FOREWORD INTRODUCTION

Hexamethylene Diisocyanate

CAS N°:822-06-0

SIDS Initial Assessment Report

for

12th SIAM

(Paris, France, 27-29 June 2001)

Chemical Name : Hexamethylene diisocyanate

CAS No : 822-06-0

Sponsor Country : Germany

National SIDS Contact Point in Sponsor Country

Lead Organization:

Name of lead organization: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit)
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Comments:

Date of Revision: 20. December 2001

OECD/ICCA - The BUA* Peer Review Process

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

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

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	822-06-0
Chemical Name	1,6-Hexamethylene diisocyanate
Structural Formula	O=C=N-$(CH_2)_6$-N=C=O

RECOMMENDATIONS

Currently a candidate for further work

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,6-Hexamethylene diisocyanate (HDI) has acute effects: LD50, rat (oral): 746 – 959 mg/kg bw, LC50 rat (inhalation): (0.124 mg/l) 18.2ppm/4h, LD50, rabbit (dermal): 599 mg/kg bw. The observed symptoms are indicative of respiratory tract irritation.
1,6-Hexamethylene diisocyanate is corrosive to the skin and the eye.
1,6-Hexamethylene diisocyanate was found to induce dermal and respiratory sensitization in animals and humans. There is no threshold known for this effect.
Inhalation studies with repeated exposures to 1,6-hexamethylene diisocyanate vapor show that the respiratory tract is the target with 1,6-hexamethylene diisocyanate showing primarily upper respiratory tract lesions (nasal cavity). 1,6-Hexamethylene diisocyanate did not show a neurotoxic effect in a combined reproduction/developmental/neurotoxicity study. Life-time inhalation exposure to rats revealed a progression of non-neoplastic respiratory tract lesions, primarily to the nasal cavity, and represented the sequelae of non-specific irritation. Based on the presence of only reversible tissue responses to irritation at the low concentration of 0.005 ppm, this concentration was a NOAEL. No carcinogenic potential in rats was observed after life-time inhalation.

1,6-Hexamethylene diisocyanate showed no mutagenic activity *in vitro* in bacterial and in mammalian cell test systems.
1,6-Hexamethylene diisocyanate showed no clastogenic activity *in vivo*.
1,6-Hexamethylene diisocyanate has no effect on fertilty and post-natal viability through post-natal day 4 in the rat after inhalation up to 0.299 ppm. The overall NOEL was 0.005 ppm.
Inhalation of 1,6-hexamethylene diisocyanate during the pregnancy of rats produced maternal effects (nasal turbinate histopathology) at concentrations ≥ 0.052 ppm. No developmental toxicity was observed up to 0.308 ppm.

Environment

HDI has a melting point of –67 °C. The substance forms oily droplets in water and hydrolyses rapidly. The vapour pressure of HDI is 0.7 Pa/20 °C. A log K_{ow} is not determinable due to the instability in water.
Hydrolysation of HDI was 90 % after a reaction period of 30 min in water at 20 °C. Hydrolysis products are hexamethylene diamine (HDA) and polyurea. Biodegradation tests on hexamethylene diamine (HAD) show the substance to be inherently biodegradable. Polyurea is more or less inert and because of it's molecular size not bioavailable. The favourite compartment for HDA is water as suggested by the high water solubility. Mackay level I distribution for HDA is not applicable as this substance is protonated under environmental pH conditions. Due to the high solubility in water of HDA (800 g/l at 15.6 °C) and its log

Kow of 0.02 no bioaccumulation is expected.

In air HDI is indirectly photodegradable with t½ = 48.4 h.
As the inherent property of HDI is to hydrolyse rapidly in an aquatic environment the ecotoxicological tests were conducted with the hydrolysis product(s) under defined conditions. The acute toxicity has been determined for fish (Brachydanio rerio) with a 96 h-LC_0 of >= 82.8 mg/l, for Daphnia magna with a 48h-EC_0 of >= 89.1 mg/l, and for algae (Scenedesmus subspicatus) a 72 h-EC_{50} of >77.4 mg/l and a 72h-NOEC of 11.7 mg/l A PNECaqua of 77.4 µg/l is derived from the EC_{50}-value for algae using an assessment factor of 1000. This factor is chosen because only short-term tests are available.

Exposure

The world production capacity of name in full(HDI) amounts to about 110,000 t/a, thereof about 49,000 t/a are produced in the USA (2 producers), about 11,000 t/a in Japan (3 producers), and about 50,000 t/a in Western Europe (3 producers). HDI is not used as the monomer but is industrially processed to higher molecular weight compounds. These are used in industrial applications (mainly surface coatings) where especially lightfastness and weatherstability are required. Exposure to consumers cannot be excluded because there are a limited number of products that consumers can use which contain low concentrations of HDI. In certain occupational settings exposure may occur from the inappropriate use of products containing small concentrations of HDI.

NATURE OF FURTHER WORK RECOMMENDED

The chemical is an irritant and a respiratory sensitizer without a known threshold. There is a need for further work (exposure assessment) in situations where there are dispersive uses (e.g. car lacquers). SIAM was informed that it is adequately controlled during manufacture (at 8 sites) and in industrial processes.

FULL SIDS SUMMARY

CAS NO: 822-06-0		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point			-67 °C
2.2	Boiling Point			255 °C (at 1013 hPa)
2.3	Density		DIN 53217/2	1.05 g/cm³ at 25 °C
2.4	Vapour Pressure			0.7 Pa at 20 °C
2.5	log Kow ; BCF			not determinable
2.6 A	Water Solubility			not determinable
B	pH			
	pKa			
2.12	Oxidation: Red. Potential			
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		AOPWIN 1994	in air t ½ = 48.4 h ($5 * 10^5$ OH/cm³; under the conditions in Western Europe)
3.1.2	Stability in Water			fast hydrolysation DT90 30-50 min
3.2	Monitoring Data			in air = mg/m³ in surface water = µg/l in soil/sediment = mg/kg dw in biota = mg/kg dw
3.3	Transport and Distribution		Henry Constant	not applicable
			Mackay Level 1	not applicable
3.5	Biodegradation		Activated Sludge,domestic	42 % after 28 d
			Industrial Sewage	0 % after 28 d
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	Brachydanio rerio	92/69/EEC C.1	LC_0 (96 h) >= 82.8 mg/l*
4.2	Acute Toxicity to Aquatic Invertebrates	Daphnia magna	92/69/EEC C.2	EC_0 (48 h) >= 89.1 mg/l*
4.3	Toxicity to Aquatic Plants e.g. Algae	Scenedesmus subspicatus	92/69/EEC C.3	EC_{50} (72 h) > 77.4 mg/l*
4.4	Toxicity to Microorganisms e.g. Bacteria	Activated Sludge	88/302/EE C	EC_{50} (3h) = 842 mg/l*
4.5.1	Chronic Toxicity to Fish			no data
4.5.2	Chronic Toxicity to Aquatic Invertebrates			no data
4.6.1	Toxicity to Soil Dwelling Organisms			no data

