day, may be exposed to 3-aminomethyl-3,5,5-trimethylcyclohexylamine. Exposure is possible during sampling, cleaning, and filling operations, the total duration of which is less than 30 minutes per shift. Exposure is controlled by local exhaust ventilation at the filling station and in the laboratory as well as by wearing gloves, goggles, and protective clothes during these operations (BASF, 2002).

In the Degussa plant, 40 different persons may be exposed to 3-aminomethyl-3,5,5-trimethylcyclohexylamine, but occasions are rare. Exposure is possible during sampling (once daily), cleaning

(twice annually), and leakages (usually significantly less than once a year). It is controlled by a state of the art DCS control system as well as by wearing goggles and protective clothes, e.g. hard hat, steel cap shoes. Occupational exposure is monitored for ammonia as the lead substance instead, which is done annually. In 2002, ammonia concentrations from 8 hour shift sampling ranged from < 1 to 1.9 mg ammonia/m^3. It is expected that the concentration of 3-aminomethyl-3,5,5-trimethylcyclohexylamine is well below that of ammonia, presumably at least by one order of magnitude (Degussa, 2002b).

No additional information is available on processing, formulation and use as an epoxy resin hardener.

2.3.2 Consumer Exposure

In the Swedish Product Register (Feb. 2002), 36 consumer products containing 3-aminomethyl-3,5,5-trimethylcyclohexylamine are listed. "Hardeners for paints, adhesives and plastics, floor covering materials, paints, anti-corrosive paints" are given as the main uses.

In the Swiss Product Register (Dec. 2001), a total of 21 consumer products containing 3-aminomethyl-3,5,5-trimethylcyclohexylamine (concentration mostly 10 - 50 %, one product > 50 %) are listed. The majority of the consumer products containing 3-aminomethyl-3,5,5-trimethylcyclohexylamine (18/21) are hardeners. The product registers of Denmark (Feb 2002) and Finland (Year of reference 2001) list 407 and 157 products, respectively, containing 3-aminomethyl-3,5,5-trimethylcyclohexylamine at various concentrations up to 100 %. The total annual quantities of 3-aminomethyl-3,5,5-trimethylcyclohexylamine are 193 tons in Denmark and 983 tons in Finland, respectively. No information is reported on how many of these products are for private users or consumers (Danish Product Register, 2002; Finnish Product Register, 2002).

Probably as a consequence of its use as a hardener, 3-aminomethyl-3,5,5-trimethylcyclohexylamine was identified (not quantified) in drinking water samples taken from water mains relined with epoxy resin (Watts et al., 1984).

No information is available on the magnitude of indirect exposure via the environment. Conclusions on the toxicological significance of such exposure can be drawn from observations in cases of occupational contact dermatitis (see chapter 3.1.4), which is the key hazard of 3-aminomethyl-3,5,5-trimethylcyclohexylamine. The predicted environmental concentrations (≤ 34 µg/l (Emscher) and ≤ 0.22 µg/l (Rhine), see chapter 2.2) are far below the threshold of 0.5 % 3-aminomethyl-3,5,5-trimethylcyclohexylamine for active sensitisation determined by Jolanki (1991). This indicates that the background concentration of 3-aminomethyl-3,5,5-trimethylcyclohexylamine is of low toxicological significance.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

No studies with respect to these endpoints have been performed.

3.1.2 Acute Toxicity

Studies in Animals

Oral

The oral LD_{50} in male Sprague-Dawley rats was determined to be 1,030 mg/kg b.w. (Klimmer, 1965). Doses of 0.5, 1.0, 1.5, 2.0, or 2.5 ml/kg bw of a 50 % v/v solution in water were applied by gavage followed by a post dose observation period of 14 days. Clinical signs observed from 1 hour after dosing were restlessness, thirst, rough fur and tiredness. At necropsy, irritation of the intestinal mucosa was observed. A few animals (no further data) showed a slight increase in kidney weight and protein in the urine, which may indicate that the kidney is a target organ.

Conclusion

There is only one valid but limited acute toxicity study of 3-aminomethyl-3,5,5-trimethylcyclohexylamine available. The LD_{50} after oral application to male rats is 1,030 mg/kg bw and the kidney is the potential target organ. Valid acute inhalation or dermal studies are not available.

3.1.3 Irritation

Skin Irritation

Studies in Animals

In a study with rabbits and rats, undiluted 3-aminomethyl-3,5,5-trimethylcyclohexylamine was massaged into the depilated back skin of the animals and covered with gauze and adhesive tape. Under these conditions (duration of the exposure not reported), 3-aminomethyl-3,5,5-trimethylcyclohexylamine penetrated the skin and caused swelling, irritation and inflammatory effects. Repeated application led to severe effects with formation of crusts and necroses. Effects were more pronounced with rabbits than with rats (Klimmer, 1965). Lack of documentation limits the value of the study, but the result is in reasonable agreement with the pKb of the substance (ca. 3.6; VEBA-Chemie, 1975), with its classification as corrosive, and with observations in occupational medicine.

Eye Irritation

Studies in Animals

In a study according to OECD TG 405 with rabbits (Small white Russian), undiluted 3-aminomethyl-3,5,5-trimethylcyclohexylamine produced serious injury (corrosive effects, opalescence) almost immediately after application. Twenty-four hours after application of the test substance, conjunctivae showed necrosis (Hüls AG, 1983b).

Conclusion

Based on a limited skin irritation study with rabbits and rats, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is deemed to be a strong irritant (duration of the exposure not reported) and corrosive after repeated application. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is corrosive to the eyes of rabbits when tested according to OECD TG 405.

3.1.4 Sensitisation

Studies in Animals

Skin

In a guinea pig maximisation test according to OECD TG 406, sensitisation was observed in 18 of 20 animals 24 hrs after using a challenge concentration of 5 %. With a challenge concentration of 2.5 %, 7 of 20 animals were positive (Hüls AG, 1983a).

The sensitising properties of 3-aminomethyl-3,5,5-trimethylcyclohexylamine were also observed in two other guinea pig maximisation tests (Inveresk, 1981; Thorgeirsson, 1978).

Studies in Humans

Skin

There are several publications describing 3-aminomethyl-3,5,5-trimethylcyclohexylamine related contact dermatitis:

Three out of 15 workers manufacturing plastic tennis rackets developed allergic contact dermatitis when exposed concomitantly to 3-aminomethyl-3,5,5-trimethylcyclohexylamine and epoxy resin. Symptoms appeared 3 months, 6 weeks or 3 weeks after starting this work and disappeared completely within 3 weeks after moving to a different department. Patch tests were positive with 1, 2, or 5 % 3-aminomethyl-3,5,5-trimethylcyclohexylamine in both ethanol and olive oil. After the test it became obvious that the controls were also sensitised (Lachapelle, Tennstedt and Dumont-Fruytier, 1978).

Two of the three workers positive for 3-aminomethyl-3,5,5-trimethylcyclohexylamine from the Lachapelle, Tennstedt and Dumont-Fruytier study (1978) and two additional ones who were also positive for 3-aminomethyl-3,5,5-trimethylcyclohexylamine, were patch tested 1 month later with isophorone diisocyanate (1 %). All four were positive, while five control volunteers were negative. This study may indicate a cross-sensitivity between 3-aminomethyl-3,5,5-trimethylcyclohexylamine and the corresponding diisocyanate, though its documentation is poor (Lachapelle and Lachapelle-Ketelaer, 1979).

From 142 persons considered to have skin disorders from current occupational exposure to epoxy compounds, 135 had allergic contact dermatitis. 53 of those were patch tested for 3-aminomethyl-3,5,5-trimethylcyclohexylamine, and three were positive towards this substance. Patch tests with 0.5 % 3-aminomethyl-3,5,5-trimethylcyclohexylamine were used, as this concentration was observed to induce neither irritation nor active sensitisation in the patch testing (Jolanki, 1991).

A 38-year old bricklayer had prolonged skin contact with a work shoe contaminated with a 3-aminomethyl-3,5,5-trimethylcyclohexylamine containing two-component glue. The man developed a dermatitis on the chest, upper back, arms and legs and was tested positive for 3-aminomethyl-3,5,5-trimethylcyclohexylamine (0.5%) 2 months after the generalised skin reaction had healed (Kelterer, Bauer and Elsner, 2000; short communication).

A total of 137 employees of 10 companies preparing and using epoxy resins for coating, flooring, impregnating and repairing concrete, brick and wooden structures were examined. Positive patch tests were observed in 27 of the 137 employees, predominantly with epoxy resin (25 persons / 18.5 %), but also with 0.1 % 3-aminomethyl-3,5,5-trimethylcyclohexylamine (3 persons / 2.3 %). Positive correlation with the development of an allergy were observed with the frequency of exposure, the duration of employment and the permanent wearing of gloves (van Putten, Coenraads and Nater, 1984).

A 53-year-old male employed for laying impermeable floors had a very itchy, symmetrical, erythematous, edematous eruption of the face, which had begun during work. Repeatedly, it had healed within few weeks off work but recurred when returning to work. No working colleagues had similar problems, though in the past, a man had left the job following a similar history. From several patch tests with standard series and with his working materials, only 3-aminomethyl-3,5,5-trimethylcyclohexylamine was positive with erythema from 0.1 %, and erythema, oedema and vesicles from 1 % and 5 % after three days (Patussi et al., 1995).

A 44-year old man working at a lamination machine, having had no previous skin problems except photosensitisation, after 2 years at the lamination machine observed eczema on the hands and wrists, as well as on the right upper arm. Enclosure of the process was improved. Four years later, his dermatitis worsened covering particularly typical sites of sun exposure. It healed during 2 weeks off work. In patch testing, positive reactions were observed for 3-aminomethyl-3,5,5-trimethylcyclohexylamine, the two glue components, plastic-laminated fiber cloth as such, perfume mix, and epoxy resin (Tarvainen et al., 1998).

During January 1984 to May 1992, Tosti et al. (1993) patch tested 39 patients with occupational allergic contact dermatitis to epoxy resin system substances. Positive reactions for 3-aminomethyl-3,5,5-trimethylcyclohexylamine were observed in 0/18 persons from electronics industry, 1/8 painters, 0/3 from fiberglass handling, 1/8 from gluing, 0/1 dental technicians, and 1/1 mechanics. The documentation of this study is not sufficient to allow a judgment on its validity.

In a further poorly documented study, all persons from the contact dermatitis database at Waikato Hospital (Hamilton, NZ) with relevant and work related contact dermatitis to epoxy resin compounds, i.e. 16 males, average age 37 years (range 21-53 years), were subject to several patch tests. Among them, one reacted positive with 3-aminomethyl-3,5,5-trimethylcyclohexylamine (0.1 % in petrolatum) (Rademaker, 2000).

Kanerva et al. (1999) studied the relative frequency of occupational contact dermatitis towards 53 sensitisers by patch testing all patients exposed to plastics and remitted to an occupational dermatology clinic during the years 1991 - 1996. 311 patients were tested using occlusive patches with 0.5 % 3-aminomethyl-3,5,5-trimethylcyclohexylamine in petrolatum for 48 hours followed by three readings, usually on days 2, 3, and 4-6. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine was among the 26/53 substances which induced no allergic reaction, but it induced irritation in one case. Maximum frequencies were 5.1 % for sensitisation and 9.5 % for irritation.

Respiratory Tract

A 44-year old man had a serious attack of bronchial obstruction after working with resins and hardeners, releasing fumes of a mixture of trimethyl-1,6-hexanediamine and 3-aminomethyl-3,5,5-trimethylcyclohexylamine. Eight hours after deliberate challenge with the hardener, a large increase of airway resistance was found. Seventy-two hours after challenge, eosinophilia in the bronchoalveolar fluid together with a decrease in peripheral eosinophils was seen. After cessation of contact with this hardener, no more acute episodes were seen, though maintenance treatment with a topical corticosteroid and a beta2-agonist remained necessary (Aleva et al., 1992).

Conclusion

3-Aminomethyl-3,5,5-trimethylcyclohexylamine was found to induce dermal sensitisation when tested according to OECD TG 406 in guinea pigs. From a number of publications there is evidence that frequent occupational exposure to 3-aminomethyl-3,5,5-trimethylcyclohexylamine may lead to the development of allergic contact dermatitis in humans. Since there is only one publication on possible airway effects of 3-aminomethyl-3,5,5-trimethylcyclohexylamine (describing a single human case) no definite conclusion can be drawn on respiratory sensitisation.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

3-Aminomethyl-3,5,5-trimethylcyclohexylamine was evaluated for repeated inhalation toxicity in male CD(SD)BR rats (10/dosage group) exposed nose-only to nominal aerosol/vapour concentrations of 18, 200, and 550 mg/m³, 6 hours/day for two weeks (4 - 5 days/week). In total, there were 9 exposures in the low and medium dose groups, while the high dose group was ended after 4 exposures due to unexpected mortality of four rats, the other six rats being necropsied the next day. Following the last exposure, 5 rats from each group (except high dose) were sacrificed and necropsied, while the remaining were sacrificed after a subsequent 20-day recovery period. Treatment with 550 mg/m³ was associated with significantly reduced bodyweights (-7.8 % within 4 days vs +0.7 % in control group). Dose-dependent histopathology was identified in the nose (18, 200, 550 mg/m³), trachea (200, 550 mg/m³), larynx (200, 500 mg/m³), and lungs (200, 550 mg/m³). Observed effects were: Degeneration/necrosis in the olfactory epithelium (nose: 5/6 “minimal” at 18 mg/m^3; 5/5 “mild” at 200 mg/m^3; 1/10 “minimal”, 8/10 “mild”, 1/10 “moderate” at 550 mg/m^3) and in the respiratory epithelium (nose, trachea, and larynx: 3/5 “minimal” at 200 mg/m^3; 1/10 “minimal”, 6/10 “mild”, 3/10 “moderate” at 550mg/m^3); hyperplasia/squamous metaplasia (nose and larynx: 5/5 “mild”, only nose at 18 mg/m^3; 2/5 “mild”, 3/5 “moderate” at 200mg/m^3; 1/10 “minimal”; 8/10 “mild” at 550mg/m^3), and hypertrophy/hyperplasia (trachea and lungs: 2/5 “minimal” at 200mg/m^3; 3/10 “minimal”, 4/10 “mild” at 550mg/m^3). By the end of the 20-day recovery period, the lungs and trachea of rats exposed to 18 and 200mg/m3 were within normal limits. Tissue repair was still in progress in the nose and larynx of these same rats; however, close to full microscopic restitution was expected. A NOEL for this study could not be determined (DuPont, 1997).

In a follow-up study, the effects of repeated inhalation exposure to lower concentrations of 3-aminomethyl-3,5,5-trimethylcyclohexylamine were investigated. Again, there were 9 nose-only inhalation 6 h/day exposures within two weeks (4 or 5 per week) of male Sprague-Dawley rats (10 per group). The test concentration was 2 mg/m3 (nominal); 2.2 +/- 0.25 (range 1.0 - 3.0) mg/m^3 (analytical). Each five rats per group were sacrificed and necropsied the day after the last exposure and after a two week recovery period, respectively. Microscopic studies focussed on the respiratory tract: Lungs, trachea, pharynx/lanrynx, nose (first sacrifice); nose (recovery sacrifice). The only exposure related findings were minimal (2/5) to mild (3/5) degeneration of respiratory nasal mucosa in the anterior dorsal nose. They were reversible and had resolved by the end of the recovery period (DuPont, 2001).

Oral

In a 13-week oral toxicity study according to OECD TG 408 (RCC Research and Consulting Company, 1986), 3-aminomethyl-3,5,5-trimethylcyclohexylamine was administered in the drinking water to Wistar rats (20 animals/sex/dose) which received nominal daily doses of 0, 20, 60, and 160 mg/kg bw (actual dose 21.5 / 59 / 150 mg/kg bw day for males, 22.6 / 62 / 147 mg/kg bw day for females). No treatment-related clinical signs, symptoms or mortality were noted during the study. Food and water consumption and body weight gain were significantly reduced in high dose animals. In addition, animals of this group revealed higher absolute and relative liver and kidney weights:

Table 2: Influence of 3-aminomethyl-3,5,5-trimethylcyclohexylamine on water consumption, body weight gain and kidney weights

Influence on:	**160 mg/kg bw/day**	
	Male animals	**Female animals**
Mean water consumption (g/animal/day; compared to control)	-40 %	-48 %
Net body weight gain (compared to control)	-16 %	-21 %
Absolute kidney weights (g; compared to control)	+8 % (not significant)	+14 %
Relative kidney weights (g; compared to control)	+16 %	+25 %
Absolute liver weights (g; compared to control)	-3 % (not significant)	-14 %

In the 60 mg/kg bw/day group there was a statistically significant decrease in total leukocyte count (-20.2 %) and increase in the absolute liver weights (+20.7 %) and the relative liver weights (+16.7 %) for males. Along with some other statistically significant hematological and clinical chemical findings in the higher dose groups, the decrease in total leukocyte count was considered to be secondary and not treatment-related, as these effects were in general not supported by morphological findings. The variations in liver weights were also considered to be not treatment related because of the lack of dose-dependency and supporting morphological findings.