CAS NO: 822-06-0		SPECIES	PROTOCOL	RESULTS
4.6.2	Toxicity to Terrestrial Plants			no data
4.6.3.	Toxicity to other Non-Mammalian Terrestrial Species (incl. Birds)			no data
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat male Rat male		LD_{50} = 746 mg/kg LD_{50} = 959 mg/kg
5.1.2	Acute Inhalation Toxicity	Rat	OECD 403	LC_{50} = 124 mg/m^3 (18.2 ppm)
5.1.3	Acute Dermal Toxicity	Rabbit male	Exposure time: 24 h	LD_{50} = 599 mg/kg
5.2	Corrosiveness and Irritation			
5.2.1	Skin Irritation	Rabbit	OECD 404 (occlusive)	corrosive
5.2.2	Eye Irritation	Rabbit	OECD 405	corrosive
5.3	Sensitization - skin	Guinea pig	OECD 406	Sensitizing
	- lung	Guinea pig	Induction: 3 x intradermal (day 0, 2,4) or 1 x intradermal (day 0) 5 x 3h inhalation (day 0-4) Challenge: inhalation (day 21,22, 23, 28)	Sensitizing
5.4	Repeated Dose Toxicity	Rat	Inhalation, 3 weeks, 5 h/d, 5 d/week	NOEL = 0.005 ppm (0.034 mg/m^3; ca. 0.002 mg/kg bw/d)
		Rat	Inhalation, 13 weeks, 6 h/d, 5 d/week	LOEL = 0.01 ppm (0.068 mg/m^3; ca. 0.004 mg/kg bw /d)
		Rat	Inhalation, 2 years, 6h/d, 5 d/week	NOAEL = 0.005 ppm (0.034 mg/m^3; ca. 0.002 mg/kg bw/d)
5.5	Genetic Toxicity in Vitro			
A	Bacterial Test (Gene Mutation)	Salmonella typhimurium TA 98; 100, 1535 und 1537		- (with metabolic activation) - (without metabolic activation)
B	Non-Bacterial in Vitro Test	HPRT assay (CHO cells)		- (with metabolic activation) - (without metabolic activation)
5.6	Genetic Toxicity in Vivo			
	Cytogenetic assay	Mouse bone marrow cells	single inhalation	-

CAS NO: 822-06-0		SPECIES	PROTOCOL	RESULTS
5.8	Toxicity to Reproduction	Rat	OECD 422	NOEL Maternalt. (systemic toxicity) = 0.299 ppm (2.03 mg/m^3) NOEL Maternalt. (local effect in the nasal cavity)= 0.005 ppm (0.034 mg/m^3) NOEL Offspring= 0.299 ppm (0.002 mg/l)
5.9	Developmental Toxicity/Teratogenicity	Rat	OECD 414	NOEL Maternalt. (systemic toxicity)= 0.308 ppm (2.1 mg/m^3)) NOEL Maternalt. (local effect in the nasal cavity)= 0.005 ppm (0.034 mg/m^3)NOEL Teratogen.: 0.308 ppm (2.1 mg/m^3)
5.11	Experience with Human Exposure	Exposed workers		Sensitization (repiratory hypersensitivity, dermal sensitization) and irritation (chronic decrease in pulmonary function) predominate

* effect data refer to the degradation products

SIDS Initial Assessment Report

1. IDENTITY

CAS Number 822-06-0

Name 1,6-Hexamethylene diisocyanate / HDI

Molecular formula C8 H12 N2 O2

Structure:

$O=C=N-(CH_2)_6-N=C=O$

Physico-Chemical Properties:

HDI is a colourless or slightly yellow liquid with a melting point of -67 °C. With a density of 1.05 g/cm³ (at 25 °C) HDI is not much heavier than water. The substance forms oily droplets in water and hydrolyses rapidly (Sopac & Boltromejuk 1974; Bayer AG SDS 2000). The vapour pressure of HDI is 0.7 Pa (at 20 °C) (DFG 1988). A log K_{ow} is not determinable due to the instability in water.

The purity of the substance is given with > 99.5 % w/w (Bayer AG SDS 2000).

2. GENERAL INFORMATION ON EXPOSURE

The world production capacity of HDI amounts to about 110,000 t/a. This figure can be split up as follows:

USA, 2 producers:	about 49,000 t/a
Japan, 3 producers:	about 11,000 t/a
Western Europe, 3 producers:	about 50,000 t/a

HDI can be produced by phosgenation of hexamethylene diamine and by a phosgene free process. In the phosgenation process HDI is produced continuously by reacting 1,6-hexamethylene diamine with phosgene in a solvent. The solvent and excess phosgene are recovered and returned to the production process.

In the phosgene free process HDI is produced continuously by reacting 1,6-hexamethylene diamine with urea and n-butanol. Ammonia, which is formed as a by-product of the urethanization step is removed by a thermal exhaust purification. Butanol is recovered and returned to the production process. The crude HDI product is purified by distillation. Production and processing to higher molecular compounds is carried out in closed systems.

HDI is not used as the monomer. It is industrially processed to polymers like, uretdiones, isocyanurates, and biurets. Furthermore HDI can be industrially processed with polyols to higher molecular weight adducts. These products typically contain up to 0.5 % residual monomer HDI. They are mainly used in industrial or professional applications of surface coatings with excellent lightfastness and weatherstability even without stoving.

The Swedish product register gives the information that HDI is present in 18 products available to consumers. Most products are hardeners for paints but also for sealants, caulking and putty compounds and adhesives. HDI is present only at low concentrations (all below 0.5 % and typically approx. 0.3 %).

In the Danish product register (June 2001) there is a total of 385 products containing HDI. Most products (340) have HDI concentrations between 0 and 1 %; however there are also products that contain HDI in amounts of 20 to 100 %. Product types are adhesives, binding agents, process regulators and paints, lacquers and varnishes.

HDI may be reformed when HDI-based materials are heated to decomposition leading to HDI exposure.

2.1 Environmental Exposure and Fate

2.1.1 Environmental Exposure

At Bayer production and processing of HDI takes place in closed systems. The exhaust air is connected to a thermal exhaust purification plant (TAR). Thus during normal operation of the TAR no HDI is emitted into the atmosphere (HDI was no subject for the official German Emission

Declaration). There is no waste water from production. If cleaning of the operation plant is needed, the used solvent for cleaning is burned; devices with little dirt are treated with high pressure jet of water; this is disposed in the biological water purification plant. Due to the rapid hydrolysis of HDI and negligible amounts of HDI reaching the sewage system, no analysis of HDI is made at the sewage treatment plant outlet.
An exposure of sewage treatment plants or the terrestrial compartment to HDI is unrealistic as HDI hydrolyses rapidly.

There is no information on emission of HDI at other production / processing sites.

HDI can be released into the environment during spray applications of polymer paints containing residual amounts of monomer HDI.

2.1.2 Environmental Distribution and Fate

The environmental fate and distribution of HDI is determined by its property to react rapidly with water.

Sopac & Boltromejuk (1974) have reported that three main findings determine the result of the hydrolysis of HDI:

1. HDI is not soluble in the low mg/l range in water without another solvent. It forms oily droplets in water.
2. The diisocyanate groups of HDI react with water forming the diamine and CO_2.
3. The diisocyanate groups of HDI can also react with the amine already formed by hydrolysis, resulting in oligo- and than polyurea.

Sopac & Boltromejuk (1974) found in a test on the stability of HDI in drinking water the reduction of the substance was 90 % after a reaction period of 30 min. Initial concentration of HDI was 200 mg/l, no organic solvent was used, and the temperature was 20°C. The reaction rate was dependent on the initial concentration of HDI and on the temperature. From this paper it can be concluded that emissions of HDI into the aquatic environment via effluent from a sewage treatment plant will not occur. The ratio of the formed hydrolysis products is strongly dependent on test procedures (slow or fast stirring, duration of stirring…).