However, under the conditions of the experiment, the test article produced morphological alterations in the kidneys of rats at 160 mg/kg bw/day. The findings consisted of an increased incidence in tubular basophilia (both sexes), and tubular casts (both sexes) along with a higher incidence of lymphoid foci (both sexes). These changes are indicative for tubular nephrosis and may correspond to some of the clinical chemical findings, particularly the increased urea level for high dose males (+40.4 %). All findings were of minor severity degrees, but were statistically significant. The remainder of findings recorded did not differ between controls and rats treated with the test article. They were considered to be within the range of spontaneous background lesions which may be recorded in Wistar rats of this strain and age (RCC Research and Consulting Company, 2000). The NOAEL was 59 mg/kg bw/day for males and 62 mg/kg bw/day for females.

Conclusion

From two 14-day inhalative exposure studies with rats no NOAEL could be determined. At the first study's LOAEL of 18 mg/m^3, degeneration/necrosis in the olfactory epithelium of the nose were observed. Trachea, larynx and lungs were affected at 200 mg/m^3 and above (degeneration/ necrosis, hyperplasia, squamous metaplasia). At the LOAEL of the follow-up study, i.e. at 2.2 mg/m³, reversible minimal to mild degeneration of respiratory nasal mucosa in the anterior dorsal nose was observed. In a subchronic drinking water study according to OECD TG 408, the administration of 150 mg/kg bw/day led to reduced absolute and relative kidney weights in male and female rats (histopathology being indicative for tubular nephrosis), while 59 mg/kg bw/day (males) and 62 mg/kg bw/day (females) were determined as a NOAEL.

3.1.6 Mutagenicity

Studies in Animals

In vivo Studies

In a micronucleus assay with NMRI mice according to OECD TG 474, 5 male/female animals per group were orally administered single doses of 50, 150, or 500 mg/kg bw 3-aminomethyl-3,5,5-trimethylcyclohexylamine. The highest dose was considered the maximum tolerable dose (MTD) based on the induction of toxic effects without major effects on survival within 72 hours of test substance administration. Sampling times were 24, 48, and 72 hrs after test substance administration. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine treatment did not result in an increase in the number of micronucleated polychromatic erythrocytes (PCE), nor did it negatively affect the PCE/NCE ratio (Cytotest Cell Research, 1990). This result was confirmed in another study with a slightly different design (Hüls AG, 1988a). Here a single dose of 100 mg/kg bw was administered, which – based on the absence of cytotoxic effects – was determined as the MTD. Sampling times were 24, 48, and 72 hrs after test substance administration.

In vitro Studies

In an Ames test performed according to Directive 84/449/EEC B.14 (1984) 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. At non-toxic test substance concentrations, a significant increase in mutant frequency was not observed (Hüls AG, 1990). The same result was obtained in another test with comparable design (Hüls AG, 1988b; method according to the original publication by B. Ames, 1975).

In a HPRT test with Chinese Hamster ovary (CHO) cells according to OECD TG 476 (1984), 3-aminomethyl-3,5,5-trimethylcyclohexylamine concentrations of 20 - 2,000 mg/l (+/- S9 mix from Aroclor 1254 induced rat livers) did not significantly increase the mutant frequency of treated cells. Cytotoxicity was not observed at any of the concentrations tested (Hüls AG, 1992c).

In a cytogenetic assay with Chinese Hamster Ovary (CHO) cells (according to OECD TG 473), concentrations of 156.25 – 1,375 mg/l (+/-S9 mix from Aroclor 1254-induced rat livers) were employed. A significant, test compound related increase in chromosomal aberrations was not observed (Safepharm, 1992).

Conclusion

3-Aminomethyl-3,5,5-trimethylcyclohexylamine was not mutagenic in bacteria and mammalian cell systems *in vitro* (Ames test according to Directive 84/449/EEC B.14 (1984) and HPRT test according to OECD TG 476 (1984)). It did not induce chromosomal aberrations in CHO cells *in vitro* in a test performed in accordance with OECD TG 473 (1981). *In vivo* mouse micronucleus tests (one performed according to OECD TG 474 (1983) for the induction of micronucleated polychromatic erythrocytes were clearly negative. From all *in vitro* and *in vivo* tests performed there is no evidence that 3-aminomethyl-3,5,5-trimethylcyclohexylamine has a mutagenic or clastogenic potential.

3.1.7 Carcinogenicity

No study with respect to this endpoint has been performed.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

No studies have been performed to explicitly address the question of reproductive effects in animals caused by 3-aminomethyl-3,5,5-trimethylcyclohexylamine. Histopathological results of a subchronic 90-day investigation on rats according to OECD TG 408 showed no effects regarding the reproductive organs (epididymides, mammary gland, ovaries, seminal vesicles, testes and uterus) in concentrations up to 160 mg/kg bw/day. Testes weights were also not affected (RCC Research and Consulting Company, 1986).

Developmental Toxicity

Based on the results of a dose finding study, three groups of 24 mated female Sprague-Dawley rats received 3-aminomethyl-3,5,5-trimethylcyclohexylamine by daily oral administration (gavage) at 0 (water = control), 10, 50 and 250 mg/kg/day from day 6 to day 19 post-coitum inclusive. On day 20 post-coitum, the dams were sacrificed and subjected to macroscopic examination. The study was designed according to OECD TG 414.There was no treatment-related death in any of the dams. Clinical signs were not observed, except for ptyalism in most females of the 250 mg/kg/day group (from day 11, 12, 13 or 14 post-coitum until hysterectomy; effect not considered as adverse). Loud breathing and hold-up in the esophagus were recorded in 4 females of this group and a significantly lower body weight gain (-35%) was recorded after the first three days of treatment. Thereafter, the body weights were similar to that of the controls. Over the whole treatment period, the difference remained slight (-10 %, not statistically significant). The net body weight gain was also significantly lower at this dose-level (-25 %) when compared to the control group. In the 250 mg/kg/day group, a significant decrease in food consumption was recorded during the treatment period (-7%), with a more marked effect during the first three days of treatment (-21 %).Abortions or total resorptions were not observed in any of the groups, nor were there any macroscopic findings that were ascribed to treatment with the test item. No treatment related effects were observed on pre- or post-implantation loss, fetal weight or sex-ratio. With respect to the fetuses, no test item related external, soft tissue or skeletal malformations or variations were detected. There was an increase in fetal incidence of incomplete ossification of the 5th sternebra in the 250 mg/kg bw/day group (106/134 fetuses = 79.1 %, $p < 0.01$ were affected vs. 88/130 = 67.7 % in control group, statistically insignificant on a fetus/litter basis). Because these findings are of low concern and occur only in the presence of maternal toxicity, they are considered to be secondary. In the same group there was a statistically nonsignificant increase in fetal incidence of incomplete ossification of the rib(s) (9/137 fetuses = 6.7 % vs. 2/130 = 1.5 % in control group. When ossification was incomplete, cartilage was generally present, demonstrating that the skeletal variations recorded corresponded to slight fluctuations in the time of ossification rather than being a persistent alteration. In conclusion, these findings were considered to be incidental and of no toxicological significance. The NOAEL for maternotoxicity was 50 mg/kg/day and the NOAEL for embryonic development was 250 mg/kg/day (CIT, 2002).

Conclusion

No studies have been performed on the toxicity of 3-aminomethyl-3,5,5-trimethylcyclohexylamine to reproduction. Data from an oral 90-day study in rats according to OECD TG 408 did not reveal any adverse effects on the male and female reproductive organs.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine did not show any teratogenic or embryofetotoxic effects in a gavage study with rats performed in accordance with OECD TG 414 (2001) up to and including the highest tested dose level of 250 mg/kg bw/day. The NOAEL for maternal toxicity was

50 mg/kg bw/day, effects at 250 mg/kg bw/day were reduced food consumption and reduced body weight gain. The NOAEL for developmental toxicity is 250 mg/kg bw/day.

3.2 Initial Assessment for Human Health

There is no information available on toxicokinetics and metabolism of 3-aminomethyl-3,5,5-trimethylcyclohexylamine.

There is only one valid but limited acute toxicity study of 3-aminomethyl-3,5,5-trimethylcyclohexylamine available. The LD_{50} after oral application to male rats is 1,030 mg/kg bw and the kidney is the potential target organ. Valid acute inhalation or dermal studies are not available.

Based on a limited skin irritation study with rabbits and rats, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is deemed to be a strong irritant (duration of the exposure not reported) and corrosive after repeated application. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is corrosive to the eyes of rabbits when tested according to OECD TG 405.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine was found to induce dermal sensitisation when tested according to OECD TG 406 in guinea pigs. From a number of publications there is evidence that frequent occupational exposure to 3-aminomethyl-3,5,5-trimethylcyclohexylamine may lead to the development of allergic contact dermatitis in humans. Since there is only one publication on possible airway effects of 3-aminomethyl-3,5,5-trimethylcyclohexylamine (describing a single human case) no definite conclusion can be drawn on respiratory sensitisation.

From two 14-day inhalative exposure studies with rats no NOAEL could be determined. At the first study's LOAEL of 18 mg/m^3, degeneration/necrosis in the olfactory epithelium of the nose were observed. Trachea, larynx and lungs were affected at 200 mg/m^3 and above (degeneration/ necrosis, hyperplasia, squamous metaplasia). At the LOAEL of the follow-up study, i.e. at 2.2 mg/m^3, reversible minimal to mild degeneration of respiratory nasal mucosa in the anterior dorsal nose was observed. In a subchronic drinking water study according to OECD TG 408, the administration of 150 mg/kg bw/day led to reduced absolute and relative kidney weights in male and female rats (histopathology being indicative for tubular nephrosis), while 59 mg/kg bw/day (males) and 62 mg/kg bw/day (females) were determined as a NOAEL.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine was not mutagenic in bacteria and mammalian cell systems *in vitro* (Ames test according to Directive 84/449/EEC B.14 (1984) and HPRT test according to OECD TG 476 (1984)). It did not induce chromosomal aberrations in CHO cells *in vitro* in a test performed in accordance with OECD TG 473 (1981). *In vivo* mouse micronucleus tests (one performed according to OECD TG 474 (1983) for the induction of micronucleated polychromatic erythrocytes were clearly negative. From all *in vitro* and *in vivo* tests performed there is no evidence that 3-aminomethyl-3,5,5-trimethylcyclohexylamine has a mutagenic or clastogenic potential.

No studies have been performed on the toxicity of 3-aminomethyl-3,5,5-trimethylcyclohexylamine to reproduction. Data from an oral 90-day study in rats according to OECD TG 408 did not reveal any adverse effects on the male and female reproductive organs.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine did not show any teratogenic or embryofetotoxic effects in a gavage study with rats performed in accordance with OECD TG 414 (2001) up to and including the highest tested dose level of 250 mg/kg bw/day. The NOAEL for maternal toxicity was 50 mg/kg bw/day, effects at 250 mg/kg bw/day were reduced food consumption and reduced body weight gain. The NOAEL for developmental toxicity is 250 mg/kg bw/day.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

In a semistatic test with *Leuciscus idus* according to 84/449/EEC, C.1, 1984, fish were exposed for 96 hrs to concentrations of 70 - 280 mg/l 3-aminomethyl-3,5,5-trimethylcyclohexylamine. The LC50 (96 h) was determined to be 110 mg/l (Hüls AG, 1993a). A possible contribution of the basic properties of the test substance and of the resulting high pH (up to 9.6 at the LC_{100}) to the observed effects was not discussed by the authors, but cannot be excluded. This also applies to the following studies on aquatic invertebrates, while the report on the algae toxicity study states that the increase in pH was considered not to affect growth.

The acute toxicity of 3-aminomethyl-3,5,5-trimethylcyclohexylamine to *Daphnia magna* was determined in a static test conducted according to OECD 202 (I) (1984). After 48 h of exposure, the EC50 was calculated to 23 mg/l (Infracor GmbH, 2002b). In a test according to DIN 38412, part 11 a nominal EC_{50} (24 h) of 44 mg/l was reported (Hüls AG, 1996a). The aquatic toxicity of 3-aminomethyl-3,5,5-trimethylcyclohexylamine was also tested in the marine invertebrate *Chaetogammarus marinus*. The 96 hour-EC_{50} determined in this semistatic test is 324 mg/l (Adema, 1982). In spite of good test performance and documentation, the result with this non-standard organism may at present only serve as an indication that the sensitivity of marine invertebrates towards the test substance is probably not higher than that of freshwater organisms.

The growth inhibition of 3-aminomethyl-3,5,5-trimethylcyclohexylamine on the freshwater alga *Scenedesmus subspicatus* was tested by Hüls AG (1993b) according to a test procedure similar to OECD Guideline 201. The algae were exposed to 7 concentrations between 0.75 and 50 mg/l and one control. Based on growth rate an E_rC_{50} of > 50 mg/l and a 72h-E_rC_{10} of 11 mg/l (NOEC 1.5 mg/l) were determined (nominal concentrations). Based on biomass development an E_bC_{50} of 37 mg/l and a 72h-E_bC_{10} of 3 mg/l were determined.

Chronic Toxicity Test Results

The effects of 3-aminomethyl-3,5,5-trimethylcyclohexylamine on the reproduction rate of Daphnia magna were tested in a chronic test according to OECD 202, part 2, but modified according to EC requirements (Hüls AG, 1993c). Under semistatic conditions, the daphnids were exposed for 21 days to concentrations of 0.1 – 30.0 mg/l 3-aminomethyl-3,5,5-trimethylcyclohexylamine. Concentrations up to 3.0 mg/l (NOEC) had no influence on survival of the daphnids or their reproduction rate (10 % mortality, which was observed at the lowest test concentration but not at the next three concentration levels, is considered insignificant because this mortality rate is allowed in the controls according to the OECD test guideline). At 10 mg/l (LOEC), survival was reduced to 80 % with no significant reduction of the reproduction rate. The next (highest) concentration of 30.0 mg/l led to 100 % mortality.

Toxicity to Microorganisms

In a bacterial toxicity test using *Pseudomonas putida* (Hüls AG, 1996b) an 18 h-EC10 of 1,120 mg/l was obtained.

4.2 Terrestrial Effects

There are no data available, however, significant exposure in the terrestrial compartment is not expected.

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 3-aminomethyl-3,5,5-trimethylcyclohexylamine will be water (99.8 %), followed by sediment and soil (both 0.08 %). The calculated Henry's law constant of 0.000446 Pa m^3/mol indicates very low volatility from surface waters. With a calculated K_{oc} of 340.4 l/kg, the sorption potential to soil or sediment organic matter is expected to be moderate. It has to be considered that under environmental relevant pH conditions the substance is available as cation and therefore the prediction of the environmental distribution using the data for the uncharged molecule is not appropriate. Binding of the substance to the matrix of soils with high capacities for cation exchange (e.g. clay) cannot be excluded.

In the atmosphere, 3-aminomethyl-3,5,5-trimethylcyclohexylamine is rapidly removed by reaction with hydroxyl radicals with a calculated half-life of 0.2 days. In water, it is expected to hydrolyse at a low rate under environmental conditions ($t_{1/2}$ > 1 year at 25 °C). Photolytical degradation in surface waters is expected to be of minor importance due to the chemical structure. 3-Aminomethyl-3,5,5-trimethylcyclohexylamine is not readily biodegradable (OECD 301A: 8 % after 28 days). However, in a simulation test with activated, non-adapted sludge, a degradation of 42 % (including a minor, though not negligible contribution by adsorption to sludge) was measured after a contact time of 6 hrs. The log K_{ow} value of 0.99 indicates a low bioaccumulation potential.

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

Leuciscus idus:	96-h LC_{50} = 110 mg/l
Daphnia magna:	48-h EC_{50} = 23 mg/l
Scenedesmus subspicatus:	72-h E_rC_{50} >50 mg/l

Chronic aquatic toxicity data are available for two trophic levels:

Daphnia magna:	21-d NOEC = 3.0 mg/l
Scenedesmus subspicatus:	72-h E_rC = 11 mg/l

An assessment factor of 50 was applied to the lowest of two long-term results covering two trophic levels. The PNEC of 0.06 mg/l for aquatic organisms was calculated from the NOEC for daphnia = 3.0 mg/l.

5 RECOMMENDATIONS

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.

Human Health:

The chemical is currently of low priority for further work. The chemical possesses properties (sensitisation, corrosive effects) indicating a hazard for human health. In view of the magnitude of the potential for effects, consumer products are considered to be adequately labelled and

occupational exposure is controlled sufficiently in the Sponsor country to ensure safe handling, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by Sponsor countries.