There are several test on biodegradation of the hydrolysis product HDA available. In a MITI I test 56 % biodegradation (on the upward trend) were found after 2 weeks (CITI, 1992). In addition there is a BOD_5/COD ratio of 104.8 % available (Institut Kuhlmann, 1989). As the BOD_5 was measured using industrial activated sludge, a statement concerning the ready biodegradability of HDA cannot be made based on this test. In a Zahn-Wellens test on HDA the pass level for inherent biodegradation was reached (Zahn/Wellens 1980). Therefore, HDA is classified at least as inherently biodegradable. Polyurea is more or less inert and because of it's molecular size not bioavailable. A test with HDI and the resulting hydrolysis products on ready biodegradation showed 42 % biodegradation after 28 days. The way of introducing the test substance was by direct weight.

A distribution calculation according to Mackay is not appropriate for the chemical HDI, due to its hydrolysing properties. If HDI reaches into water it hydrolyses to HDA and polyurea. A Mackay level I distribution for HDA is also not applicable as this substance is protonated under environmental pH conditions. However, the high water solubility suggests that HDA would largely partition into the water environment (OECD SIDS Hexamethylene diamine). Bioaccumulation of HDA is not expected due to its high water solubility of 800 g/l at 15.6 °C as well as a log K_{ow} of 0.02.

HDI reaching into the air will be photodegraded by OH-radicals, as a calculation according to Atkinson shows. The half-life due to indirect photodegradation of HDI is calculated to be 48.4 hours. The calculated half-life is regarded as worst case, since HDI will react with air humidity.

For assessment purposes it is assumed that HDI released via wastewater hydrolyses completely to HDA before reaching surface waters. This is a worst-case scenario as the other hydrolysis product polyurea is not bioavailable.

2.2 Human Exposure

The main process to manufacture HDI is by a phosgenation process. Thus special safety measures are taken to prevent any risk of exposure. For HDI itself occupational exposure limit values are laid down: In Germany a maximum limit value (MAK, TRGS 900) with 0.005 ml/m³ is sound. The same value is sound for short term exposure (15 minutes). In the USA the same value with 0.005 ml/m³ as TLV-TWA exists: a short term exposure limit value has not been established.

Personal protection equipment needs to be worn at the workplace depending on the extent of contact with the product as well as with coating material. Special advice for different workplaces and operations are given.

Exposure to consumers cannot be excluded because there are a limited number of products that consumers can use which contain low concentrations of HDI. In certain occupational settings exposure may occur from the inappropriate use of products containing small concentrations of HDI..

3. HUMAN HEALTH HAZARDS

Effects on Human Health

3.1 Acute Oral Toxicity

The LD_{50} resulting from a single oral (gavage) administration ranged from 746 to approximately 959 mg/kg bw for the male rat (Smyth 1969; Union Carbide Co. 1964, Bayer 1970). Soon after dosing the animals appeared to be extremely sluggish. All deaths occurred within the first day.

Conclusion: The acute toxicity of HDI after oral administration is moderate.

3.2 Acute Inhalation Toxicity

Several studies have evaluated the acute inhalation toxicity of HDI.

The inhalation LC_{50} in rats of both sexes was determined to be 124 mg/m^3 (= 18.2 ppm) for 4 hours of exposure to HDI vapour according to the OECD Test guideline 403 (Bayer 1997). Exposures to concentrations of $\geq$ 55.08 mg/m^3 (= 8.1 ppm) were followed by concentration-dependent signs indicative of respiratory tract irritation, such as bradypnea, dyspnea, laboured breathing pattern, rales, nostril/snout area with red encrustations, cyanosis, prostration (lying on belly), reduced motility, ungroomed haircoat, hypothermia, decrease in body weights, and piloerection.

In rats, Woolrich (1973) as cited in NIOSH (1978) reported a 6 hour value of 0.385 mg/l, while Bunge et al. (1976) and BAYER (1970) reported 4 hour LC_{50} values of 0.31 and 0.15 mg/l respectively, and BAYER (1970) reported a 1 hour LC_{50} of 0.29 mg/l. For mice Lomonova & Frolova (1968) as cited in NIOSH (1978) reported 0.03 mg/l for a 2 hour exposure. Limited information was provided in all these studies on the mode of exposure, generation and characterization of test atmospheres therefore the assessment of acute inhalation toxicity is based on the most recent BAYER study (1997).

Conclusion: The evaporated HDI has a high acute inhalation toxicity to rats.

3.3 Acute Dermal Toxicity

The dermal LD_{50} following a 24-hour application of the test material to the skin is approximately 599 mg/kg bw in rabbits (Smyth 1969; Union Carbide Co. 1964). All deaths occurred within 24 hours after dosing. No information available with regard to clinical signs and local effects.

Conclusion: The acute toxicity of HDI after dermal administration is moderate.

3.4 Skin Irritation

There is one study available which was conducted according to OECD guideline (Schreiber 1981). Immediately after patch removal all treated animals showed severe oedema and erythema (grade 4). 24 hours later there were induration and necrosis at the application site of all animals. No reversibility could be observed at the end of the post observation period of 8 days.

Conclusion: HDI is corrosive to the skin when tested according to the OECD Guideline 404 (Schreiber 1981).

3.5 Eye Irritation

There is one study available which was conducted according to OECD guideline (Schreiber 1981). The examination of the eyes showed already 1 hour after instillation severe effects in all animals with regard to cornea, iris and conjunctivae. All effects had a tendency to get worse during the 8 day post observation period. Sometimes the examination of the eyes was impossible due to swelling.

Conclusion: HDI is corrosive to the eye when tested according to the OECD Guideline 405 (Schreiber 1981).

3.6 Sensitization

3.6.1 Skin Sensitization

HDI was found to be positive in mice using ear swelling test (Gad 1986, Karol 1996, Thorne 1987) and the murine local lymph node assay (Hilton 1995). Using a guinea pig model (Buehler Test and Maximization Test according to OECD Guideline 406) several studies reported positive findings (Basketter 1996, Zissu 1998, Clemmensen 1984, Bayer 1983)

Conclusion: HDI was found to induce dermal sensitization in animals.

3.6.2 Respiratory Sensitization

Using a standard approach that included either three intradermal injections (one per day) or 5x3 hrs inhalation exposures, including one additional intradermal injections, followed by inhalation challenge with HDI, acetylcholine and conjugate by inhalation, the lung sensitization potential of HDI was examined in guinea pigs (Bayer 1996). This study provides clear evidence that HDI is a respiratory sensitizer in this guinea pig bioassay.

3.7 Repeated Dose Toxicity

In a 21-day inhalation study (Sangha 1984) rats were exposed up to 0.300 ppm (2.04 mg/m3) of HDI vapor. A sub-set of animals was allowed a two-week period for recovery. There were no mortality and no effects on body weight, feed consumption, clinical chemistry, hematology, urinalysis and gross pathology observed. Compound related ocular and nasal irritation were observed in animals exposed to HDI concentration ≥ 0.0175 ppm (≥ 0.119 mg/m^3). At 0.005 ppm (0.034 mg/m^3) and 0.0175 ppm (0.119 mg/m^3) the changes were minimal to mild in severity, and were similar to the control even though the incidence was slightly higher in the 0.0175 ppm males. There was recovery at 0.0175 (0.119 mg/m^3) and 0.15 ppm (1.02 mg/m^3), but not at 0.3 ppm. The NOEL was 0.005 ppm (0.034 mg/m^3).