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I U C L I D

Data Set

Existing Chemical	:	ID: 2855-13-2
CAS No.	:	2855-13-2
EINECS Name	:	3-aminomethyl-3,5,5-trimethylcyclohexylamine
EC No.	:	220-666-8
TSCA Name	:	Cyclohexanemethanamine, 5-amino-1,3,3-trimethyl-
Molecular Formula	:	C10H22N2

Producer related part

Company	:	Degussa AG
Creation date	:	14.03.2001

Substance related part

Company	:	Degussa AG
Creation date	:	14.03.2001
Status	:	
Memo	:	Submission to OECD (ICCA Initiative) in 2003
Printing date	:	27.04.2004
Revision date	:	20.11.2003
Date of last update	:	27.04.2004
Number of pages	:	68
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	:	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	:	BASF AG
Contact person	:	Dr. Matthias Andreae
Date	:	29.09.2002
Street	:	
Town	:	67056 Ludwigshafen
Country	:	Germany
Phone	:	+49 621 60-42259
Telefax	:	+49 621 60-49134
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

Type	:	cooperating company
Name	:	DuPont Chemical Solutions Enterprise
Contact person	:	Dr. Robert W. Freerksen
Date	:	23.09.2002
Street	:	BMP-23/2306, P.O. Box 80023
Town	:	19880 Wilmingon, DEL

Country : United States
Phone : +1 302-892-7781
Telefax : +1 302-992-5336
Telex :
Cedex :
Email : Robert.W.Freerksen@USA.dupont.com
Homepage :

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type : Manufacturer
Name of plant : Degussa AG
Street : Herzogstrasse 28
Town : 44651 Herne
Country : Germany
Phone : +49 2325/68-3313
Telefax : +49 2325/68-3166
Telex :
Cedex :
Email :
Homepage :

(10)

Type : Manufacturer
Name of plant : BASF AG
Street :
Town : 67056 Ludwigshafen
Country : Germany
Phone : +49 621 60-42259
Telefax : +49 621 60-49314
Telex :
Cedex :
Email :
Homepage :

(4)

Type : Manufacturer
Name of plant : E.I. DuPont De Nemours, Inc.
Street : Pontchartrain Plant, 586 Highway 44
Town : 70068 LaPlace, LA
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

(14)

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 : liquid
Purity : >= 99.7 % w/w
Colour :
Odour :

Remark : Company (site): Degussa AG, Herne (Germany)
Test substance : cis isomer: CAS RN 71954-30-8
trans isomer: CAS RN 71954-29-5
The cis/trans ratio is constant at about 25:75

(26)

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : >= 99.7 % w/w
Colour :
Odour :

Remark : Company (site): BASF AG, Ludwigshafen (Germany)

(4)

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : ca. 99.7 % w/w
Colour :
Odour :

Remark : Company (site): E.I. DuPont De Nemours, LaPlace (LA, USA)

(14)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1,3,3-Trimethyl-1-aminomethyl-5-aminocyclohexane

1-Amino-3,3,5-trimethyl-5-aminomethylcyclohexane

1-Amino-3-aminomethyl-3,3,5-trimethylcyclohexane

3-Aminomethyl-3,5,5-trimethylcyclohexylamin (German)

3-Aminomethyl-3,5,5-trimethylcyclohexylamine

5-Amino-1,3,3-trimethylcyclohexanemethylamine

Cyclohexanemethanamine, 5-amino-1,3,3-trimethyl-

Degamin IPDA

Isophorondiamin (German)

Isophorone diamine

VESTAMIN IPD

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No : 7732-18-5
EC-No : 231-791-2
EINECS-Name : water, distilled, conductivity or of similar purity
Molecular formula :
Value : <= .2 % w/w

(10)

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name : aminonitriles
Molecular formula :
Value : < .15 % w/w

(10)

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name : secondary and tertiary amino compounds
Molecular formula :
Value : < .15 % w/w

(10)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : ca. 10000 - 50000 tonnes produced in 2002

Result : Worldwide production rate: ca. 35 000 tons/year
Flag : Critical study for SIDS endpoint
20.04.2004 (4) (10) (14)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits : yes
Symbols : C, , ,
Nota : , ,
R-Phrases : (21/22) Harmful in contact with skin and if swallowed
(34) Causes burns
(43) May cause sensitization by skin contact
(52/53) Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S-Phrases : (1/2) Keep locked up and out of reach of children
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(36/37/39) Wear suitable protective clothing, gloves and eye/face protection
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
(61) Avoid release to the environment. Refer to special instructions/Safety data sets

Remark : 25 % <= C : C; R21/22-34-43
10 % <= C < 25 %: C; R34-43
5 % <= C < 10 %: Xi; R36/38-43
1 % <= C < 5 %: Xi; R43
Index No. 612-067-00-9

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : corrosive
R-Phrases : (34) Causes burns
Specific limits :

Classified : as in Directive 67/548/EEC
Class of danger : harmful
R-Phrases : (21/22) Harmful in contact with skin and if swallowed
Specific limits :

Classified : as in Directive 67/548/EEC
Class of danger :
R-Phrases : (43) May cause sensitization by skin contact
Specific limits :

Classified : as in Directive 67/548/EEC
Class of danger :
R-Phrases : (52/53) Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Specific limits :

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Non dispersive use

(4) (10)

Type of use : type
Category : Use in closed system

(4) (10) (14)

Type of use : type
Category : Wide dispersive use

Remark : Sweden (February 2002):
Total number of products = 247
Number of consumer products = 36
Switzerland (December 2001):
Total number of products = 595
Number of consumer products = 21

(53) (54)

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

(4) (10) (14)

Type of use : use
Category : Intermediates

Remark : The substance is used to produce hardeners (crosslinking agents) for solventless, room temperature curing epoxies. It is further used in the production of non-crystalline speciality polyamides, as a chain extender in polyurethanes and as an intermediate in dyes.

(4) (10) (14)

Type of use : use
Category : Process regulators

Remark : crosslinking agent = hardener

Degussa: The substance has large application in epoxy-based self-levelling and trowelable flooring systems, and various civil engineering applications such as paving, concrete protection and repair. Other applications include coatings for superior corrosion protection of metal, adhesives and anchoring compounds.

Swedish Product Register: Hardeners for paints, adhesives and plastics, floor covering materials, paints, anti-corrosive paints

(10) (53) (54)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Synthesis
Type : Production

Method : Continuous 2-step process:
Step 1: isophorone + hydrocyanic acid => isophorone nitrile;
Step 2: isophorone nitrile + ammonia + hydrogen => isophorone diamine + water
Step 3: Distillation, storage
Remark : Company (site): BASF AG, Ludwigshafen (Germany)

(4)

Origin of substance : Synthesis
Type : Production

Method : Hydrogenation of isophorone nitrile in liquid ammonia in the presence of a catalyst at high pressure (continuous process)
Remark : Company (site): Degussa AG, Herne (Germany)

(10)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

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. 1202 in catalogue

1.8.4 MAJOR ACCIDENT HAZARDS

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

Country : Germany
Remark : Stoerfallverordnung 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 : Human: exposure by production
Exposure to the : Substance

Remark : Company (site): BASF AG, Ludwigshafen (Germany)
Result : - Number of persons: One person per shift, i.e. two persons per day, may be exposed to isophorone diamine.
- Relevant operations: Sampling, cleaning, filling; total duration < 0.5 h per shift.
- Exposure control:
Engineering: Local exhaust ventilation at the filling station and in the laboratory;
Personal: Gloves, goggles, protective clothes

22.12.2003 (4)

Source of exposure : Human: exposure by production
Exposure to the : Substance

Remark : Company (site): Degussa AG, Herne (Germany)
Result : Occupational exposure is determined only for ammonia as the lead substance in annual routine measurements.
- Year of latest determination: 2002
- Method: Ion selective electrode, 8 hour shift sampling
- Range of concentrations: < 1 - 1.9 mg/m3
- Number of persons: 40 (total).
- Relevant operations: Sampling (once daily), cleaning (twice annually), leakages (rare)
- Exposure control:
Engineering: State of the art DCS control system
Personal: Goggles, protective clothes, e.g. hard hat, steel cap shoes

22.12.2003 (10)

Source of exposure : Human: exposure by production
Exposure to the : Substance

Remark : Company (site): E.I. DuPont De Nemours, LaPlace (LA, USA)
Result : Range of concns.: Not detectable - 0.0061 ppm = 0.043 mg/m3
Median: 0.0008 ppm = 0.0057 mg/m3
95% percentil: 0.001 ppm = 0.0071 mg/m3
- Number of persons: 8/day may be exposed to isophorone diamine.
- Relevant operations: Sampling, loading connections, leaks.
- Exposure control:
Engineering: Leak detection system, Deluge system;
Personal: Job dependant: Butyl gloves, goggles, Tychem SL coverall, Level A Chemsuit, respirator w/canister, air-line respirator
Test condition : Time: 5 years (1996-2000)
Number of measurements: 260
Method: Air sampling using Tenax sorbent tubes
Sampling period: Mostly 8-hour personal air samples, some various duration area samples

22.12.2003 (14)

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

Remark : Company (site): BASF AG, Ludwigshafen (Germany)
Result : Release to air: Exhaust gases to flare
Release to water: < 5,000 kg/year (approximately) to WWTP; receiving water: river Rhine, gauge Worms, low flow rate 734 m3/s)
Solid waste: none; incineration of WWTP sludge

22.12.2003 (4)

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

Remark : Company (site): Degussa AG, Herne (Germany)
Result : - Release to air: Total combustion of offgas, no release.
- Release to water: approximately
1 m3/h waste water with 700 mg/l DOC for 8000 hours/year
= 8000 m3/year x 993 g isophorone diamine/m3 = 7940 kg/year
This water is conducted into a biological WWTP.
Receiving water = River Emscher; mean flow rate at low flow = 8.13 m3/s (gauge Bottrop-Süd) according to
http://www.emscher.nrw.de/offen/projekt_emscher/steckbrief_emscher/steckbrief_emscher.htm (as of 28 Nov 2003)
Pipeline to river Rhine in preparation; mean flow rate at low flow = 1090 m3/s.
- Other waste is transferred in liquid state to complete incineration.

22.12.2003 (10)

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

Remark : Company (site): E.I. DuPont De Nemours, LaPlace (LA, USA)
Result : Approximately 1000 kg/year of 3-aminomethyl-3,5,5-trimethylcyclohexylamine is released to the air, primarily as fugitive emissions. There are no releases of process wastewater to any receiving surface waters. Process wastewater of approximately 7000 m3/year from this unit is disposed of by deepwell injection after treatment in a series of

carbon adsorption units. The concentration of 3-aminomethyl-3,5,5-trimethylcyclohexylamine in the process waste water disposed of by deepwell injection is typically below 100 ppm. Approximately 2000 m3/year of other process waste, containing approximately 20 m3/year 3-aminomethyl-3,5,5-trimethylcyclohexylamine is transferred in liquid state to an on-site energy recovery unit where 3-aminomethyl-3,5,5-trimethylcyclohexylamine is completely destroyed.

20.04.2004 (14)

1.11 ADDITIONAL REMARKS

Memo : UN No.

Result : UN No. = 2289

(17)

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 3, 4, 5
Date of search : 07.02.2002

Type of search : External
Chapters covered : 3, 4
Date of search : 07.10.2003

Type of search : External
Chapters covered : 5
Date of search : 22.10.2003

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 10 °C
Decomposition	:	no, at °C
Sublimation	:	no
Method	:	other: no data
Year	:	
GLP	:	no
Test substance	:	no data
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
Flag	:	Critical study for SIDS endpoint

(17) (26) (60) (62)

2.2 BOILING POINT

Value	:	= 247 °C at 1013 hPa
Decomposition	:	no
Method	:	other: DIN 53171
Year	:	
GLP	:	no
Test substance	:	no data
Remark	:	thermal decomposition above 260 degree C with formation of ammonia
Result	:	Additional data in Reference VEBA-Chemie: 20 mm Hg = 27 hPa at 132 degree C 5 mm Hg = 6.7 hPa at 103 degree C
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
Flag	:	Critical study for SIDS endpoint

(17) (26) (60) (62)

Value	:	= 252 °C at 1013 hPa
Decomposition	:	
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Data from handbook or collection of data

(41)

2.3 DENSITY

Type	:	density
Value	:	= .92 g/cm³ at °C
Method	:	other: no data
Year	:	
GLP	:	no
Test substance	:	no data
Reliability	:	(2) valid with restrictions Data from handbook or collection of data

(17)

Type : density
Value : = .92 - .925 g/cm³ at 20 °C
Method : other: Mohr'sche Waage
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

(26) (62)

Type : density
Value : = .922 g/cm³ at 20 °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

(60)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : ca. .02 hPa at 20 °C
Decomposition :
Method : other (measured): no data
Year :
GLP : no
Test substance : no data

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

(17) (26)

Value : = .18 hPa at 25 °C
Decomposition :
Method : other (calculated): Solaris V4.67, Advanced Chemistry Development (ACD) Software
Year : 2003
GLP : no
Test substance : other TS: Isophorone diamine

Reliability : (4) not assignable
Documentation insufficient for assessment

(52)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = .99 at 23 °C
pH value :
Method : Directive 92/69/EEC, A.8
Year : 1998
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : OECD Test Guideline 107 (1995)
Result : Pow = 9.8 +/- 1.08; log Pow = 0.99
Test condition : Concentration in two phases determined by gas chromatography
Test substance : Purity: 99.6 % (gas chromatogram / FID area, two isomers)
Reliability : (1) valid without restriction
Guideline study
Flag : Critical study for SIDS endpoint

(34)

Partition coefficient : octanol-water
Log pow : = .79 at 23 °C
pH value :
Method : other (measured): OECD Guideline 107 (1981)
Year : 1989
GLP : no
Test substance : as prescribed by 1.1 - 1.4

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

(23)

Partition coefficient : octanol-water
Log pow : = 1.9 at °C
pH value :
Method : other (calculated): SRC Kowwin v1.66 Computer Program, integrated in U.S. EPA's EPI program Vers. 3.10
Year : 2002
GLP :
Test substance :

Reliability : (2) valid with restrictions
Accepted calculation method

(9)

Partition coefficient : octanol-water
Log pow : = 1.556 at °C
pH value :
Method : other (calculated): CLOGP3 Computer program, MedChem Project, Pomona College
Year : 1989
GLP :
Test substance :

Reliability : (2) valid with restrictions
Accepted calculation method

(23)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	at 20 °C
pH value	:	ca. 11.6
concentration	:	8.5 g/l at 20 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	miscible
Stable	:	
Deg. product	:	
Method	:	other: no data
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
Flag	:	Critical study for SIDS endpoint

(26) (62)

Solubility in	:	Water
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	miscible
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

(17)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 112 °C
Type	:	open cup
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	no data
Reliability	:	(2) valid with restrictions Data from handbook or collection of data

(17) (41) (60)

Value : = 110 °C
Type : open cup
Method : other: no data
Year :
GLP : no data
Test substance : no data

Reliability : (2) valid with restrictions
Data from handbook or collection of data
(62)

Value : = 117 °C
Type : closed cup
Method : other: DIN 51758
Year :
GLP : no
Test substance : no data

Reliability : (2) valid with restrictions
Data from handbook or collection of data
(26)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant : pKb
Method : other: no data
Year :
GLP : no
Test substance : other TS: Isophorone diamine of VEBA Chemie (production plant subsequently assigned to Hüls AG, Creanova GmbH, Degussa-Hüls AG, Degussa AG), purity >= 99.7 %

Result : pK ca. 3.6
Reliability : (2) valid with restrictions
Data from handbook or collection of data
(62)

Acid-base constant : pKa
Method : other: calculated with Solaris V4.67, Advanced Chemistry Development (ACD) Software
Year : 2003
GLP : no

Test substance : other TS: Isophorone diamine

Result : pKa = 10.72 +/- 0.20
Reliability : (2) valid with restrictions
In spite of lacking documentation, there is sufficient experience with structure-activity relationships for this parameter to assume that it has been estimated with acceptable precision.