A 90-day inhalation study (Shiotsuka 1988) was conducted with HDI . Rats were exposed to vapor concentrations of 0, 0.01, 0.04, and 0.14 ppm (0, 0.068, 0.272 and 0.952 mg/m^3). There were no compound related effects on mortality, body weight, clinical chemistry, hematology, urinalysis, gross pathology or organ weights. The only compound-related findings were ocular irritation and histopathologic lesions of the anterior nasal cavity. Ocular irritation occurred in all HDI-treated animals. Hyperplasia and/or squamous metaplasia of the respiratory epithelium were the most important lesions in both sexes. Hyperkeratosis, mucus cell hyperplasia and inflammatory cell infiltration were also observed in the nasal cavity. These histopathological lesions were observed at all three concentrations. The concentration of 0.01 ppm (0.068 mg/m^3) was considered to approximate a threshold for respiratory tract lesions, but a clear NOEL was not established for this study.

A combined reproductive/developmental/neurotoxicity study according to OECD Guideline 422 was conducted with HDI (Astroff 1999, 2000a). Rats were exposed, via whole body exposure, to either 0, 0.005, 0.053, or 0.299 ppm (0.034, 0.361 or 2.033 mg/m^3) during a 14-day premating phase, up to a 14-day mating phase, and a 21-day gestation phase. Neurobehavioral testing (automated measures of activity and a functional observational battery) was conducted before exposure, after the premating phase, and before termination. Evidence of toxicity was demonstrated in the 0.299 ppm and to a lesser extent in the 0.053 ppm dose group. Microscopic alterations in the nasal cavity, primarily epithelial hyperplasia, squamous metaplasia, chronic-active inflammation, and more seriously, degeneration of the olfactory epithelium were observed at concentrations ≥ 0.053 ppm (≥ 0.361 mg/m^3). No histopathological effects were observed in the 0.005 ppm dose level. No effects on neurologic parameters (functional observation battery; assessment of motor and locomotor activity) were seen at any dose level. This means the the no-observed-effect-level (NOEL) for neurotoxicity was 0.299 ppm (2.033 mg/m^3). The NOEL for hematology and clinical chemistry for this study was 0.299 ppm (2.033 mg/m^3), too. Therefore the overall NOEL was 0.005 ppm (0.034 mg/m^3).

A combined chronic toxicity/oncogenicity study (Shiotsuka 1989) with rats according to OECD Guideline 453 was conducted with HDI using concentrations of 0, 0.005, 0.025 and 0.164 ppm (0.034, 0.17 and 1.115 mg/m^3) HDI vapor. The exposure regimen was 6 hours/day, 5days/week for one year (chronic toxicity assessment) or two years (toxicity and oncogenicity assessment). There

were no compound related effects on mortality, ophthalmology, clinical biochemistry, urinalysis and organ weights. Those effects determined to be compound related were transient ocular irritation in males, small but consistent decrease in body weight of females and slight anemia in females at 0.164 ppm (1.115 mg/m^3). Compound-related non-neoplastic histopathologic changes in the nasal cavity and to a lesser extent the lungs were also observed. Nasal lesions in the interim (1-year) sacrifice were restricted to the nasal mucosa at all exposure concentrations. The following nasal lesions were observed: hyperkeratosis, hyperplasia of the squamous epithelium, chronic active inflammation, squamous metaplasia, mucus secretory cell or goblet cell hyperplasia, hyaline droplet degeneration and minimal degeneration of the olfactory epithelium. All of these lesions were also observed after two years of exposure. The most prominent lesion was degenerative changes in the olfactory epithelium (destruction of epithelial architecture, atrophy, focal erosion or ulceration) The changes in the olfactory epithelium were concentration-related in terms of incidence and severity, and displayed progression with duration of exposure. Lung lesions were epithelialization, interstitial pneumonia or macrophage accumulationin alveolar space in both sexes at mid- and high dose groups after two years of exposure. No clear concentration-response relationship was observed in the lungs. No evidence of compound-related oncogenicity was found. A maximum Tolerated Dose (MTD) was achieved at high dose based on decrease in body weight and slight anemia of females and microscopic changes in the nasal cavity of both sexes. Analysis of the results from the principal study revealed that compound-related effects were limited to histopathology in the nasal passages. Although some lesions were noted in the nasal tract of animals from all exposure groups, Foureman et al. (1994) concluded that the olfactory epithelial degeneration should be considered as the significant effect in this study, with a NOAEL of 0.005 ppm (0.034 mg/m^3) and a LOAEL of 0.025 ppm (0.17 mg/m^3), because it followed a concentration-response relationship for both incidence and severity. The data for this lesion show its absence at the lowest concentration with parallel increases in both incidence and severity at the two highest concentrations. For the other lesions, including chronic inflammation, mucus cell hyperplasia, epithelial hyperplasia, hyaline droplet degeneration, and squamous metaplasia no concordance in incidence and severity was found. In response to an irritant, the character of lesions in the nasal tract such as squamous metaplasia, mucus cell hyperplasia, and hyaline droplet formation appears to be more adaptive than adverse..

Conclusion: The major conclusion from the available inhalation studies is that the respiratory tract is the target with HDI showing primarily upper respiratory tract lesions (nasal cavity). HDI does not pose a neurotoxic hazard. Life-time inhalation exposure to rats revealed a progression of non-neoplastic respiratory tract lesions, primarily to the nasal cavity, and represented the sequelae of non-specific irritation. Based on the presence of only reversible tissue responses to irritation at the low concentration of 0.005 ppm (0.034 mg/m^3), this concentration was a NOAEL.

For respiratory sensitization see section 3.6.2.

3.8 Genotoxicity (Gene Mutation)

HDI was tested in two independent bacterial reverse mutation assays, using S. typhimurium tester strains in the presence and absence of metabolic activation (Andersen 1980, CMA data 1998a,

Wagner 2000). Both studies took the volatility of the test compound into account (vapor phase exposure). Some details (i.e. doses, positive control) of the study published in the open literature are missing but the recent study confirmed the result. HDI did not induce any mutagenic activity with any of the tester strains with and without metabolic activation. While the toxicity criteria for a valid test outlined in the protocol have not been met, the data generated, which includes acceptable positive control responses, do not indicate the presence of any mutagenic activity (CMA data 1998a, Wagner 2000).

HDI was also tested in the CHO/HPRT Mutation Assay (CMA data 1998b, Wagner 2000). HDI did not cause a positive response in the non-activated systems and S9-activated systems and was concluded to be negative. The criteria for a valid study (i.e. marked mutagenic effect in the positive control) were met

No further data are available with regard to the induction of gene mutation by HDI.

Conclusion: HDI showed no mutagenic activity in bacterial and in mammalian cell test systems.

3.9a Genotoxicity: (Cytogenicity) in Vitro

No data available

Conclusion: See Cytogenetic in Vivo (chapter 3.9b)

3.9b Genotoxicity (Cytogenicity) in Vivo

The clastogenic potential of HDI as measured by its ability to induce micronucleated polychromatic erythrocytes in bone marrow following inhalation exposure (CMA data 1998c, Wagner 2000). Mice were once exposed to HDI vapors up to 1.5 ppm (10.2 mg/m^3) for 6 hours. No animals died during the course of the study. Mice exposed to HDI at 0.15 ppm (1.02 mg/m^3) had no apparent test substance effects. Mice exposed to 0.75 and 1.5 ppm (5.1 and 10.2 mg/m^3) showed considerable weight losses. Reductions of 2 to 17% in the ratio of polychromatic erythrocytes to total erythrocytes were observed in the test substance-treated males relative to the air control group at 48 hour harvest. No significant increase in micronucleated polychromatic erythrocytes in test substance-treated groups relative to the respective air control group was observed at 24, or 48 hours after exposure.

Conclusion: HDI showed no clastogenic activity in vivo.

3.10 Carcinogenicity

A combined chronic toxicity/oncogenicity study (Shiotsuka 1989) with rats according to OECD Guideline 453 was conducted. Male and female Fischer 344 rats were exposed to HDI using

concentrations of 0, 0.005, 0.025 and 0.164 ppm (0, 0.034, 0.17 and 1.152 mg/m^3) HDI vapor. A Maximum Tolerated Dose (MTD) was established at the highest concentration and no compound-related oncogenicity was observed (for detailed reference , see chapter 3.7).

Conclusion: After life-time inhalation of HDI no carcinogenic potential in rats was observed.

3.11 Toxicity to Reproduction

To evaluate the potential for HDI administered via inhalation, to elicit reproductive, developmental, and neurotoxicological effects in the rat a screening test was conducted in accordance with the OECD Guideline 422 (Astroff 1999, 2000a). Rats were exposed to either 0, 0.005, 0.053, or 0.299 ppm (0, 0.034, 0.361 and 2.03 mg/m^3) during 14-day premating phase, up to a 14-day mating phase, and a 21-day gestation phase. Evidence of microscopic alterations in the nasal cavity was demonstrated in the 0.299 ppm and to a lesser extent in the 0.053 ppm dose group. No effects on any reproductive or neurologic parameters or any effects on pup growth and development were observed at any dose level.

Conclusion: HDI has no effect on the reproduction (including neonatal development) in the rat after inhalation up to 0.299 ppm (2.03 mg/m^3). The overall NOEL was 0.005 ppm (0.034 mg/m^3).

3.12 Developmental Toxicity

A developmental toxicity study was conducted with HDI in the rat according to OECD Guideline 414 (Astroff 1999, 2000b). Inseminated rats were exposed to concentrations of 0, 0.005, 0.052, or 0.308 ppm (0, 0.034, 0.354 or 2.1 mg/m^3) HDI via inhalation on days 0 through 19 of gestation. No clinical signs and no changes in body weight gain during gestation were observed in dams. Test compound-related maternal effects were restricted to histopathological findings in the nasal cavity of the 0.308 and 0.052 ppm dose groups. No pathological alterations were noted in the larynx, trachea, or lungs in any dose group. No test compound-related effects were observed on any reproductive parameter, or any embryonic endpoints, including pre/post-implantation loss and resorptions. There were no effects on litter size or the number of fetuses per implantation site and no effects on fetal or placental weights were observed. No test compound-related fetal external, visceral, or skeletal findings were observed. No effect on the fetal or litter incidence of total malformations or variations was observed and there was no difference in the incidence of malformations between males and females.

Conclusion: Inhalation of HDI during the pregnancy of rats produced maternal effects (nasal turbinate histopathology) at concentrations ≥ 0.052 ppm (≥ 0.354 mg/m^3). No developmental toxicity was observed up to 0.308 ppm (2.1 mg/m^3).

3.13 Other Toxicological Endpoints

Sensory Irritation

Sensory irritation studies using laboratory animal models demonstrated evidence of sensory irritation but no evidence of pulmonary irritation to HDI. Sangha et al. (1981) reported a 3-hour RD50 (concentration required to reduce respiratory rate by 50%) of 1.17 mg/m^3 (0.17 ppm) using Swiss Webster mice. A comparable study using male Fisher 344 rats (Sangha 1982) resulted in a 30-minute RD50 of 9.94 mg/m^3 (1.42 ppm) The exposure of female Sprague Dawley rats resulted in a 3-hour RD50 of 11.83 mg/m^3 (1.69 ppm)(Mobay 1987a). In a study to assess the effects of repeated exposures on respiratory rate, female Sprague Dawley rats were exposed 3 hours/day for 5 consecutive days to a mean concentration of 8.084 mg/m^3 (1.17 ppm). The extent of daily decrease in respiratory rate of approximately 60%, relative to pre-exposure mean for day 1, showed that repeated exposures did not produce a cumulative effect on respiratory rate depression during daily exposures (Mobay 1987b).

Health Effects In Workers

Adverse health effects reported for humans are primarily related to the respiratory tract and to some extent to the exposed skin (ATSDR 1998; DFG 1996, 1998). The findings in exposed workers are consistent with the findings in laboratory animals. Sensitization (dermal sensitization, respiratory hypersensitivity) and irritation (chronic decrease in pulmonary function) predominate and cross-sensitivity of humans to diisocyanates such as TDI and MDI have been described. However, a correlation between HDI-specific IgE or IgG and occupational asthma has not been firmly established. Small cohorts, lack of mechanistic information, and limited information on exposure in the human studies preclude establishment of a concentration-response relationship for pulmonary sensitization. A few human studies were identified that described health effects evaluations associated with measured or reconstructed exposure concentrations for HDI. Brorson et al. (1990) reported no adverse health effects following a single 7.5-hour exposure at concentrations of HDI ranging from 25 to 29 µg/m^3 (3.6 to 4.3 ppb). In a second report a matched case-control epidemiologic study of a production plant population presented information from workers exposed for approximately three years (Shepperly & Hathaway, 1991). Exposures were generally less than 34 µg/m^3 (5 ppb) with occasional excursions in the range of 69 -137 µg/m^3 (10-20 ppb). No significant difference in pulmonary function data was detected. A follow up study of this same population reported by DeWilde & Hathaway (1994) again found no statistically significant differences in pulmonary function data. The exposure concentration was estimated to be between 0.5 and 7 ppb (3.4 and 47.6 µg/m^3). The Alexandersson et al. (1987) study was determined not to be suitable for use in deriving a (L)(N)OAEL for workers, due to the fact that workers were simultaneously exposed to both the monomeric as well as the trimer forms of HDI.

Toxicokinetics

In animal studies the uptake of radiolabeled HDI into blood from the respiratory tract was immediate and increased linearly during exposure over a range of concentrations. In controlled studies in human volunteers, HDI (3.6 ppb for 7.5 h) appears to be rapidly absorbed via the respiratory tract and approximately up to 39% of the estimated inhaled dose is excreted in the urine which could be detected after acid hydrolysis as HDA (DFG 1996). No HDA was detectable in plasma. The relative amount excreted in feces and exhaled air or that proportion remaining bound to macromolecules and tissues have not been reported.

4. HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The inherent property of HDI is to hydrolyse rapidly in an aquatic environment
Depending on the use of a solvent or not, the size of the drops when direct weight is used, and the speed of a magnetic stirrer or of ultrasonic if used, determine the quantitative proportion of the hydrolysis products HDA and polyurea. The problem with tests on HDI is the inhomogeneous distribution of the substance in the test medium water because of formation of droplets. With these droplets a “real” concentration of HDI in water is neither analytically determinable nor can a reproducible and thus reliable exposure concentration for test organisms be fixed. The pure substance HDI, as it is in the droplets, showed to be lethal to the aquatic species. The acute toxicity of HDA has to be classified as harmful and polyureas are, because of their molecular size, not bioavailable.