(52)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Ignition; Explosive limits

Result : Lower explosion limit: 1.2 % v/v
Ignition temperature: 380 degree C (DIN 51794)
Reliability : (2) valid with restrictions
Data from handbook or collection of data

(17)

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/cm³
Rate constant	:	= .0000000000847 cm³/(molecule*sec)
Degradation	:	= 50 % after 4.5 hour(s)
Deg. product	:	
Method	:	other (calculated): AOP Computer Program, Vers. 1.90, integrated in U.S. EPA's EPI program Vers. 3.10
Year	:	2002
GLP	:	
Test substance	:	
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

(9)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 1 year at 25 °C
t1/2 pH7	:	> 1 year at 25 °C
t1/2 pH9	:	> 1 year at 25 °C
Degradation	:	< 10 % after 5 day(s) at pH and 50 °C
Deg. product	:	
Method	:	other: Directive 92/69/EEC, C.7 and OECD Test Guideline 111 (1981)
Year	:	2002
GLP	:	yes
Test substance	:	other TS
Result	:	- Preliminary test: Less than 10 % degradation was observed after 5 days at 50 degree C and pH 4, 7, and 9. Observed degree of hydrolysis (determined twice): pH 4: 2.58 %, 3,68 % pH 7: 1.36 %, 2.59 % pH 9: not detectable (-3.16 %, -1.18 %) - Main test: not required
Test substance	:	Degussa AG, Batch No. LIMS-Nr. 02006502, manufactured 03 May 2002 - 0730 Sample No. 1903/020516, ID No. 0649/82219 purity 99.75 %
Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint

(35)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

Type of measurement : concentration at contaminated site
Media : drinking water
Concentration :
Method : freeze drying; dichloromethane extraction; HPLC; Field desorption mass spectrometry

Remark : The aim of the study was the development of analytical methods for the identification of non-volatile organic substances in water.
Result : Isophoronediamine was identified (not quantified) in drinking water samples taken from water mains relined with epoxy resin.
Reliability : (2) valid with restrictions
Data from handbook or collection of data

20.04.2004 (63)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2002

Method : Level I V 2.11 Model
Remark : The value for the water solubility is based on a QSAR Henry's Law constant of 0.000446 Pa m3/mol and a vapour pressure of 2 Pa:
Water Solubility = 2 Pa x 170.30 g/mol / (0.000446 Pa m3/mol x 1000 l / m3)
Result : Air: 0.0157 %
Water: 99.8287 %
Soil: 0.0771 %
Sediment: 0.0780 %
Susp. Sediment 5.01E-4 %
Fish: 4.88E-5 %
Aerosol: 9.39E-7 %
Test condition : Data used:
Molecular weight: 170.30 g/mol
log Kow: 0.99
Vapour pressure: 2 Pa
Water solubility: 764 g/l
Melting point: 10 degree C
Temperature: 20 degree C

Volumes, densities, and organic carbon / fat concentration:
Air: 6 000 000 000 m3, 1.206 kg/m3
Water: 7 000 000 m3, 1000 kg/m3
Soil: 45 000 m3, 1500 kg/m3, 2 % OC
Sediment: 21 000 m3, 1300 kg/m3, 5 % OC

Susp. sediment: 35 m3, 1500 kg/m3, 16.7 % OC
Fish: 7 m3, 1000 kg/m3, 5 % fat
Aerosol: 0.12 m3, 1500 kg/m3

Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
(9)

Media : water - air
Method : other (calculation): SRC Henry v3.00 Computer Program and database, Syracuse
Research Corporation: Bond estimation method
Year : 2002

Result : Henry's Law Constant = 4.4 x 10-9 atm m3/mol
= 0.000446 Pa m3/mol
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
(9)

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 : 2002

Result : Koc = 340.4; log Koc = 2.532
"moderate" potential for geoaccumulation (Blume scale)
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
02.12.2003 (9)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : predominantly domestic sewage
Concentration : 6.9 mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time :
Degradation : = 8 (±) % after 28 day(s)
Result : other: not readily biodegradable
Kinetic of testsubst. : 7 day(s) = 4 %
14 day(s) = 4 %
21 day(s) < 0 %
27 day(s) = 3 %
28 day(s) = 8 %
Control substance : Benzoic acid, sodium salt
Kinetic : 7 day(s) = 99 %
14 day(s) = 99 %
Deg. product : not measured
Method : Directive 92/69/EEC, C.4-A
Year : 1993

GLP : yes
Test substance : other TS: Isophorone diamine of Hüls AG, purity 99.9 % (area), produced 23 March 1992, ID No. 3630/81404

Test condition : INOCULUM/TEST ORGANISM
- Sampling site: Municipal WWTP Marl-Ost, sampled 27 Oct 1992
- Preparation of inoculum: sampling, centrifugation (1100 g / 10 min), discard supernatant and resuspend with mineral medium, repeat centrifugation as above, resuspension of sludge (5.17 g dry weight/l), aeration through frit
- Initial cell concentration: 25.9 mg/l
TEST SYSTEM
- Culturing apparatus: 2000 ml Erlenmeyer flask covered loosely with aluminum sheet, filled with 900 ml test soln.
- Number of culture flasks per concentration: 2 with test substance (10.5 mg DOC/l) and inoculum; 2 with control substance (9.7 mg DOC/l) and inoculum; 1 with inoculum only
- Aeration device: shaking for 28 days
METHOD OF PREPARATION OF TEST SOLUTION:
- Stock solution: 431 mg DOC/l
ANALYTICAL PARAMETER: DOC (Carbon analyzer, Shimadzu), determination with and without removal of inorganic carbon
SAMPLING: Days 0, 7, 14, 21, 27, 28
TEST CONDITIONS
- Composition of medium:
  a 8.5 g KH_2PO_4/l
    21.75 g K_2HPO_4/l
    33.3 g Na_2HPO_4/l x 2 H_2O
    20.0 g $(NH_4)Cl$/l
  b 22.5 g $MgSO_4$ x 7 H_2O/l
  c 27.5 g $CaCl_2$/l
  d 0.25 g $FeCl_3$ x 6 H_2O/l
- Test temperature: 21.8-22.1 degree C
REFERENCE SUBSTANCE: purity 97 %, concn. 9.7 mg DOC/l, stock solution 570 mg DOC/l
Reliability : (1) valid without restriction
Guideline study
Flag : Critical study for SIDS endpoint

(31)

Type : aerobic
Inoculum : activated sludge, non-adapted
Concentration : 10.1 mg/l related to DOC (Dissolved Organic Carbon)
15.9 mg/l related to Test substance
Contact time : 6 hour(s)
Degradation : = 42 (±) % after
Result : other
Deg. product : not measured
Method : other: OECD Guide-line 303 A (1981), modified according to DIN 38412, part 26
Year : 1992
GLP : yes
Test substance : other TS: Isophorone diamine of Hüls AG, purity 99.9 % (area), produced 23 March 1992, ID No. 3630/81404

Remark : 3 Outliers were not considered.
Result : The mean of 19 measurements at approximately regular intervals is 42.0 +/- 5.01 % degradation.

Test condition : INOCULUM/TEST ORGANISM
- Source: municipal WWTP Marl-West, sampled 07 Jul 1992
- Pretreatment: fed into test apparatus ca. 40 min after sampling

TEST SYSTEM
- Culturing apparatus: flow-through (3 l; 0.5 l/h)
- Number of culture flasks per concentration: 1
- Aeration device: pump
- Measuring equipment: TOC 500 Infrared analyzer (Shimadzu)
- Closed vessels used: no

DURATION OF THE TEST: 31 days
ANALYTICAL PARAMETER: DOC
TEST CONDITIONS
- Composition of synthetic waste water:
  88 mg/l Pepton (Unipath)
  55 mg/l meat extract (Unipath)
  15 mg/l urea, CAS RN 57-13-6
  3.5 mg/l sodium chloride p.a., CAS RN 7647-14-5
  2 mg/l calcium chloride x 2 H2O p.a.
  1 mg/l magnesium sulfate x 7 H2O p.a.
  14 mg/l K2HPO4 p.a.
  98 mg/l NaHCO3 (Ferak)
- Additional nutrition substrate A:
  32 g/l Pepton
  22 g/l meat extract
  6 g/l urea
  1.4 g/l sodium chloride
  0.8 g/l calcium chloride x 2 H2O
  0.4 g/l magnesium sulfate x 7 H2O
  substrate B
  - 33.5 g/l K2HPO4 is stored separately
  - 47 g/l NaHCO3 is stored separately
  - 5 ml K2HPO4 soln. + 25 ml NaHCO3 soln + 11 l tap water
  This soln. and nutrition substrate A (30 ml/l) are added separately
- Test temperature: 21.8-26.2 degree C
- Other relevant factors: mean retention time 6 hours

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: Distinction between elimination by biodegradation and by adsorption not possible

Flag : Critical study for SIDS endpoint

19.04.2004 (25)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : other: QSAR estimate
Exposure period : at °C
Concentration :
BCF : = 3.16
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: 0.99
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
02.12.2003 (9)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	= 70
LC50	:	= 110
LC100	:	= 140
Limit test	:	no
Analytical monitoring	:	yes
Method	:	Directive 84/449/EEC, C.1 "Acute toxicity for fish"
Year	:	1993
GLP	:	yes
Test substance	:	other TS: Hüls AG, purity 99.9 % (area), produced 23 March 1992, ID No. 3630/81404
Remark	:	The basic properties / high pH may have contributed to the observed effects, but this is not discussed by the authors.
Result	:	- Concentration / response curve: concn., mg/l: 70 100 140 200 280 control % mortality 0 30 100 100 100 0 (96 hours) % mortality 0 20 100 100 100 0 (72 hours) % mortality 0 10 60 100 100 0 (48 hours) % mortality 0 0 0 90 100 0 (24 hours) - LC50 after 24 hours: 170.4; 48: 130.3; 72: 113.2; 96: 110.0 mg/l
Test condition	:	TEST ORGANISMS - Strain: Leuciscus idus melanotus HECKEL - Supplier: Eggers, Hohenwestedt - Wild caught: no - Age/size/weight/loading: 6 +/- 2 cm, 1.5 g average weight - Feeding: TetraMin, approximately 3 % of body weight / day - 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: 56.0005 g test substance in 2 l demineralized water, no additional solvent DILUTION WATER - Source: dechlorinated drinking water (Gelsenwasser AG) - Aeration: continuous - Hardness: 12.7 degree dH TEST SYSTEM - Concentrations: 70 / 100 / 140 / 200 / 280 mg/l (nominal) 70.3 / 101.8 / 142.3 / 202.0 / 281.0 mg/l (analytic) nominal concentrations were used for evaluation - Exposure vessel type: 20 l aquarium - Number of replicates, fish per replicate: 1, 10 - Test temperature: 20 +/- 1 degree C - Dissolved oxygen: 8.1 - 9.3 mg/l - pH: after 0 / 24 / 48 / 72 / 96 h: control: 7.6 / 7.6 / 7.6 / 7.6 / 8.3 70 mg/l: 9.0 / 9.1 / 9.2 / 9.2 / 8.4 100 mg/l: 9.2 / 9.4 / 9.3 / 9.4 / 8.8 140 mg/l: 9.4 / 9.6 / 9.6 / 8.8 / - 200 mg/l: 9.7 / 9.8 / - 280 mg/l: 9.9 / 9.6 / -

- Photoperiod: 16 hours bright / 8 hours dark
MONITORING OF TEST SUBSTANCE CONCENTRATION: gas chromatography

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

19.04.2004 (28)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC0	:	= 4.2
EC50	:	= 23
EC100	:	= 66.4
Limit Test	:	no
Analytical monitoring	:	yes
Method	:	other: Directive 92/69/EEC, C.2; OECD Test Guideline 202 (I) (1984)
Year	:	2002
GLP	:	yes
Test substance	:	other TS: Degussa AG, Batch No. LIMS-Nr. 02006502, manufactured 03 May 2002 - 0730 Sample No. 1903/020516, ID No. 0649/82219 purity 99.75 %
Remark	:	The basic properties / high pH may have contributed to the observed effects, but this is not discussed by the authors.
Result	:	RESULTS: EXPOSED - Concentration / response table: 0.0; 2.1; 4.2; 8.3; 16.6; 33.2; 66.4 mg/l nominal 0; 0; 0; 15; 30; 40; 100 % immobile (24 hours) 0; 0; 0; 10; 30; 65; 100 % immobile (48 hours) - 95 % confidence interval of EC50: 18 - 40 mg/l (24 hours); EC50 = 27 mg/l 17 - 31 mg/l (48 hours); EC50 = 23 mg/l RESULTS: TEST WITH REFERENCE SUBSTANCE - Concentrations: 1.0; 2.0 mg/l - Results: 40; 100 % immobilization
Test condition	:	TEST ORGANISMS - Strain: Daphnia magna Straus, clone 5 - Source/supplier: received from Bayer AG in 1991, further bred inhouse - Breeding method: in 1 l beakers with M4 medium, water renewal each 2-3 days, isolation of juveniles for further breeding each ca. 4 weeks - Age: < 24 hours - Feeding: Desmodesmus subspicatus, as much as consumed - Pretreatment: Filtration of adults 24 h prior to testing - Feeding during test: no - Control group: 1 blank control simultaneously and 2 reference substance controls each 3 months STOCK AND TEST SOLUTION AND THEIR PREPARATION - Concentration: 1.04 g/l; 0.52 g of the test item were equilibrated directly in 500 ml synthetic fresh water. REFERENCE SUBSTANCE: potassium dichromate, CAS RN 7778-50-9 DILUTION WATER

- Source: Synthetic:
  CaCl2 x 2 H2O: 294 mg/l
  MgSO4 x 6 H2O: 114 mg/l
  NaHCO3: 65 mg/l
  KCl: 6 mg/l
- Ca/Mg ratio: 4:1
- Na/K ratio: 10:1
- Hardness: 14 degree German hardness = 250 mg CaCO3/l
TEST SYSTEM
- Concentrations:
  0.0; 2.1; 4.2; 8.3; 16.6; 33.2; 66.4 mg/l nominal
  - ; 1.9; 3.9; 7.7; 15.5; 32.1; 66.3 mg/l analytical (48 hours)
  7.6; 7.9; 8.2; 8.5; 8.9; 9.2; 9.6 = pH (0 hours)
  7.8; 7.9; 7.9; 7.9; 8.1; 8.0; 8.2 mg O2/l (48 hours)
- Exposure vessel type: 10 ml round-bottom test tubes
- Number of replicates, individuals per replicate:
  4 replicates with 5 individuals each
- Test temperature: 20.22 - 20.28 (mean 20.25) degree C
- Intensity of irradiation: dark
- Photoperiod: -
- Aeration: no
DURATION OF THE TEST: 48 hours
TEST PARAMETER: immobilisation

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

19.04.2004 (36)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
EC0 : = 25
EC50 : = 44
EC100 : = 70
Limit Test : no
Analytical monitoring : no
Method : other: DIN 38412 part 11
Year : 1985
GLP : no
Test substance : other TS: Hüls AG, commercial sample

Remark : The basic properties / high pH may have contributed to the observed effects, but this is not discussed by the authors.

Result : RESULTS: EXPOSED
- Concentration / response table:
  12; 18; 25; 35; 50; 70; 100 mg/l
  0; 0; 0; 35; 60; 100; 100 % immobile
- 95 % confidence interval of LC50: 35-50 mg/l
RESULTS: TEST WITH REFERENCE SUBSTANCE
- Concentrations: 0.9; 1.9 mg/l
- Results: 10; 65 % immobilization

Test condition : TEST ORGANISMS
- Strain: Daphnia magna, Huels
- Source/supplier: Huels AG (inhouse)
- Breeding method: in 1 l jars with dechlorinated drinking water, water renewal every 2-3 days, isolation of juveniles for further breeding every ca. 4 weeks
- Age: < 24 hours

- Feeding: Chlorella vulgaris, as much as consumed
- Pretreatment: Filtration of adults 24 h prior to testing
- Feeding during test: no
- Control group: 2 reference substance controls; no blank
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Concentration: 1 g/l, no solvent or vehicle
REFERENCE SUBSTANCE: potassium dichromate, CAS RN 7778-50-9
DILUTION WATER
- Source: Synthetic:
  CaCl2 x 2 H2O: 294 mg/l
  MgSO4 x 7 H2O: 123 mg/l
  NaHCO3: 63 mg/l
  KCl: 5.5 mg/l
- Ca/Mg ratio: 4:1
- Na/K ratio: 10:1
TEST SYSTEM
- Concentrations:
  12; 18; 25; 35; 50; 70; 100 mg/l
- Exposure vessel type: 25 ml graduated cylinder
- Number of replicates, individuals per replicate:
  4 replicates with 5 individuals each
- Test temperature: 20 +/- 1 degree C
- Intensity of irradiation: dark
- Photoperiod: -
- Aeration: no
DURATION OF THE TEST: 24 hours
TEST PARAMETER: immobilisation

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

19.04.2004 (32)

Type : semistatic
Species : other aquatic crustacea: Chaetogammarus marinus
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : = 100
EC50 : = 324
Limit Test : no
Analytical monitoring : no
Method : other: see Test Conditions
Year : 1981
GLP : no data
Test substance : other TS: From ICN Pharm. Inc.; no further information

Remark : The basic properties / high pH may have contributed to the observed effects, but this is not discussed by the authors.
Result : LC and confidence intervals after
24 hours: 572 (505-648) mg/l
48 hours: 388 (339-444) mg/l
72 hours: 362 (318-412) mg/l
96 hours: 324 (286-366) mg/l
Test condition : TEST ORGANISMS
- Breeding method: Readily grown in seawater aquarium systems with shelter for concealment
- Age: Young gammarids, about 5 mm long
- Feeding: Fucus spec.
- Feeding during test: yes (Fucus or Tetramin); reason: to prevent cannibalism
- Control group: natural seawater

DILUTION WATER
- Source: Eastern Scheldt (NL), prepared by sand filtration, filtration over activated charcoal and 0.2 um millipore filter
- pH: about 8
- Salinity: 28 o/oo
TEST SYSTEM
- Concentrations: 0; 32; 56; 100; 180; 320; 560; 1000 mg/l
- pH: 8.0; 8.5; 8.8; 9.1; 9.5; 10.0; 10.2; 10.2 for test concentrations as above
- Renewal of test solution: once a day
- Aeration: no
- Exposure vessel type: 1 l glass beakers with 1 l test solution, covered with a watch glass
- Number of replicates, individuals per replicate:
2 beakers with 10 animals each for each concentration
- Test temperature: 15 +/- 1 degree C
- Dissolved oxygen: almost saturated for the whole test
- Adjustment of pH: no
TEST PARAMETER: mortality; counting and removal of dead animals daily accompanied by visual inspection of survivors

Reliability : (1) valid without restriction
Test procedure in accordance with generally accepted scientific standards and described in sufficient detail

19.04.2004 (1)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	= 1.5
EC10	:	= 3.1
EC50	:	= 37
EC90	:	= 436.5
Limit test	:	no
Analytical monitoring	:	no
Method	:	Directive 87/302/EEC, part C, p. 89 "Algal inhibition test"
Year	:	1993
GLP	:	yes
Test substance	:	other TS: Hüls AG, purity 99.9 % (area), produced 23 March 1992, ID No. 3630/81404

Remark : An increase of pH observed with some test solutions was considered not to affect the growth.