In the following the toxicity of the hydrolysis product(s) (see chap. 2.1.2) are reported for tests which have been conducted with specially layed down test conditions and which are thus reproducible tests.

The acute toxicity has been determined for fish with 96 h-LC_0 of >= 82.8 mg/l (Brachydanio rerio). The test result refers to concentration of the test substance which was calculated directly from analytically determined TOC-value. The test was conducted according to Council Directive 92/69/EEC C.1 (1992). A water accommodated fraction was prepared for testing by stirring the substance in water with Ultra turrax 60 sec/8000 rpm, 24 hours magnetic stirrer and filtration. Only one concentration was tested. The pH of the test solution was around 8 (Bayer AG 2000).
In a previous fish test, conducted according to UBA-Verfahrensvorschlag "Letale Wirkung beim Zebrabärbling" (1984), a 96 h-LC_0 of 22 mg/l and 96 h-LC_{100} of 31 mg/l (Brachydanio rerio) was determined. In this test the test substance was prepared by stirring in water with Ultra turrax 60 sec/8000 rpm and waiting only for 1 hour (Bayer AG 1992). This time was regarded as too short for a complete hydrolysis of HDI because there were still oily droplets of undissolved HDI. Because of the short half-live of HDI, testing with the degradation product is required and has been conducted as seen in the first test. Therefore the second test has not been taken into account for the classification of HDI.
For acute toxicity of HDI to Daphnia magna a 48 h-EC_0 of >= 89.1 mg/l has been determined (92/69/EEC C.2 (1992)) proceeding in the same way as described in the first fish test above. The pH of the test solution was 7.8 (Bayer AG 2000).
In an algal growth inhibition test (92/69/EEC C.3 (1992)) of Scenedesmus subspicatus an 72 h-EC_{50} of >77.4 mg/l and a 72h-NOEC of 11.7 mg/l was observed. The proceeding for preparation of the test solution was in the same way as described in the first fish test above. However, from the stock solution a dilution series was prepared and tested. The pH of the test solution was between 7.9 and 8.2 at test start and between 9.8 and 10.2 at test end (Bayer AG 2000).

The effect of HDI on the respiration of activated sewage sludge has been tested, using a method comparable to 88/302/EEC. After 3 hours incubation an EC_{50} of 842 mg/l was determined. In this test direct weight has been used (Bayer AG 2000).

The following endpoints on aquatic toxicologic tests are available for the pure hydrolysis product HDA (124-09-4):

Fish

Lepomis macrochirus 48 h-LC_{50}: 73.5 mg/l and 48h-NOEC > 56 mg/l

(no information on pH; OECD SIDS on HDA)

Pimephales promelas 96h-LC_{50}: 1825 mg/l

(pH: 8.0 – 8.5; E.I. du Pont, 1985b)

Daphnia

Daphnia magna 48 h-LC_{50}: 23.4 mg/l

(pH: 7.9 - 8.5; E.I. du Pont, 1985a)

Algae

Selenastrum capricornutum 96 h-EC_{50}: 14.8 mg/l

(pH of test solution was between 8.0 and 10.8; E.I. du Pont, 1993)

In the BUA-Report on HDI (1993) two tests are reported for HDA showing that non-neutralized and neutralized test media exhibit significant differences on the toxicity of HDA to the organisms:

Fish

Leuciscus idus 96 h-LC_{50}: 62.2 mg/l non-neutralized

96 h-LC_{50}: >215.0 mg/l neutralized

Microorganisms

Pseudomonas putida 20 h-EC_0: 37.5 mg/l non-neutralized

20 h-EC_0: 12,500 mg/l neutralized

For the derivation of the PNECaqua the effect values found in the tests with HDI and its hydrolysis products are used. Algae were the most sensitive species. An 72h-EC50 of > 77.4 mg/l was found that is used as basic value for the PNECaqua. As only short-term tests are available, an assessment factor of 1000 is used.

PNECaqua = 77.4 mg/l / 1000 = 77.4 µg/l

In addition, a PNECaqua for the pure hydrolysis product HDA is derived. The lowest available effect value is the 96h-EC_{50} of 14.8 mg/l for green algae. The pH at the concentration 25 mg/l was 9.9 at test start and 8.7 at test end. Therefore, it cannot be excluded that effects may also be caused by pH. However, at the next lowest concentration of 10 mg/l, where the alga growth was almost comparable to the control, the pH was between 9.5 and 9.7. At the next higher concentration of 25 mg/l nearly no growth could be observed at a pH between 8.1 and 10.2. Therefore, it can be assumed that the effect value of 14.8 mg/l is caused by intrinsic properties of the test substance and

not by pH and this value is used as basic value for the PNEC derivation. As only short-term tests are available an assessment factor of 1000 is used.

PNECaqua = 14.8 mg/l / 1000 = 14.8 µg/l

As it is unclear which hydrolysis products are formed to which extent under environmental conditions, it can be assumed as a worst case that all HDI released via the wastewater is hydrolysed completely to HDA before reaching surface waters. This HDA concentrations has then to be compared with the PNECaqua for HDA.

4.2 Terrestrial Effects

There are no data available.

4.3 Other Environmental Effects

There are no data available.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Production and processing:

The world production capacity of HDI amounts to about 110,000 t/a, thereof about 49,000 t/a are produced in the USA (2 producers), about 11,000 t/a in Japan (3 producers), and about 50,000 t/a in Western Europe (3 producers). HDI is not used as the monomer but industrially processed to homopolymers and to higher molecular weight adducts. These products are mainly used in surface coatings. At Bayer production and processing of HDI takes place in closed systems. There is no emission of HDI during normal operation while producing and processing HDI.

Environmental behaviour:

Hydrolysation of HDI was 90 % after a reaction period of 30 min in water at 20 °C. Hydrolysis products are hexamethylene diamine (HDA) and polyurea. Biodegradation tests on HDA show the substance to be at least inherently biodegradable. Polyurea is more or less inert and because of its molecular size not bioavailable. The favourite compartment for HDA is water as suggested by the high water solubility. Mackay level I distribution for HDA is not applicable as this substance is protonated under environmental pH conditions. Due to the high solubility in water of HDA (800 g/l at 15.6 °C) and its log K_{ow} of 0.02 no bioaccumulation is expected. A calculation showed HDI to be indirectly photodegradable in air HDI with $t_{½}$ = 48.4 h.

As the inherent property of HDI is to hydrolyse rapidly in an aquatic environment the ecotoxicological tests were conducted with the hydrolysis product(s) under defined conditions. The acute toxicity has been determined for fish (Brachydanio rerio) with a 96 h-LC_0 of >= 82.8 mg/l, for Daphnia magna with a 48 h-EC_0 of >= 89.1 mg/l, and for algae (Scenedesmus subspicatus) with a 72 h-EC_{50} of >77.4 mg/l and a 72h-NOEC of 11.7 mg/l. A PNECaqua of 77.4 µg/l is derived from the EC_{50} for algae using an assessment factor of 1000. In addition a PNECaqua of 14.8 µg/l is derived from ecotoxicity tests for the pure hydrolysis product HDA.

As it is unclear which hydrolysis products are formed to which extent under environmental conditions, it can be assumed as a worst case that all HDI released via the wastewater is hydrolysed completely to HDA before reaching surface waters. This HDA concentrations has then to be compared with the PNECaqua for HDA.

Human health:

HDI has acute effects: LD50, rat (oral): 746 – 959 mg/kg bw, LC50 rat (inhalation): 124 mg/m^3/4h, LD50, rabbit (dermal): 599 mg/kg

HDI is corrosive to the skin and the eye.

HDI was found to induce dermal and respiratory sensitization in animals.

Inhalation studies with repeated exposures to HDI vapor show that the respiratory tract is the target showing primarily upper respiratory tract lesions (nasal cavity). did not show a neurotoxic effect in

a combined reproduction/developmental/neurotoxicity study. Life-time inhalation exposure to rats revealed a progression of non-neoplastic respiratory tract lesions, primarily to the nasal cavity, and represented the sequelae of non-specific irritation. Based on the presence of only reversible tissue responses to irritation at the low concentration of 0.005 ppm (0.034 mg/m^3), this concentration was a NOAEL. No carcinogenic potential in rats was observed after life-time inhalation.

HDI showed no mutagenic activity in bacterial and in mammalian cell test systems.

HDI showed no clastogenic activity in vivo.

HDI has no effect on the reproduction (including neonatal development) in the rat after inhalation up to 0.299 ppm (2.03 mg/m^3). The overall NOEL was 0.005 ppm (0.034 mg/m^3).

Inhalation of HDI during the pregnancy of rats produced maternal effects (nasal turbinate histopathology) at concentrations ≥ 0.050 ppm (≥ 0.354 mg/m^3). No developmental toxicity was observed up to 0.308 ppm (2.1 mg/m^3).

5.2 Recommendations

Concerning environment, the substance is currently of low priority for further work.

Concerning human health: The chemical is an irritant and a respiratory sensitizer without a known threshold. There is need for further work (exposure assessment) in situations where there are dispersive uses (e.g. car lacquers). SIAM was informed that exposure is adequately controlled during manufacture (at 8 sites) and in industrial processes.

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SIDS Dossier including Robust Study Summaries

Existing Chemical	:	ID: 822-06-0
CAS No.	:	822-06-0
EINECS Name	:	hexamethylene diisocyanate
EC No.	:	212-485-8
Molecular Weight	:	168.2
Molecular Formula	:	C8H12N2O2

Producer related part

Company	:	Bayer AG
Creation date	:	12.08.1994

Substance related part

Company	:	Bayer AG
Creation date	:	12.08.1994
Status	:	
Memo	:	
Printing date	:	27.02.2002
Revision date	:	22.05.1995
Date of last update	:	13.12.2001
Number of pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : organic
Physical status : liquid
Purity : = 98 % w/w
Colour :
Odour :

Remark : as fine chemical, Aldrich Chemical GmbH
Flag : Critical study for SIDS endpoint
23.11.2000

Purity type :
Substance type : organic
Physical status : liquid
Purity : >= 99.5 % w/w
Colour :
Odour :

Remark : Bayer AG
Flag : Critical study for SIDS endpoint
23.11.2000

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1,6-Hexamethylendiisocyanat

Flag : Critical study for SIDS endpoint

1,6-Hexylendiisocyanat

Flag : Critical study for SIDS endpoint

Desmodur H (Trade name)

Flag : Critical study for SIDS endpoint

HDI

Flag : Critical study for SIDS endpoint

Hexamethylen-1,6-diisocyanat

Flag : Critical study for SIDS endpoint

Hexamethylendiisocyanat

Flag : Critical study for SIDS endpoint

Hexane, 1,6-diisocyanato- (CA-Index name)

Flag : Critical study for SIDS endpoint

Hexylendiisocyanat

Flag : Critical study for SIDS endpoint

1.3 IMPURITIES

Purity :
CAS-No :
EC-No :
EINECS-Name :
Molecular formula :
Value : < .5 % w/w

Remark : contained solvent residues and a minor volume of 6-chloro-1-iso-cyanatohexane
Flag : Critical study for SIDS endpoint
04.06.1998

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 10000 - 50000 tonnes produced in 1993

Flag : Critical study for SIDS endpoint
23.11.2000

Quantity : 10000 - 50000 tonnes produced in 1997

Flag : Critical study for SIDS endpoint
23.11.2000

Quantity : 10000 - 50000 tonnes produced in 2000

Flag : Critical study for SIDS endpoint
23.11.2000

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :
Symbols : T, , ,
Nota : , ,
R-Phrases : (23) Toxic by inhalation
(36/37/38) Irritating to eyes, respiratory sys tem and skin
(42/43) May cause sensitization by inhalation and skin contact
S-Phrases : (26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(28) After contact with skin, wash immediately with plenty of plenty of water and soap
(38) In case of insufficient ventilation, wear suitable respiratory equipment
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)

Flag : Critical study for SIDS endpoint
29.03.2001

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : toxic
R-Phrases : (23) Toxic by inhalation
(36/37/38) Irritating to eyes, respiratory system and skin
(42/43) May cause sensitization by inhalation and skin contact
Specific limits :

Flag : Critical study for SIDS endpoint

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Non dispersive use

Flag : Critical study for SIDS endpoint
23.06.1998

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

Flag : Critical study for SIDS endpoint

Type of use : use

Category : Intermediates

Flag : Critical study for SIDS endpoint

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : other: MAK (TRGS 900, DE)
Limit value : .005 ml/m3
Short term exposure limit value
Limit value : .005 ml/m3
Time schedule : 15 minute(s)
Frequency : times

Remark : Limit value: 0.005 ml/m3 = 0.035 mg/m3
Flag : Critical study for SIDS endpoint
28.02.2001 (1)

Type of limit : other: TLV-TWA (ACGIH, US)
Limit value : .005 ml/m3

Remark : A short term exposure limit value is not established.
Flag : Critical study for SIDS endpoint
28.02.2001 (2)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : other: Bayer AG, self classification
Labelled by :
Class of danger : 1 (weakly water polluting)

Flag : Critical study for SIDS endpoint
16.01.2001

1.8.4 MAJOR ACCIDENT HAZARDS

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

Remark : genannt in Anhang II Nr. 4c; III Teil 2 - Kat. 2; IV Kat. 2 (giftige Stoffe)
Flag : Critical study for SIDS endpoint
23.06.1998

1.8.5 AIR POLLUTION

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

Flag : Critical study for SIDS endpoint

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered :
Date of search :

Remark : 09/1999
Flag : Critical study for SIDS endpoint
23.11.2000

1.13 REVIEWS

Memo : BUA Report No. 112 (Hexamethylenediisocyanate), VCH, April 1993

Flag : Critical study for SIDS endpoint
23.11.2000

Memo : OECD SIDS "Hexamethylenediamine" (Canada, 1995)

Flag : Critical study for SIDS endpoint
23.11.2000

Memo : IUCLID Dataset "Hexamethylenediamine" (ECB 2000)

Flag : Critical study for SIDS endpoint
23.11.2000

2.1 MELTING POINT

Value : = -67 °C
Decomposition : yes, at °C

Flag : Critical study for SIDS endpoint
27.03.2001 (3)