Result : RESULTS
- Cell density data: (x 1.0E+04 cells/ml)

concentration	0 hours	24 hours	48 hours	72 hours
control	2	6	25	98
0.75 mg/l	2	5	24	97
1.5 mg/l	2	6	24	92
3.0 mg/l	2	6	23	82
6.0 mg/l	2	6	24	78
12.5 mg/l	2	7	25	69
25 mg/l	2	5	20	54
50 mg/l	2	4	10	31

STATISTICAL RESULTS:
Probit analysis according to Cavalli-Sforza (1972) was

applied to the areas under the growth curves.
The following results were obtained for growth rate:
EC10 (72 h) = 11.2 mg/l
EC50 (72 h) > 50.0 mg/l

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.
- Method of cultivation:
Erlenmeyer flasks on tables exposed to light
- Controls: yes
- Initial cell concentration: ca. 20,000 cells/ml
STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Concentration of vehicle/ solvent:
1 g test substance/l, no vehicle or solvent
DILUTION WATER
- Aeration: yes, sterile
TEST SYSTEM
- Concentrations:
control; 0.75; 1.5; 3.0; 6.0; 12.5; 25; 50 mg/l nominal
- Renewal of test solution: no
- Number of replicates: 5 (exposed) or 8 (control)
- Test temperature: 24 +/- 2 degree C
- pH: 7.9-8.9 at start, 8.4-9.0 at end of test
- Intensity of irradiation: ca. 8000 lux white
- Monitoring of algae: photometric at 685 nm, calibration with standard curve

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

(29)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : Pseudomonas putida (Bacteria)
Exposure period : 18 hour(s)
Unit : mg/l
EC10 : = 1120
Analytical monitoring : no
Method : other: Bringmann and Kühn (1977), Z. Wasser Abwasser Forsch. 10, 87-98
Year : 1986
GLP : no
Test substance : other TS: Hüls AG

Result : EC10 = 1200 mg/l (Test 1)
1040 mg/l (Test 2);
mean = 1120 mg/l

Test condition : - Number of replicates:
5 growth controls
4 controls
3 replicates of 4 concentrations
all performed twice
- Test vessel: 250 ml Erlenmeyer flasks, sterile, capped

with
cellulose
- Stock solution: 5.00 g test substance/l gave pH = 11.5, which was neutralized with 10 % hydrochloric acid
- pH: 7.1 (Test 1); 7.0 (Test 2)
- Test concentration: 500 / 1,000 / 2,000 / 4,000 mg/l
- Duration of test: 18 +/- 1 hours
- Temperature: 25 +/- 2 degree C
- Quantification: photometric determination of turbidity at 436 nm, graphical evaluation

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

(33)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species	:	Daphnia magna (Crustacea)
Endpoint	:	reproduction rate
Exposure period	:	21 day(s)
Unit	:	mg/l
NOEC	:	= 3
LOEC	:	= 10
Analytical monitoring	:	yes
Method	:	other: OECD Guide-line 202, part 2 (1984)
Year	:	1993
GLP	:	yes
Test substance	:	other TS: Hüls AG, purity 99.9 % (area), produced 23 March 1992, ID No. 3630/81404

Remark : With reference to the development of new EC methods for the 21 day daphnia test, the test conditions deviate from the OECD test guideline. Reporting is also done according to EU protocols. An effect on the test results is, however, not expected.
Evaluation was based on nominal concentrations. A slight increase of pH was considered to have no effect on the results.
10% mortality, which was observed at the lowest test concentration but not at the next three concentration levels, is considered insignificant because this mortality rate is allowed in the controls according to the OECD test guideline.

Result : RESULTS
- Nominal/measured concentrations:
  nominal: 0.1 0.3 1.0 3.0 10.0 30.0 mg/l
  analyzed: - - 1.3 3.1 10.1 30.3 mg/l
- Concentration / response curve:
  concentration: % mortality / % reproduction / % inhibition
  control: 0 / 51.3+/-13.2 / -
  0.1 mg/l: 10 / 44.4+/-5.1 / 13.5 (not significant)
  0.3 mg/l: 0 / 53.1+/-16.4 / -3.5
  1.0 mg/l: 0 / 48.0+/-4.7 / 6.4 (not significant)
  3.0 mg/l: 0 / 55.7+/-19.6 / -8.6
  10.0 mg/l: 20 / 42.1+/-14.8 / 17.9 (not significant)

30.0 mg/l:100 / 0.0+/-0.0 / 100

Test condition : TEST ORGANISMS
- Strain: Daphnia magna Straus, clone 5
- Supplier: inhouse
- Breeding method: in synthetic medium according to Elendt (1990), water renewal every 2-3 days, isolation of juveniles for further breeding every ca. 4 weeks
- Age/size/weight/loading: < 24 hours
- Feeding: Scenedesmus subspicatus, as much as consumed
- Pretreatment: Filtration of adults 24 h prior to testing
- Feeding during test: Scenedesmus subspicatus,
  days 0-6: 4.0E+06 cells/(individual x day)
  days 7-21: 2.0E+07 cells/(individual x day)
- Controls: yes

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Vehicle, solvent: M4 medium
- Concentration of vehicle/ solvent: 0.2 g/l

DILUTION WATER
- Synthetic freshwater according to Elendt (1990)

TEST SYSTEM
- Test type: semistatic
- Concentrations: 0.1; 0.3; 1.0; 3.0; 10.0; 30.0 mg/l
- Renewal of test solution: each Monday, Wednesday and Friday
- Exposure vessel type: beakers, 250 ml filled with 200 ml test solution (days 0-6), 150 ml filled with 80 ml (days 7-21)
- Number of replicates, individuals per replicate:
  days 0-6: 4 replicates, 5 individuals each
  days 7-21: <= 10 replicates, 1 individual each
- Test temperature: 20 +/- 1 degree C
- Dissolved oxygen: range of 9 determinations
  Control: 94-107 %
  0.1 mg/l: 94-105 %
  0.3 mg/l: 93-100 %
  1.0 mg/l: 93-105 %
  3.0 mg/l: 95-106 %
  10.0 mg/l: 96-110 %
  30.0 mg/l: 103/113 % (interrupted after 2 determinations)
- pH: range of 9 determinations
  control: 7.5-8.0
  0.1 mg/l: 7.1-7.9
  0.3 mg/l: 7.5-7.9
  1.0 mg/l: 7.3-7.9
  3.0 mg/l: 7.6-7.9
  10.0 mg/l: 7.6-8.2
  30.0 mg/l: 8.3/8.2 (interrupted after 2 determinations)
- Adjustment of pH: no
- Intensity of irradiation: 58 W = ca. 1000 Lux
- Photoperiod: 20 hours bright / 4 hours dark

MONITORING OF TEST SUBSTANCE CONCENTRATION: only at >= 1 mg/l; 0.1 and 0.3 mg/l below detection limit

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

19.04.2004 (30)

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	:	= 1030 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male
Number of animals	:	5
Vehicle	:	water
Doses	:	
Method	:	other: see Test Conditions
Year	:	1965
GLP	:	no
Test substance	:	other TS: Isophorone diamine, no data on purity
Result	:	MORTALITY: - Time of death: after 12 to 18 hours in lateral position, no data on mortality / dose group CLINICAL SIGNS: 1 hour after dosing, animals showed restlessness, thirst, rough fur and tiredness. NECROPSY FINDINGS: irriation of the intestinal mucosa, with a few animals showing a slight increase in kidney weight and protein in the urine POTENTIAL TARGET ORGANS: kidney
Test condition	:	TEST ORGANISMS: - Weight at study initiation: 110-130 g ADMINISTRATION: - Doses: 50 % v/v solution in water, 0.5, 1.0, 1.5, 2.0 and 2.5 ml per kg b.w. - Route: oral gavage - Post dose observation period: 14 days EXAMINATIONS: organs not listed
Reliability	:	(2) valid with restrictions Comparable to guideline study with acceptable restrictions: no data on mortality / dose group and how LD50 was calculated, only male animals used. Evidence from repeated dose studies indicates that there is no significant difference in sensitivity between males and females and that the acute oral toxicity is not higher by an order of magnitude or more (chapter 5.4 entry # 1: 13 week LOAEL ca. 150 mg/g bw/day for males and females).
Flag	:	Critical study for SIDS endpoint

(42)

Type	:	LD0
Value	:	= 100 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other: no data
Year	:	1988
GLP	:	no
Test substance	:	other TS: Isophorone diamine, no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment

(22)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other: Approximate lethal concentration (ALC)
Value	:	= 4.6 mg/l
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	no data
Doses	:	
Exposure time	:	4 hour(s)
Method	:	other: no data
Year	:	1997
GLP	:	no data
Test substance	:	other TS: Isophorone diamine, no data on purity

Remark : Range-finding study for repeated dose inhalation study reported in chapter 5.4; no separate or detailed documentation

Reliability : (4) not assignable
Documentation insufficient for assessment

(12)

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	other: rabbit and rat
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	no data
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	irritating
Classification	:	
Method	:	other: The undiluted substance was applied to the depilated back skin, massaged into the skin by means of a glass rod and covered with gauze and adhesive tape ("Leukoplast") (duration of the occluded exposure not reported).
Year	:	1965
GLP	:	no
Test substance	:	other TS: Isophorone diamine, no data on purity

Result : The substance penetrated the skin well and caused swelling.
Treatment resulted in irritation and inflammatory effects.
The effects were more intensive with rabbits than with rats.

Repeated application led to severe effects on the skin with formation of crusts and necroses.

Test condition : ADMINISTRATION/EXPOSURE
- Occlusion: covered with gauze and leukoplast
- Total volume applied:
rats: 50 ul; rabbits: 100-200 ul

Reliability : (4) not assignable
Documentation insufficient for assessment, particularly the duration of exposure is not reported.

Flag : Critical study for SIDS endpoint
20.04.2004 (42)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	24 hour(s)
Comment	:	not rinsed
Number of animals	:	1
Vehicle	:	none
Result	:	corrosive
Classification	:	
Method	:	other: OECD Guideline 405 (1981)
Year	:	1983
GLP	:	no
Test substance	:	other TS: Isophorone diamine, purity: 99.70 % 0.14 % isophorone aminonitril 0.12 % N-methyl isophorone diamine

Result : The undiluted substance produced serious injury almost immediately after application (corrosive effects, opalescence). 24 hours after treatment conjunctiva showed necrosis. Due to the corrosive effect of the test material, only 1 animal was used and the experiment terminated after 24 hours.

Test condition : TEST ANIMALS:
- Strain: Small white Russian
- Sex: female
- Source: Dr. Karl Thomae, Biberach
- Weight at study initiation: 2.3 kg
- Controls: right eye

ADMINISTRATION/EXPOSURE
- Postexposure period: 24 hours

EXAMINATIONS
- Ophtalmoscopic examination: 1 and 24 hours after application
- Scoring system: Draize
- Observation period: 24 hours

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint
21.11.2003 (19)

5.3 SENSITIZATION

Type	:	Guinea pig maximization test
Species	:	guinea pig
Concentration	:	1st: Induction .1 % intracutaneous 2nd: Induction 7.5 % occlusive epicutaneous 3rd: Challenge occlusive epicutaneous
Number of animals	:	20
Vehicle	:	other: 10 % ethanol
Result	:	sensitizing
Classification	:	sensitizing
Method	:	other: OECD Guideline 406 (1981)
Year	:	1983
GLP	:	no
Test substance	:	other TS: Isophorone diamine of Hüls AG, purity >= 99.7 %
Result	:	RESULTS OF TEST - Sensitization reaction: Challenge concentration 2.5 %: 7/20 animals showed a sensitization 24 hours after the patch test, 5/20 animals 48 hours after the test and 2/20 72 hours after the test. Challenge concentration 5 %: 18/20 animals showed a sensitization 24 hours after the patch test, 15/20 animals 48 hours after the patch test and still 10/20 72 hours after the test. No animal of the control group showed any positive reaction. - Clinical signs: 24 hours after intracutaneous applications, animals mainly from the test substance treated group displayed poorly healing necrotic inflammations. After the induction patch treatment, the animals treated with the test substance had bleeding and matter discharging inflammations at the places of injections leading to thick crusts. After removal of the challenge patch, severe inflammation and itching were observed, causing particularly the animals treated with test substance to scratch their skins open in the area of injection.
Test condition	:	TEST ANIMALS: - Strain: Dunkin-Hartley (Bor: DHPW) - Sex: male - Source: Winkelmann, Borchen (Germany) - Weight at study initiation: 363 g (mean) - Dose group: 20 animals - Controls: 10 animals; vehicle treatment ADMINISTRATION/EXPOSURE - Induction schedule: injection followed 1 week later by patch treatment (0.3 ml) for 48 hours; - Injection details: 0.1 ml each at 6 positions on shoulders: 2 x Freund's Complete Adjuvant 2 x test substance in 10 % ethanol 2 x Freund's Complete Adjuvant / 0.2 % test substance (1:1) simultaneous and symmetrical application of each solution controls: 10 % ethanol instead of test substance - Challenge schedule: 2 weeks after end of induction patch treatment for 24 hours - Concentrations used for challenge: 2.5 and 5 %; readings 24, 48, and 72 hours after removal of patch - Rechallenge: no

- Positive control: no
EXAMINATIONS
- Grading system: possible scores 0 / 1 / 2 / 3
- Pilot study: dose range finding study

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions: no positive control group (not required by 1981 version of guideline)

Flag : Critical study for SIDS endpoint

01.12.2003 (18)

Type : Guinea pig maximization test
Species : guinea pig
Concentration : 1st: Induction 1 % intracutaneous
2nd: Induction 1 % occlusive epicutaneous
3rd: Challenge 10 % occlusive epicutaneous
Number of animals : 20
Vehicle : water
Result : sensitizing
Classification : sensitizing
Method : other: Similar to OECD Guideline 406 (1981)
Year : 1981
GLP : no
Test substance : other TS: Isophorone diamine, Hüls AG, no data on purity

Result : RESULTS OF PILOT STUDY: no responses were observed at any concentration
RESULTS OF TEST
- Sensitization reaction:
12/20 animals positive (i.e. erythema) at 10% challenge concentration
no animals positive at 5% challenge concentration
no erythema in control group

Test condition : TEST ANIMALS:
- Strain: Dunkin-Hartley
- Sex: female
- Source: Porcellus Animals Limited (UK)
- Weight at study initiation: 300-350 g
- Dose group: 20 animals
- Controls: 10 animals, Freund's Complete Adjuvant
ADMINISTRATION/EXPOSURE
- Induction schedule: intradermal injection followed after one week by occlusive patch treatment for a further 48 hours
- Injection details: 0.1 ml each at 6 positions in scapular region:
2 x Freund's Complete Adjuvant (FCA)
2 x test material (1% in dist. water)
2 x 1:1 emulsion of FCA / test material (1% in dist. water)
simultaneous and symmetrical application of each solution;
control and dose finding animals: 2 x 0.1 ml FCA only each
- Challenge schedule: 3 weeks after injection occlusive patch treatment for 24 hours, reading 24 hours after removal of patch
- Concentrations used for challenge: 10% and 5%
- Rechallenge: no
- Positive control: no
EXAMINATIONS
- Grading system: possible scores 0, 1, 2, 3
- Pilot study: 2 dose-finding animals for determination of maximum non-irritant concentration of test material; occlusive patch application of 10%, 5%, 2%, and 1% for 48 hours, parallel to induction phase

Reliability : (2) valid with restrictions

Comparable to guideline study with acceptable restrictions: no positive control group (not required by 1981 version of guideline)

Flag : Critical study for SIDS endpoint

(37)

Type : Guinea pig maximization test
Species : guinea pig
Concentration : 1st: Induction .5 % intracutaneous
2nd: Induction .5 % other: epicutaneous, occlusion not reported
3rd: Challenge 2 % occlusive epicutaneous
Number of animals : 15
Vehicle : other: acetone, CAS RN 67-64-1
Result : sensitizing
Classification : sensitizing
Method : other: Magnusson B, Kligman AM (1969). J. Invest. Dermatol. 52, 268.
Year : 1977
GLP : no data
Test substance : other TS: commercial isophorone diamine supplied by the Swedish Plastics Federation, no data on purity

Remark : 73 of the test animals were positive in another test after induction with an adduct of isophorone diamine and a low molecular weight epoxy resin (5% in both induction steps) and challenge with isophorone diamine (2 %).
Result : RESULTS OF TEST
- Sensitization reaction: 100 % of the animals positive
Test condition : TEST ANIMALS:
- Controls: vehicle and Freunds Complete Adjuvant
ADMINISTRATION/EXPOSURE
- Induction schedule: not reported
- Challenge schedule: two weeks after the second stage of sensitization, 24-hour patch test, evaluation 24 hours after removal of patch
EXAMINATIONS
- Grading system: obvious redness and swelling judged by two persons independently
Reliability : (2) valid with restrictions
Study well documented, meets generally accepted scientific principles, acceptable for assessment
Flag : Critical study for SIDS endpoint

(57)

Type : Guinea pig maximization test
Species : guinea pig
Number of animals : 15
Vehicle :
Result : sensitizing
Classification : sensitizing
Method : other: no data
Year : 1977
GLP : no data
Test substance : no data

Remark : This test is probably identical with that reported by Thorgeirsson, A. (1978).
Result : All animals (100 %) were sensitized.
Reliability : (4) not assignable
Secondary literature

(15)

Type	:	Guinea pig maximization test
Species	:	guinea pig
Concentration	:	1st: Induction intracutaneous 2nd: Challenge .1 % 3rd:
Number of animals	:	10
Vehicle	:	other: propylene glycol, CAS RN 57-55-6
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	other: Allied Chemical Corporation Dermal Toxicology Protocol MA-P-03-78
Year	:	1978
GLP	:	no data
Test substance	:	other TS: Isophorone diamine, no data on purity
Test condition	:	TEST ANIMALS: - Controls: yes, 10 animals ADMINISTRATION/EXPOSURE: 0.05 ml challenge volume EXAMINATIONS: 24 hours after challenge - Grading system: maximum 4 scores each for erythema and eschar formation and for edema formation
Reliability	:	(4) not assignable Documentation insufficient for assessment

(3)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	drinking water
Exposure period	:	13 weeks
Frequency of treatm.	:	daily
Post exposure period	:	none
Doses	:	20, 60, or 160 mg/kg bw d (nominal) = groups 2, 3, and 4
Control group	:	yes
NOAEL	:	ca. 60 mg/kg bw
LOAEL	:	ca. 150 mg/kg bw
Method	:	other: OECD Guideline 408 (1981)
Year	:	1986
GLP	:	yes
Test substance	:	other TS: Isophorone diamine, purity 99 %
Result	:	NOAEL = 59 mg/kg bw d (males), 62 mg/kg bw d (females) ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX males 21.5 / 59 / 150 mg/kg bw d females 22.6 / 62 / 147 mg/kg bw d TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - Mortality and time to death: No animal died during the study - Clinical signs: No treatment-related sign or symptom was noted. - Body weight gain: Lower in group 4 than in other groups (statistically significant: males -16%; females -21%) - Food/water consumption:

The mean food consumption of the group 4 animals was reduced when compared with that of the control rats (statistically significant for males at week 9-13 and for females at week 8-10).

The mean water consumption was decreased when compared with the controls (statistically significant in group 4 animals):
Males group 2: -18.0%; group 3: -20.1%, group 4: -40.4%
Females group 2: -13.5%; group 3: -19.9%; group 4: -47.8%

- Ophthalmoscopic examination:

No treatment-related finding was observed in any animal.

- Clinical chemistry: The assessment of clinical biochemical data indicated no changes of toxicological significance. Some treatment-unrelated effects were noted and considered to be secondary. They were not supported by morphological findings. The following changes were statistically significant:

urea level for group 4 males +40.4%

calcium level for group 3 females (-3.1%) and for group 4 males (-4.0%) and females (-7.1%)

phosphorus levels for group 3 males (-10.5%) and females (-15.4%) and for group 4 males (-18.7%) and females (-27.5%)

total protein levels for group 4 females -7.0%

albumin fraction (absolute) of the protein electrophoretic pattern for group 4 females -7.7%

alpha-1 globulin fraction (relative males -14.0%, females -10.4% and absolute males -18.1%, females -16.3%) of the protein electrophoretic pattern for group 4 animals

alpha-2 globulin fraction (relative -18.6% and abolute-21.4%) for group 4 males

- Haematology: The assessment of hematological data indicated no changes of toxicological significance after 13 weeks of treatment. Some treatment-unrelated effects were noted and considered to be secondary. They were not supported by morphological findings. The following changes were statistically significant:

hemoglobin in group 4 females -6.2%

platelet count in group 4 males (+29.0%) and females (+12.5%)

reticulocyte count for group 4 females +46.7%

total leukocyte count for group 2 males (-20.2%), group 3 males (-20.2%) and females (-24.1%), and group 4 males (-22.9%) and females (-25.3%)

prolonged prothrombin time for group 4 females +4.7%

- Organ weights:

Kidney weights in group 4 males absolute +8.1% (not significant), relative +16.4% (statistically significant) and females absolute +13.5%, relative +25.0% (both statistically significant)

Liver weights absolute +20.7%, relative +16.7% (both statistically significant) in group 3 males, absolute -13.8% (statistically significant), relative -4.8 % (not significant) in group 4 females, absolute -3.3%, relative +3.6% (both insignificant) in group 4 males

Other absolute and relative organ weights were not affected significantly.

- Gross pathology: No treatment-related macroscopic findings were observed. A few spontaneous gross lesions were encountered in both control and treated rats. Their incidence and severity are considered to be similar in all groups.

- Histopathology: In further examination of the kidneys (see addendum to the pathology report, Reference RCC 1989), isolated very small foci of tubular atrophy were recorded in one organ only. The statistical analysis for positive trend with respect to dose rate yielded a significant result for males (Z=2.29, one-tailed P=0.01) and a negative one for females (Z=1.61, one-tailed P=0.55).

Under the conditions of the experiment, the test article produced morphological alterations in the kidneys of rats at 160 mg/kg bw/day (group 4) (see second addendum to the report, Reference RCC 2000). The

findings consisted of an increased incidence in tubular basophilia (both sexes of group 4), and tubular casts (both sexes of group 4) along with a higher incidence of lymphoid foci (both sexes of group 4). These changes are indicative for tubular nephrosis. All findings were of minor severity degrees, but were statistically significant. The remainder of findings recorded did not differ between controls and rats treated with the test article.

Frequency of findings treated (control)

Tubular basophilia males 17/20 (0/20), females 13/20 (6/20)
Tubular casts males 8/20 (1/20), females 11/20 (1/20)
Lymphoid foci males 16/20 (5/20), females 13/20 (4/20)

- Other: The remainder of findings recorded did not differ between controls and rats treated with the test article. They were considered to be within the range of spontaneous background lesions which may be recorded in Wistar rats of this strain and age.

Test condition : TEST ORGANISMS
- Age: 6 weeks
- Weight at study initiation:
  males 136-157 g, females 117-139 g
- Number of animals:
  Total 80 males, 80 females; 20 per sex and group

ADMINISTRATION / EXPOSURE
- Duration of test/exposure: 13 weeks
- Type of exposure: oral, drinking water
- Post exposure period: -
- Vehicle: drinking water
- Doses:
  Group 1 = control; group 2 = 20 mg/kg bw/day;
  group 3 = 60 mg/kg bw/day; group 4 = 160 mg/kg bw/day

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: twice daily
- Mortality: twice daily
- Body weight: weekly
- Food consumption: weekly (7 day consumption)
- Water consumption: weekly (24 hours consumption)
- Ophthalmoscopic examination: at pretest and end of study;
  10 animals per group (lowest ID numbers) and sex examined
- Haematology: end of study, 10 animals per group and sex
  (highest ID numbers)
- Biochemistry: end of study, 10 animals per group and sex
  (highest ID numbers)

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: all organs listed below under "Microscopic";
  weights of adrenals, kidneys, liver, testes
- Microscopic: (all rats of groups 1 and 4 plus those which had gross lesions): adrenal glands, aorta (thoracic), bone (sternum), bone marrow (sternum), brain, cecum, colon, duodenum, epididymides, esophagus, eyes, Harderian glands, heart, ileum, jejunum, kidneys, liver, lungs with mainstem bronchi, lymph nodes (mandibular, mesenteric), mammary gland, ovaries, pancreas, pituitary gland, prostate, rectum, salivary gland (mandibular, sublingual), sciatic nerve, seminal vesicles, sekletal muscle, skin, spinal cord, spleen, stomach, testes, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus

STATISTICAL METHODS:
Univariate one-way analysis of variance for significance of

intergroup differences;
Dunnett-test for comparison between treated groups and control group (if normal distribution assumed)
Steel-test (if normal distribution not assumed)
Fisher's exact test for spontaneous mortalities
OTHER EXAMINATIONS: (see addendum to the pathology report)
In an attempt to further elucidate the toxicological significance of findings in the kidneys, a larger sample of renal tissue was re-examined from rats of all groups. In addition to the already available sections, another set of histological slides was prepared from the wet tissue of rats of groups 1 and 4 which was matched by two sections from each rat of groups 2 and 3.

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

20.04.2004 (47) (48) (49)

Type	:	
Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	14 days
Frequency of treatm.	:	6 h/day, 4-5 days/week
Post exposure period	:	20 days
Doses	:	18; 200; 550 mg/m3
Control group	:	yes, concurrent no treatment
LOAEL	:	= 18 mg/m³
Method	:	other: see Test Conditions
Year	:	1997
GLP	:	no
Test substance	:	other TS: Isophorone diamine of E.I. du Pont de Nemours and Company, Wilmington, Delaware, Lot UJ1109080296; Purity: 99.70 % Impurities: 0.13 % Isophorone aminonitrile 0.04 % N-Methyl isophoronediamine 0.03 % water balance secondary a

Result : TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: 1 on day 3, 2 on day 4, and 1 on day 5 in high concentration group; 1 by accident after day 12 in low concentration group
- Clinical signs: nasal/ocular discharge at all concentrations; gasping, hunched posture, irregular respiration, lung noise, and weakness in high concentration group. Alopecia and stained fur were the only other clinical signs observed. The clinical signs observed in the low and medium concentration groups (i.e. nasal / ocular discharge, alopecia, stained fur) were isolated and transient and were considered not to be compound related.
- Body weight gain: significantly reduced in high concentration group (-7.8 % within 4 days vs +0.7 % in control group). Not significantly affected in other groups.
- Clinical chemistry: The following observations were statistically significant but considered to be not biologically adverse:
200 mg/m3 group, two-week sampling: aspartate aminotransferase - 10.3%, sorbitol dehydrogenase -26.5 %, not relevant to organ injury or

dysfunction
200 mg/m3 group, two-week sampling: mean total protein -4.7%, biologically inconsequential, no significant changes in serum albumin or globulin concentration
200 mg/m3 group, two-week sampling: mean creatinine concentration -25%, not relevant to organ injury or dysfunction
200 mg/m3 group, two-week sampling: mean phosphate concentration +8.4%, magnitude of changes small and biologically inconsequential
18 and 200 mg/m3 groups, two-week sampling: mean chloride concentration + 2.0% (both groups), magnitude of changes small and biologically inconsequential
18 mg/m3 group, two-week sampling time: mean sodium concentration -1.4%, no dose-response relationship
18 mg/m3 group, end of recovery period: mean albumin concentration -6.4%, no dose-response relationship
- Haematology: No statistically significant or test substance related changes
- Urinalysis: No statistically significant or test substance related changes
- Organ weights: no effects were observed
- Gross pathology: no effects were observed
- Histopathology:
Respiratory system: Dose-dependent, compound-related microscopic changes were observed in the nose, trachea, larynx and lungs of rats exposed to 200 and 550 mg/m3, and in the nose of rats exposed to 18 mg/m3. Immediately following exposure, degeneration/necrosis was detected in the olfactory epithelium (nose) of rats exposed to 18 mg/m3 (5/6 "minimal"), 200 mg/m3 (5/5 "mild"), and 550 mg/m3 (1/10 "minimal", 8/10 "mild", 1/10 "moderate") and in the respiratory epithelium (nose, trachea, and larynx) of rats exposed to 550 (1/10 "minimal", 6/10 "mild", 3/10 "moderate") mg/m3; 3/5 rats exposed to 200 mg/m3 also had minimal degeneration/necrosis in the respiratory epithelium of the nose. During the same period, hyperplasia/squamous metaplasia was detected in the nose and larynx (200 mg/m3: 2/5 "mild", 3/5 "moderate"; 550 mg/m3: 1/10 "minimal"; 8/10 "mild"), and hypertrophy/hyperplasia was detected in the trachea and lungs of rats exposed to 200 (2/5 "minimal") and 550 (3/10 "minimal", 4/10 "mild") mg/m3; in addition, mild hyperplasia/squamous metaplasia was detected in the nose of 5/5 rats exposed to 18 mg/m3. By the end of the 20-day recovery period, the lungs and trachea of rats exposed to 18 and 200 mg/m3 were within normal limits. Tissue repair was still in progress in the nose and larynx of these same rats; however, close to full microscopic restitution was expected.
Thymus: Atrophy of the thymus, seen in three rats from the 550 mg/m3 group, was attributed to stress, rather than a direct toxic effect.
Other organs: Liver and heart necrosis and cardiomyopathy in four rats from the 550 mg/m3 group were attributed to hypoxia secondary to the respiratory tract lesions and are not indicative of target organ toxicity. Necrotic hepatocytes were centrilobular and hypoxic inury to hepatocytes in this area is well documented. Similarly, hypoxic effects on myocardium are well known.
- Other: Target organ: Respiratory system

Test condition : TEST ORGANISMS
- Age: ca. 9 weeks old at study initiation
- Supplier: Charles River Breeding Laboratories
- Weight at study initiation: 265-341 g
- Number of animals: 10/dose group

ADMINISTRATION / EXPOSURE
- Doses: 9 nose-only exposures in low and medium dose groups; high dose group ended after 4 nose-only exposures due to unexpected mortality of 4 rats

- Particle size: mass mean aerodynamic diameters 1.2-4.1 um; >= 64 % less than 10 um
- Type or preparation of particles: flash evaporation (171-201 degree C) of substance in air; condensation aerosol formed in the exposure chambers resulting in mixed aerosol / vapour exposure
- Concentrations: 20 / 200 / 700 or 500 mg/m3 (nominal); 18 / 200 / 550 mg/m3 (analytically determined mean); high concentration group initially 700 mg/m3 (nominal), lowered to 500 mg/m3 following the third exposure. No attempt was made to control the respirable range of the aerosol component. The vapour concentration was about 8.6 / 11 / 10 mg/m3, the rest was particulate
- Other: The temperature was 24-28 degree C for all groups except two with 27-30 degree C, which is somewhat higher than the generally acceptable range of 20-26 degree C.

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: prior to + during + following each exposure, twice each week during recovery period
- Mortality: prior to + during + following each exposure
- Body weight: prior to each exposure, twice each week during recovery period
- Haematology and Biochemistry: day after final exposure except high concentration group; erythrocytes, leukocytes, platelets, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, neutrophils, band neutrophils, lymphocytes, atypical lymphocites, monocytes, eosinophils, basophils plus serum chemical parameters alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, bilirubin, cholesterol, total protein, albumin, globulin, glucose, urea nitrogen, creatinine, phosphate, calcium, sodium, potassium, chloride
- Urinalysis: day after final exposure except high concentration group; volume, osmolality, urobilinogen, pH, hemoglobin or occult blood, glucose, protein, bilirubin, ketone

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: at least five animals per group were sacrificed on the day after the last exposure (including the six survivors of the high concentration group), the remaining rats after a 20-day recovery period, for pathological examination of: liver, kidneys, urinary bladder, lungs, heart, spleen, thymus, brain (cerebrum, midbrain, cerebellum, medulla/pons), spinal cord (cervical, thoracic, lumbar), stomach, duodenum, jejunum, ileum, pancreas, cecum, colon, rectum, mesenteric lymph node, adrenal glands, sciatic nerve, thyroid gland, parathyroid glands, trachea, esophagus, pharynx/larynx, sternum (with bone marrow), eyes, prostate, seminal vesicles, testes, epididymides, nose (four cross sections), and gross lesions.
- Weights of liver, kidneys, lungs, testes, and brain were determined
- Microscopic: All tissues as listed under macroscopic of: control and high concentration groups plus rats found dead and sacrificed in extremis plus first five rats of medium concentratione group. Additional examination of nose, pharynx/lanrynx, trachea, lungs, liver, kidneys, testes and gross lesions for low

concentration group (first sacrifice) and control, low, and medium concentration groups after second sacrifice
OTHER EXAMINATIONS:
observation of potential reaction to auditory stimulus before / six times during / after exposure

STATISTICAL METHODS:
- one-way analysis of variance (ANOVA) for body weight related data, organ weights (excluding high concentration group) and clinical laboratory measurements ($p < 0.05$);
- Dunnett's test for pairwise intergroup comparisons ($p < 0.05$);
- Bartlett's test for homogeneity of variances for clinical laboratory and organ weight data ($p < 0.005$)

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

19.04.2004 (12)

Type	:	
Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	11 days
Frequency of treatm.	:	6 h/day, 4-5 days/week
Post exposure period	:	2 weeks (5 animals per group)
Doses	:	2 mg/m3 (nominal); 2.2 +/- 0.25 (range 1.0-3.0) mg/m3 (analytical)
Control group	:	yes, concurrent no treatment
LOAEL	:	= 2.2 mg/m³
Method	:	other: see Test Conditions
Year	:	2000
GLP	:	yes
Test substance	:	other TS: Isophorone diamine of E.I. du Pont de Nemours and Company (Wilmington, DEL, USA). Lot No. UQ0657011100. Purity 99.5 %, known impurities: isophorone amino nitriles (1000 ppm), related secondary amines (200 ppm).
Result	:	TOXIC RESPONSE/EFFECTS BY DOSE LEVEL: - Mortality and time to death: No mortalities during study - Clinical signs: No clinical signs of toxicity attributed to the test substance were observed. Clinical signs observed, including diarrhea and hair loss, were considered incidental findings. Ocular and/or nasal discharges after exposure were considered incidental findings typical of rats subjected to nose-only exposure. - Body weight gain: No effect of exposure on body weight or body weight gain was observed. - Organ weights: No test substance-related changes were observed. - Gross pathology: No test substance-related changes were observed. - Histopathology: Minimal (2/5) to mild (3/5) degeneration of respiratory nasal mucosa in the anterior dorsal nose was observed in the non-recovery animals. They were reversible and had resolved by the end of the recovery period. - Other: Reaction to the auditory stimulus was normal in both groups.
Test condition	:	TEST ORGANISMS - Age: ca. 8 weeks old at study initiation - Supplier: Charles River Breeding Laboratories (Crl:CD(SD)IGS BR) - Weight at study initiation: 219-265 g; mean ca. 240 g in each group - Number of animals: 10/dose group

ADMINISTRATION / EXPOSURE
- Doses: 9 nose-only 6 hour exposures; exposure # 8 was shortened to 3 hours and 37 minutes due to a building evacuation.
- Particle size: Appreciable aerosol concentration was not present.
- Type or preparation of exposure chamber atmosphere: Transport of metered liquid test substance by a nitrogen stream from an Instatherm flask (100-110 degree C) into a high-pressure air stream and further through heated glass tubing (same temperature) into the exposure chamber
- Other: Temperature 24-27 degree C (exposed), 23-27 degree C (control); 14-16 air changes per hour

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: before + during + after each exposure, recovery period
- Mortality: prior to + during + following each exposure
- Body weight: before each exposure, two or three times each week during recovery period

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: five animals per group were sacrificed on the day after the last exposure, the remaining rats after a 14-day recovery period, for pathological examination of:
liver, kidneys, lungs, heart, spleen, brain, spinal cord, stomach, duodenum, jejunum, ileum, pancreas, cecum, colon, rectum, mesenteric lymph node, thymus, adrenal glands, sciatic nerve, tyroid gland, parathyroid glands, trachea, esophagus, pharynx/larynx, eye(s), prostate, seminal vesicles, urinary bladder, testes, epididymides, sternum, nose
- Microscopic: Lungs, trachea, pharynx/lanrynx, nose (first sacrifice); nose (recovery sacrifice)
OTHER EXAMINATIONS:
observation of potential reaction to auditory stimulus three times during each exposure

STATISTICAL METHODS: $p < 0.05$
- Exposure concentration data: Descriptive statistics (e.g. mean, standard deviation)
- Incidence of clinical observations: Cochran-Armitage test for trend
- Body weight related data: Complex combination of tests

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

19.04.2004 (13)

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 - 5000 ug/plate
Cycotoxic concentr.	:	1000 / 5000 ug/plate with / without preincubation
Metabolic activation	:	with and without
Result	:	negative
Method	:	Directive 84/449/EEC, B.14
Year	:	1990
GLP	:	yes
Test substance	:	other TS: Isophorone diamine, purity: 99.70 %

Result : GENOTOXIC EFFECTS: none
PRECIPITATION CONCENTRATION: no precipitation

Test condition : SYSTEM OF TESTING
- Metabolic activation system:
Aroclor 1254 induced rat S9 liver, male Bor: WISW (SPF/Cpb)
ADMINISTRATION:
- Dosing:
main test: 8 / 40 / 200 / 1000 / 5000 ug/plate (+/- metabolic activation)
preincubation test: 125/250/500/1000/2000 ug/plate (+/- metabolic activation)
- Number of replicates: 3
- Application:
main test: 50 g/l in water
preincubation test: 40 g/l in water
- Positive and negative control groups and treatment:
positive, TA 98 and TA 1538: nitrofluorene
positive, TA 100 and TA 1535: sodium azide
positive, TA 1537: aminoacridine
negative: solvent
activity of metabolic system: aminoanthracene / TA 100
- Pre-incubation time: 30 min / 30 degree C
incubation 96 hours / 37 degree C
CRITERIA FOR EVALUATING RESULTS:
mutagenic effects at <= 5000 ug/plate

Reliability : (2) valid with restrictions
Guideline study, comparable to OECD guideline 471 with acceptable restrictions (TA 102 or E.coli WP2 were not tested, not required by applied 1983 guideline version)

Flag : Critical study for SIDS endpoint

(24)

Type : Ames test
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration : up to 5000 ug/plate
Cycotoxic concentr. : 5000 ug/plate (with pre-incubation / without S9 mix)
Metabolic activation : with and without
Result : negative
Method : other: Ames, B.N. et al. (1975). Mutation Research 31, 347-364
Year : 1988
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : No precipitation
Test condition : SYSTEM OF TESTING
- Metabolic activation system:
Aroclor 1254 induced rat S9 liver, male Bor: W/SW (SPF/TNO)
ADMINISTRATION:
- Dosing: 10 / 50 / 250 / 1000 / 5000 ug/plate
- Solvent: Water
- Number of replicates: 2
- Positive and negative control groups and treatment:
positive, TA 98 and TA 1538: 2.5 ug nitrofluorene/plate
positive, TA 100 and TA 1535: 2.5 ug sodium azide/plate
positive, TA 1537: 50 ug aminoacridine/plate
negative: solvents DMSO / water
activity of metabolic system: aminoanthracene
CRITERIA FOR EVALUATING RESULTS:
mutagenic effects at <= 5000 ug/plate

Reliability : (2) valid with restrictions
Comparable to guideline study with acceptable restrictions: No data on

purity, requirements for strains to be tested have been increased since completion of the report.

(21)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100
Test concentration	:	no data
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Method of Ames et al. (1975) as modified by Yahagi et al. (1977), Mutat Res. 48, 121
Year	:	1993
GLP	:	no data
Test substance	:	other TS: Isophorone diamine, no further data
Test condition	:	SYSTEM OF TESTING - Metabolic activation system: PCB induced rat liver S9 mix (male Sprague-Dawley rats) ADMINISTRATION: - Number of replicates: 2 - Application: solvent dimethyl sulfoxide - Pre-incubation time: 20 minutes at 37 °C CRITERIA FOR EVALUATING RESULTS: positive when number of colonies in test plate >= twice that in the reference plate pseudopositive when number of colonies in test plate >= 1.7 times that in the reference plate
Reliability	:	(3) invalid Significant methodological deficiencies: Only two strains tested, lack of documentation on test substance identity and concentrations, on controls, and on other details

(55)

Type	:	HGPRT assay
System of testing	:	CHO (Chinese hamster ovary) K1 cells
Test concentration	:	0 - 2 mg/ml
Cycotoxic concentr.	:	none over test concentration range
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: OECD Guideline 476 (1984)
Year	:	1992
GLP	:	yes
Test substance	:	other TS: Isophorone diamine of Hüls AG, purity 99.9 %, produced 25 Oct 1991; ID No. 3630/81 365
Test condition	:	SYSTEM OF TESTING - Metabolic activation system: Aroclor 1254-induced Wistar rat liver S9 ADMINISTRATION: - Dosing: preliminary toxicity test: 0; 0.02; 0.03; 0.06; 0.12; 0.2; 0.3; 0.6; 1.2; 2.0 mg/ml main study; 0; 0.02; 0.06; 0.2; 0.6; 2.0 mg/ml - Number of replicates: 2 - Application: 2E+05 cells/25 ml flask; exposure time 4 h - Positive and negative control groups and treatment: positive, without metabolic activation: 300 ug ethyl methanesulfonate (EMS)/ml in HO medium

positive, with metabolic activation:
10 ug 3-methylcholanthrene (MCA)/ml in dimethyl sulfoxide
negative: HO medium (with / without S9 mix)
CRITERIA FOR EVALUATING RESULTS: statistically significant, dose related increase in mutant frequency at concentrations of the test substance resulting in > 20 % cell survival.
Mean frequency > maximum spontaneous frequency

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

(27)

Type : Cytogenetic assay
System of testing : CHO (Chinese hamster ovary) cells
Test concentration : up to 1375 ug/ml
Cycotoxic concentr. : >= 2500 ug/ml (+ S9); >= 1250 ug/ml (-S9)
Metabolic activation : with and without
Result : negative
Method : other: OECD Guideline 473 (1981)
Year : 1992
GLP : yes
Test substance : other TS: Isophorone diamine of Hüls AG, produced 25 Oct. 1991

Result : GENOTOXIC EFFECTS:
- With metabolic activation: highly statistically significant, but only at maximum dose level and 20 hour treatment. This was demonstrated to be an artefact caused by the interaction of a high pH value and the S9 metabolic activation system.
- Without metabolic activation: no
- Positive controls: positive

MITOTIC INDEX: mean of 2 counts each; experiment 1 first
- With metabolic activation:
0 mg/l, 12 h: 7.15; 20 h: 9.5
312.5 mg/l, 12 h: 7.8; 20 h: 9.25
625 mg/l, 12 h:10.75; 20 h:10.65
1250 mg/l, 12 h: 4.8; 20 h: 6.15
0 mg/l, 12 h: 9.15; 20 h: 8.8
625 mg/l, 12 h: 4.3; 20 h:11.5
937.5 mg/l, 12 h:10.0; 20 h: 7.35
1250 mg/l, 12 h: 3.4; 20 h: 2.85
- Without metabolic activation:
0 mg/l, 12 h: 7.45; 20 h: 3.8
312.5 mg/l, 12 h: 8.65; 20 h: 3.75
625 mg/l, 12 h: 6.45; 20 h: 4.75
937.5 mg/l, 12 h: 2.0; 20 h: 2.3
0 mg/l, 12 h: 9.55; 20 h: 9.8
156.25mg/l, 12 h: 8.35; 20 h:12.3
312.5 mg/l, 12 h: 7.6; 20 h: 8.7
625 mg/l, 12 h: 6.9; 20 h: 6.8

CHROMOSOMAL ABERRATIONS (cells with aberrations - gaps): mean of 2 replicates each
- With metabolic activation:
Experiment 1
0 mg/l, 12 h: 0; 20 h: 1
312.5 mg/l, 12 h: 2; 20 h: 0
625 mg/l, 12 h: 2; 20 h: 1
1250 mg/l, 12 h: 4; 20 h: 14
Experiment 2
0 mg/l, 12 h: 1; 20 h: 1

625 mg/l, 12 h: 2; 20 h: 4
937.5 mg/l, 12 h: 3; 20 h: 4
1250 mg/l, 12 h: 2; 20 h: 21
Confirmatory experiment
0 mg/l, 20 h: 4 (with hepes buffer)
0 mg/l, 20 h: 7 (without hepes buffer)
1250 mg/l, 20 h: 6 (with hepes buffer)
1250 mg/l, 20 h: 13 (without hepes buffer)
- Without metabolic activation:
Experiment 1
0 mg/l, 12 h: 2; 20 h: 0
312.5 mg/l, 12 h: 1; 20 h: 4
625 mg/l, 12 h: 1; 20 h: 6
937.5 mg/l, 12 h: 5; 20 h: 1
Experiment 2
0 mg/l, 12 h: 3; 20 h: 3
156.25mg/l, 12 h: 2; 20 h: 2
312.5 mg/l, 12 h: 3; 20 h: 3
625 mg/l, 12 h: 3; 20 h: 6
CYTOTOXIC CONCENTRATION:
- With metabolic activation:
total absence of metaphase cells at >= 2500 mg/l
- Without metabolic activation:
total absence of metaphase cells at >= 1250 mg/l
- A dose-related increase was observed. Since addition of a buffer in the confirmatory experiment reduced toxicity, pH seems to be decisive for cytotoxicity

Test condition : SYSTEM OF TESTING
- Species/cell type: CHO-K1 BH4
- Metabolic activation system: male Sprague-Dawley rat liver S9 from Aroclor 1254 induced animals
- No. of metaphases analyzed: first 100 consecutive from each culture if possible
ADMINISTRATION:
- Dosing:
preliminary toxicity test: 0-5000 mg/l
Experiment 1:
312.5-937.5 mg/l without S9; 312.5-1250 mg/l with S9
Experiment 2:
156.25-625 mg/l without S9; 625-1250 mg/l with S9
Confirmatory experiment:
1125, 1250, and 1375 mg/l with S9, both with and without Hepes buffer
- Number of replicates: 2
- Application:
with S9: 4 hours exposure + 8 or 16 h culture period
without S9: continuous for 12 or 20 hours
- Positive and negative control groups and treatment:
negative: solvent
positive with S9: cyclophosphamide, 10 and 5 mg/l
positive without S9: mitomycin C, 0.075 and 0.05 mg/l
concentrations reduced for second experiment
CRITERIA FOR EVALUATING RESULTS: significant increase in the frequency of aberrations, Fisher's exact test

Conclusion : The test substance was shown to be non-clastogenic to CHO cells in vitro.

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

(50)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	NMRI
Route of admin.	:	oral unspecified
Exposure period	:	single dose
Doses	:	50, 150, or 500 mg/kg, dissolved in 10 ml/kg bw dose volume
Result	:	negative
Method	:	other: Directive 84/449/EEC, B.12; OECD Guideline 474 (1983)
Year	:	1990
GLP	:	yes
Test substance	:	other TS: Isophorone diamine of Hüls AG, produced 20 March 1990, ID No. 3641/81172; purity 99.85 % (GC)
Result	:	PCE/NCE RATIO: not affected (PCE = polychromatic erythrocytes, NCE = normochromatic erythrocytes)
Test condition	:	TEST ORGANISMS: - Supplier: BRL Tierfarm Füllinsdorf (Switzerland) - Age: minimum 10 weeks + 5 days acclimatization - Weight at study initiation: approximately 30 g - No. of animals per dose: 6 per dosage group and sex with 3 cases of post-treatment duration for negative control and treated groups totals 4 x 3 + 1 groups x 6 animals x 2 sexes = 156 animals; only 5 animals per group and sex were evaluated ADMINISTRATION: - in a pre-experiment 500 mg/kg bw was estimated to be the maximum tolerated dose, cytotoxic reactions were not observed - Vehicle: aqua dest. - Sampling times and number of samples: 24, 48, or 72 hours after treatment - Control groups and treatment: negative: vehicle positive: cyclophosphamide, dissolved in physiol. saline, 40 mg/kg bw EXAMINATIONS: - 1000 PCE (polychromatic erythrocytes) per animal were analysed for micronuclei - Criteria for evaluating results: either a statistically significant dose related increase in the number of micronucleated polychromatic erythrocytes, or a reproducible statistically significant positive response for at least one of the test points; confirmation by Mann-Whitney test - Criteria for selection of M.T.D.: toxic reactions without major effects on survival within 72 hours
Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint

(7)

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	NMRI
Route of admin.	:	gavage
Exposure period	:	single dose

Doses	:	100 mg/kg b.w.
Result	:	negative
Method	:	other: Directive 79/831/EEC, B.12
Year	:	1988
GLP	:	no
Test substance	:	other TS: Isophorone diamine of Hüls AG, no data on purity
Result	:	PCE/NCE RATIO: not affected
Test condition	:	TEST ORGANISMS: - Supplier: Winkelmann, Borchen (Germany) - Age: approximately 10 weeks - Weight at study initiation: mean 25 (female) / 28 (male) g - No. of animals per dose: 5 males + 5 females ADMINISTRATION: - MTD = 100 mg/kg bw - Vehicle: drinking water - Duration of test: 72 hours - Sampling times and number of samples: 24, 48, 72 hours - Control groups and treatment: positive: endoxan, 100 mg/kg b.w., contact time 24 h negative: no test substance, contact times 24, 48 and 72 h EXAMINATIONS: - 1000 PCE (polychromatic erythrocytes) per animal were analysed for micronuclei - Criteria for selection of M.T.D.: highest dose without cytotoxic effects
Reliability	:	(2) valid with restrictions Comparable to guideline study with acceptable restrictions: no data on purity ot test substance, only one dose tested

(20) (22)

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	day 6 to day 19 post-coitum inclusive
Frequency of treatm.	:	daily
Duration of test	:	until day 20 post-coitum
Doses	:	10, 50, or 250 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 50 mg/kg bw
NOAEL teratogen.	:	= 250 mg/kg bw
NOAEL Embryotoxicity	:	= 250 mg/kg bw
NOAEL Fetotoxicity	:	= 250 - mg/kg bw
Result	:	No teratogenic or embryofetotoxic effects were recorded at any dose level
Method	:	other: OECD Guideline 414 (1981)
Year	:	2002
GLP	:	yes

Test substance : other TS: Isophorone diamine of Degussa AG, batch no. 050301. Purity 99.8 %; impurity water 0.01 %

Result : NOAEL: Refers to body weight development in high dose group for maternal toxicity
ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX: Chemical analyses demonstrated satisfactory stability and agreement between nominal and actual concentrations of the test material.
MATERNAL TOXIC EFFECTS BY DOSE LEVEL:
- Mortality and day of death: One female of the high-dose group was found dead on day 16. This death was attributed to an effect of hold-up in the esophagus following gavage. No other mortalities were observed.
- Clinical signs: The only treatment-related clinical sign was ptyalism in most females of the 250 mg/kg bw/day group from day 11, 12, 13, or 14 until hysterectomy. Loud breathing and presence of material in the mouth, probably due to hold-up in the esophagus, were recorded in 4 females. These observations might be the consequence of the corrosive properties of the test item (pH between 10 and 12).
- Number pregnant per dose level:
Control 24; low- and high-dose 23; mid-dose 22
- Number aborting: No abortion in any group
- Number of resorptions: No total resorption in any group
- Pre and post implantation loss: No treatment related findings were observed at any dose level.
- Body weight gain: Not affected in low and mid dose groups. A significant decrease (-35 %) was observed in the high-dose group after the first three days of treatment. Thereafter, the body weight was similar to that of the controls. The net body weight gain was also significantly lower (-25 %) at this dose level.
- Food/water consumption: Not affected in low and mid dose groups; a slightly significant decrease was observed in the high dose group during the treatment period.
- Gross pathology incidence and severity: No treatment related findings were observed at any dose level. An exception are whitish foci on the lung in the decedent female.
FETAL DATA:
- Litter size and weights: No treatment related findings were observed at any dose level.
- Sex ratio: No treatment related findings were observed at any dose level.
- External abnormalities: No treatment related external malformations or variations were observed at any dose level.
- Soft tissue abnormalities: No treatment related soft tissue malformations or variations were observed at any dose level.
- Skeletal abnormalities: No statistically significant treatment related skeletal malformations or variations were observed at any dose level.
There was a statistically insignificant increase in fetal incidence of incomplete ossification of the 5th sternebra in the 250 mg/kg bw/day group (106/134 fetuses = 79.1%, $p<0.01$ were affected vs. 88/130 = 67.7% in control group).
In the same group there was a statistically nonsignificant increase in fetal incidence of incomplete ossification of the rib(s) (9/137 fetuses = 6.7 % vs. 2/130 = 1.5% in control group.
When ossification was incomplete, cartilage was generally present, demonstrating that the skeletal variations recorded corresponded to slight fluctuations in the time of ossification rather than being a persistent alteration. In conclusion, these findings were considered to be incidental and of no toxicological significance.

Test condition : TEST ORGANISMS
- Source: Charles River Laboratories, L'Arbresle (France)
- Age: 10-11 weeks

- Weight at study initiation: 206-301, mean 245 g.
  Mean weights in the four groups were similar.
- Number of animals: 24 per dose group; only the first 20 pregnant females were taken into consideration for fetal examinations
ADMINISTRATION / EXPOSURE
- Vehicle: Water purified by reverse osmosis
- Concentration in vehicle: 1, 5, or 25 g/l
- Total volume applied: 10 ml/kg bw/treatment
MATING PROCEDURES: Females were mated at the breeder's facilities. The day of confirmed mating (detection of a vaginal plug) was designated as day 0 post-coitum.
PARAMETERS ASSESSED DURING STUDY:
- Mortality: daily (twice during treatment period)
- Clinical signs: daily (twice during treatment period)
- Body weight gain: Days 2, 6, 9, 12, 15, 18, 20
- Food consumption: Cumulative for days 2-6; 6-9; 9-12; 12-15; 15-18; 18-20
- Examination of uterine content: Weight of gravid uterus, number or corpora lutea, number and distrubution of implantation sites (or uterine scars), number and distrubution of early and late resorptions, number and distribution of dead and live fetuses
- Examination of fetuses: weight, sex, detailed external examination (all); soft tissue including all organs and structures of head, neck, thorax, and abdomen (one half); skeleton including bone structures and cartilage of head, spine, rib cage, pelvis, limbs (other half)
ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC): Principal thoracic and abdominal organs, gross evaluation of placentas
STATISTICAL METHODS:
- Group mean values +/- standard deviation (one-way analysis of variance and Dunnett test): Maternal body weight and food consumption, fetal body weight and number of corpora lutea, implantations, fetuses and resorptions
- Proportions (Fisher exact probability test): Pre-implantation loss, post-implantation loss, fetal findings

Reliability : (1) valid without restriction
Guideline study

Flag : Critical study for SIDS endpoint

26.04.2004 (6)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis

Result : Patch tests with IPD were positive for the three sensitized persons at all concentrations and with both solvents. They were also positive for the epoxy resin but negative for the standard series.
Patch tests were all negative for control subjects. There were no signs of irritancy. However, two of the control subjects were sensitized to IPD by these tests, which was

revealed by a typically allergic flare-up at the sites of application 7 days after the test and confirmed by further patch testing at very low concentrations.

Test condition : 3 out of 15 workers employed in the manufacture of plastic tennis rackets developed allergic contact dermatitis to isophorone diamine (IPD) and concomitantly to epoxy resin. The tennis rackets were made of bisphenol A type with IPD as hardener without any means of protection. Symptoms appeared 3 months, 6 weeks, or three weeks, respectively, after beginning to work in this department, and healed completely within 3 weeks after moving to another department.
Patch tests were then performed with
- the epoxy resin (Eurepox 730) at 1 and 5 % in petrolatum,
- IPD at 1, 2 and 5 % in olive oil,
- IPD at 1, 2 and 5 % in ethanol,
- a pigment (aniline black bay-plast) at 10 % in petrolatum,
- standard series.
Investigations were conducted in 2 female and 3 male control subjects with IPD in solvents and concentrations as above (not with epoxy resin or pigment).
- Readings: at 48, 72, and 96 hours

Test substance : Isophorone diamine, no further information

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

(44)

Type of experience : Human - Medical Data

Remark : cross-sensitivity

Result : Tests were strongly positive in the four patients. None of the tests in the control subjects was positive at 48 or 96 hours.

Test condition : The cross-sensitivity between isophorone diamine (IPD) and isophorone diamine diisocyanate (IPDI) was investigated. 2 workers who showed allergic reactions to IPD and 2 volunteers who had been sensitized to IPD previously were patch-tested 1 month later with IPDI (1 % in ethanol). The tests were removed at 48 h, and read at 48 and 96 hours. At the same time 5 adult volunteers were patch-tested with IPDI (1 % in ethanol).

Test substance : Isophorone diamine, no further information

Conclusion : From this study it may be concluded that cross-sensitivity can occur between IPD and IPDI.

Reliability : (4) not assignable
Documentation insufficient for assessment

(43)

Type of experience : Human - Medical Data

Method : The study was aimed at persons preparing and using epoxy resins for coating, flooring, impregnating and repairing concrete, brick and wooden structures. 10 companies were selected. Housepainters were excluded.
The study was designed to determine
- the type and duration of skin exposure,
- the proportion of persons sensitized,
- the proportion of persons with complaints.

Remark : occupational contact dermatitis

Gloves were mostly made of cotton or cotton reinforced with suede (85 persons) and less frequently of rubber (25) or plactic (16).

Result : In 26 persons (19.3 %), a dermatosis localized on hands and/ore forearms had been present during the last 3 years. In 9 persons, the occupational dermatosis was still present at the time of the investigation.
Positive patch tests were observed in 27 of the 137 exposed workers (20 %), 13 of whom had never previously experienced skin problems. Positive reactions were observed predominantly with epoxy resin:
- epoxy resin: 25 persons = 18.5 %
- isophorone diamine: 3 persons = 2.3 %
- triethylenetetramine: 2 persons = 1.5 %
- xylenediamine: 4 persons = 3.0 %

The following parameters showed a correlation with the development of allergy:
- frequency of exposure: positive correlation
- wearing gloves permantly: positive correlation (!)
- duration of employment: positive correlation
- hygiene advice: not significant

Test condition : Information on the products used was gathered.
All employees of the selected companies who were known to have had skin contact with uncured epoxy resins were included in the study.
Information regarding exposure was collected, questions about skin disorders were asked, and the hands and forearms were examined.
The resulting 135 persons aged 18-59 (mean 32) were patch tested with the following materials considered relevant to their occupational exposure.
- epoxy resin (1 % in pet.)
- isophorone diamine (0.1 % in olive oil)
- triethylenetetramine (0.5 % in pet.)
- xylenediamine (0.1 % in pet.)

Results were read after 48 hours and in case of doubt also after 72 hours.

Test substance : Isophorone diamine, no further information

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

(61)

Type of experience : Human - Medical Data

Remark : occupational asthma

Result : An otherwise healthy 44-year-old man experienced a serious attack of bronchial obstruction after working with resins and hardeners, releasing fumes of a mixture of trimethyl-1,6-hexanediamine and isophorone diamine.
- Patch test: negative
- Intracutaneous skin test: No difference between sensitized person and controls
- Inhalation challenge: Eight hours after deliberate challenge with the hardener a large increase of airway resistance was found. Seventy-two hours after challenge, eosinophilia in the bronchoalveolar fluid together with a decrease of peripheral eosinophils was seen.
- Further development: After cessation of contact with this hardener, no more acute episodes occurred, although maintenance treatment with a topical corticosteroid and a beta2-agonist remained necessary.

Test condition : - Epicutaneous patch tests with the hardener at 0.1, 1.0, and 10 % in white petrolatum, readings after 48 and 72 hours
- Intracutaneous skin test with the hardener at 0.5 mg/ml, reading after 15 min, results compared with those for two control subjects
- Inhalation challenge in a closed room (3.75 m3) during 15 minutes by painting a board with the hardener (no resin)

Test substance : Commercial hardener made of trimethyl-1,6-hexanediamine and isophorone diamine, also containing benzyl alcohol and phenol.

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

(2)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis

Result : - General: 1844 were diagnosed to have occupational skin diseases (other 1887: non-occupational). Among these, 142 (92 men and 50 women) were considered to have skin disorders from current occupational exposure to epoxy compounds. Among these 142, 135 had allergic contact dermatitis, five had irritant contact dermatitis, and two had contact urticaria according to the diagnoses met.
- Substance specific: Contact allergy to isophorone diamine was diagnosed for three persons (out of 53 tested in years 1985-1990):
(1) a process man in the manufacture of two-component floor coatings (dermatitis after four months of work)
(2) a floorlayer coating concrete floors (dermatitis after five years of work)
(3) a painter (dermatitis on eyelids after one year).
A test concentration of 0.5 % was found to induce neither irritation nor active sensitization in the patch testing, as was the case when testing was performed with a test concentration of 5 %.

Test condition : - General: A total of 3713 + 18 persons examined for suspected occupational skin diseases in Helsinki + Vaasa during 1974-1990 were considered. The study was focussed on 142 persons (criteria: current + skin disease + occupational + expoxy compound caused).
- Substance specific: Patch tests with a concentration of 0.5 % isophorone diamine in petrolatum were performed to confirm allergy towards this substance. Patch tests with this substance were not performed prior to 1985.

Test substance : Isophorone diamine, no further information

Reliability : (2) valid with restrictions
Study well documented with acceptable restrictions: Lacking documentation on test substance

(38)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis

Result : 14 days later, spreading erosive erythematous vesicular dermatitis on the chest, upper back, arms and legs began to evolve. Patch testing with a standard series, 2 months after the generalized skin reaction had healed, was positive for isophorone diamine (0.5%), but not for epoxy resins or any other work-related allergens.

Test condition : A 38-year-old bricklayer had prolonged skin contact with a workshoe contaminated with an epoxy resin glue. Isophorone diamine was a major constituent of this two-component glue (50-55% in component B).

Test substance : Isophorone diamine, no further information

Reliability : (4) not assignable
Short communication
(40)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis
Result : When challenged with standard series patch tests, positive reactions were observed particularly with isophorone diamine (0.5%).
Test condition : Case reports of two patients (males aged 51 and 21, respectively) with allergic contact dermatitis from isophorone diamine. Both patients worked with epoxy resins.
Test substance : Isophorone diamine, 0.5 % in petrolatum, incorporated in ICDRG standard test series (Hermal-Trolab).
Reliability : (4) not assignable
Documentation insufficient for assessment
19.04.2004 (5) (51)

Type of experience : Human - Medical Data

Remark : contact dermatitis
Result : All three showed strong reactions with 0.5 % isophorone diamine. Among 340 patients tested with 0.5 % isophorone diamine, no cases of active sensitization were observed.
Test condition : The cases of 3 subjects (1 female aged 37, two males aged 36 and 44) are reported, who developed allergic contact dermatitis. In the past, they all had contact with coatings or adhesives.
Patch testing was performed with them.
Experience with active sensitization is reported without information on test conditions.
Test substance : Isophorone diamine, incorporated in GIRDCA standard series and plastics and glues series (Hermal-Trolab).
Reliability : (4) not assignable
Documentation insufficient for assessment
(16)

Type of experience : Human - Medical Data

Remark : erythema multiforme after contact dermatitis
Result : A case of erythema multiforme associated with an allergic contact dermatitis in response to an epoxy-based compound is reported.
The condition of the person improved considerably over 5 days off work, but 9 days after the onset of the dermatitis, a new eruption developed (no mention of a return to the workplace).
Patch tests revealed a positive reaction at 48, 96, and 168 hours to both the epoxy resin and the hardener, isophorone diamine.
Test condition : The person was a 46-year-old female swimming pool attendant, who had been engaged for 10 days in repairing and repainting the swimming pool with a swimming pool sealant that contained 55% epoxy resin (molecular weight 380) and isophorone diamine as epoxy hardener.
Aside from previous eczematous reactions to several perfumes and cosmetics, the patient's medical history was unremarkable.
Test substance : Isophorone diamine (purity not reported), 0.5% and 1% in petrolatum.
Reliability : (4) not assignable
Documentation insufficient for assessment
(64)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis
Result : Tests gave positive results with isophorone diamine for both individuals.
Test condition : Two male workers aged (1) 18 and (2) 62, who had developed dermatitis from working with epoxy resins, were patch tested with (among other substances) isophorone diamine:
(1) 0.01 % in acetone
(2) 1 % in water
Test substance : Isophorone diamine, no information on purity
Reliability : (4) not assignable
Documentation insufficient for assessment

(8)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis
The clinical appearance was typical of airborne contact dermatitis (involvement of the upper eyelids, symmetrical distribution).
Result : All persons showed positive reactions to epoxy resins. The only person with a positive reaction to isophorone diamine was a 36 year old male varnisher, who had been working for 5 years.
Test condition : 7 patients affected by contact dermatitis of the hands and face, that they suspected to be occupationally related, were patch tested with standard series (ICDRG and plastic series).
Test substance : Isophorone diamine, incorporated in ICDRG standard test series / plastic series (Hermal-Trolab).
Reliability : (4) not assignable
Documentation insufficient for assessment

(58)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis
Result :

Occupation	No. of patients	No. positive with IPDA
electronics industry	18	0
painters	8	1
fiberglass	3	0
gluing	8	1
dental technicians	1	0
mechanics	1	1

Test condition : - Test persons: 39 patients with occupational allergic contact dermatitis to epoxy resin system substances
- Test system: Patch tests (no further details)
- Year (test performed): January 1984 to May 1992
Test substance : Isophorone diamine (IPDA), no further information
Reliability : (4) not assignable
Documentation insufficient for assessment

21.11.2003 (59)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis
Result : Isophorone diamine

- allergic reactions: 0/311 patients
- irritant reactions: 1/311 patients
Other test substances
- allergic reactions: maximum 5.1 %; 26/53 substances 0.0 %
- irritant reactions: maximum 9.5 %

Test condition : - Test persons: 311 patients (Years 1991-1993: 152 patients, 1994-1996: 159 patients) exposed to plastics and remitted to an occupational dermatology clinic
- Exposure: 2 days occlusion with isophorone diamine (0.5 % in petrolatum) and ca. 50 other plastic and glue allergens
- Readings: 3 readings, usually on days 2, 3, and 4-6
- Scoring system: ICDRG recommendations for allergic reactions, not reported for irritant reactions

Test substance : Isophorone diamine from Trolab Hermal Chemie, no data on purity

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

(39)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis

Result : - History: A very itchy, symmetrical, erythematous, edematous eruption of the face had begun during work. Repeatedly, it had healed within few weeks off work but recurred when returning to work.
No working colleagues had similar problems, though in the past, a man had left the job following a similar history.
- Patch test results: Only isophorone diamine was positive with erythema from 0.1 %, and erythema, oedema and vesicles from 1 % and 5 % after three days.

Test condition : - Test person: A 53-year-old male employed for laying impermeable floors, mixing the following epoxy components with quartz powder for floor coating:
bisphenol A-type epoxy resin Araldit GY 289
benzyl alcohol plus isophorone diamine = Chemammina 93I74
- Patch testing: with
GIRDCA standard series
isophorone diamine (0.1, 1, 5 % in petrolatum)
benzyl alcohol (0.1, 1, 5 % in petrolatum)
bisphenol A (0.5 %)
epichlorohydrin (0.1 %)

Test substance : Isophorone diamine, no further information

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

(45)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis

Result : One person reacted to isophorone diamine. Assignment to the source of sensitization is not possible from the reference.

Test condition : - Test persons: All persons from the contact dermatitis database at Waikato Hospital (Hamilton, NZ) with relevant and work related contact dermatitis to epoxy resin compounds = 16 males, average age 37 years (range 21-53 years)
- Patch testing: with
European Standard series of 23 allergens,
other substances "if relevant", including
isophorone diamine (0.1 % in petrolatum)

- Testing schedule: Patches prepared in the morning and left on the upper back for 47 hours, readings at 48 hours and 96-120 hours.
- Scoring system: International Contact Dermatitis Research Group (ICDRG) grading system

Test substance : Isophorone diamine, no further information

Reliability : (4) not assignable
Documentation insufficient for assessment

(46)

Type of experience : Human - Medical Data

Remark : occupational contact dermatitis

Result : Positive reactions were observed for
isophorone diamine,
the two glue components,
plastic-laminated fiber cloth as such,
perfume mix,
epoxy resin.
Analysis of the fiber cloth gave
0.07 % isophorone diamine,
0.28 % epoxy resin (molecular weight 340)

Test condition : - Test person: A 44-year old man working at a lamination machine since 9 years
- History: Having had no previous skin problems except photosensitization, after 2 years at the lamination machine he had eczema on the hands and wrists, as well as on the right upper arm. Enclosure of the process was improved. Four years later, his dermatitis worsened covering particularly typical sites of sun exposure. It healed during 2 weeks off work.
Occupational exposure occurred while mixing the components of a 2-component glue containing 10-15 % epoxy resin and 26 % isophorone diamine, further while handling the rolls of 2-layered fabric manufactured with the machine, and to airborne dust from cutting of the fiber cloth.
- Patch testing: in Finn Chambers with
European Standard series,
series of plastics and glues (Chemotechnique Diagnostics AB, Malmö, Sweden),
the two glue components,
plastic-laminated fiber cloth as such,
isophorone diamine (1 % in petrolatum).
- Testing schedule: Occlusive patches for 48 hours, 3 readings

Test substance : Isophorone diamine of Chemotechnique Diagnostics AB, Malmö, Sweden, no data on purity

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

(56)

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