2.2 BOILING POINT

Value : = 255 °C at 1013 hPa

Flag : Critical study for SIDS endpoint
23.11.2000 (4)

2.3 DENSITY

Type : density
Value : = 1.04 g/cm³ at 20 °C

Flag : Critical study for SIDS endpoint
23.11.2000 (4)

Type : density
Value : = 1.05 g/cm³ at 25 °C
Method : other: DIN 53217/2
Year :
GLP :
Test substance :

Flag : Critical study for SIDS endpoint
29.03.2001 (3)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .007 hPa at 20 °C

Flag : Critical study for SIDS endpoint
23.11.2000 (5) (6)

2.5 PARTITION COEFFICIENT

Remark : not determinable (hydrolysis)
Flag : Critical study for SIDS endpoint

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Remark	:	not determinable (hydroylsis)
Flag	:	Critical study for SIDS endpoint

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 130 °C
Type	:	
Method	:	other: DIN 51758
Year	:	
GLP	:	
Test substance	:	
Flag	:	Critical study for SIDS endpoint

23.11.2000 (7) (8) (6)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

Result	:	other: Ignition temperature: ca. 460 °C
Method	:	other: DIN 51794
Year	:	
GLP	:	
Test substance	:	
Flag	:	Critical study for SIDS endpoint

27.03.2001 (3)

2.10 EXPLOSIVE PROPERTIES

Remark	:	explosive limits: lower: 0.9 % by vol. upper: 9.5 % by vol.
Flag	:	Critical study for SIDS endpoint

23.11.2000 (3)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	other: air, indirect photolysis
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (calculated): according to Atkinson (AOPWIN 1994)
Year	:	
GLP	:	
Test substance	:	
Remark	:	calculated half-life is based on a mean OH radical concentration of 5*10E5 molecule/cm3, 12-h day under the conditions of Western Europe
Result	:	Calculation half life: t1/2 = 48.4 h k(OH): 7.95 E-12 cm3/molecule*s
Reliability	:	(1) valid without restriction accepted calculation method
Flag	:	Critical study for SIDS endpoint

29.03.2001 (9)

Type	:	other: stability in air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Remark	:	Besides indirect photolysis, HDI in air will also be affected by air humidity. HDI is hydrolyzed to hexamethylenediamine (see also 3.8)
Flag	:	Critical study for SIDS endpoint

27.03.2001

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	other
Year	:	
GLP	:	
Test substance	:	
Result	:	Hydrolysis of HDI at different temperatures and concentrations:

Water temperature (degree C)	HDI initial conc. (mg/l)	reaction period (min.)	reduction of HDI (%)
20	200	5	50
20	200	30	90
20	2	10	50

	20	2	50	90
	4	200	25	50
	4	200	120	90

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
27.03.2001 (10)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

Remark : Due to the rapid hydrolysis (see 3.1.2) an occurence of HDI in the environment is not to be expected.
Flag : Critical study for SIDS endpoint
27.03.2001

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Remark : Because of reaction with water, Henry 's constant is not determinable
Flag : Critical study for SIDS endpoint
23.11.2000

3.3.2 DISTRIBUTION

Remark : not determinable (hydrolysis)
Flag : Critical study for SIDS endpoint
27.03.2001

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : 100 mg/l related to Test substance related to
Contact time :
Degradation : 42 (±) % after 28 day(s)
Result :
Deg. product :
Method : other: Biodegradability - Manometric Respiratory Test Method according to Council Directive 92/69 EEC Method C.4-D
Year : 2000
GLP : yes
Test substance : other TS: 99.5 %

Remark : Inoculum: 30 mg ss/l. Test substance was added by direct weighing. Test substance hydrolyzes (see also 3.8)
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
27.03.2001 (11)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Remark : not determinable (hydrolysis)
Flag : Critical study for SIDS endpoint
27.03.2001

3.8 ADDITIONAL REMARKS

Remark : Several tests on biodegradation and ecotoxicological effects have been conducted with, as it seems, contradictory or at least inconsistent results. The following will give support for understanding and assessing test results.
Fact is, as Sopac & Boltromejuk /1974) have reported in detail, that three main findings determin the results:

1. HDI is not soluble in the low mg/l range in water without another solvent. It forms oily droplets in water.
2. The diisocyanate ends of HDI react with water forming the amine and CO2.
3. The diisocyanate ends of HDI can also react with an amin end of an already hydrolysed (former HDI-) molecule, forming oligo- and than polyurea.

Depending on the use of a solvent or not, the size of the drops when direct weight is used, and the speed of a magnetic stirrer or of ultrasonic if used, determin the quantitative proportion of the hydrolysation products HDA and Polyurea.
The problems with tests on HDI is the inhomogeneous distribution of the substance in the test medium water because of forming droplets. With these droplets a "real" concentration of HDI in water is neither analytically determinable nor can a reproducible und thus reliable exposure concentration for test individuums be fixed.
The pure substance HDI, as it is in the droplets, showed to be lethal to the aquatic species. The acute toxicity of HDA has to be classified only as harmful and polyureas are, because of their molecular size, not bioavailable.
Flag : Critical study for SIDS endpoint
29.03.2001

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	>= 82.8
Limit test	:	
Analytical monitoring	:	no
Method	:	other: "Acute Toxicity for Fish" Council Directive 92/69/EEC C.1 (1992)
Year	:	2000
GLP	:	yes
Test substance	:	other TS: 99.5 %
Remark	:	Because of the rapid hydrolysis a water accommodated fraction (WAF) was prepared by direct weighing of 100 mg/l HDI into water. The test preparation was first stirred with an Ultra turrax for 60 sec/8000 rpm, then stirred for 24 hours with a magnetic stirrer and finally filtered. The resulting solution was analyzed to its TOC content and was the only test concentration used. The test concentration obtained by this WAF method was dete rmined to be 82.8 mg/l.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

27.03.2001 (11)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC0	:	>= 89.1
Analytical monitoring	:	no
Method	:	other: "Acute Toxicity for Daphnia" Council Directive 92/69/EEC C.2 (1992)
Year	:	2000
GLP	:	yes
Test substance	:	other TS: 99.5 %
Remark	:	Because of the rapid hydrolysis a water accommodated fraction (WAF) was prepared by direct weighing of 120 mg/l HDI into water. The test preparation was first stirred with an Ultra turrax for 60 sec/8000 rpm, then stirred for 24 hours with a magnetic stirrer and finally filtered. The resulting solution was analyzed to its TOC content and was the only test concentration used. The test concentration obtained by this WAF method was determined to be 89.1 mg/l.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

27.03.2001 (11)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)

Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
EC50	:	> 77.4
Limit test	:	
Analytical monitoring	:	no
Method	:	other: "Algal growth inhibition test" Council Directive 92/69/EEC C.3 (1992)
Year	:	2000
GLP	:	yes
Test substance	:	other TS: 99.5 %
Remark	:	Because of the rapid hydrolysis a water accommodated fraction (WAF) was prepared by direct weighing of 125 mg/l HDI into water. The test preparation was first stirred with an Ultra turrax for 60 sec/8000 rpm, then stirred for 24 hours with a magnetic stirrer and finally filtered. The resulting solution was analyzed to its TOC content and was used as a stock solution for further dilution steps. The arithmetic mean of the analytical values showed 72 h-EC50 values for the growth rate as well as biomass to be > 77.4 mg/l. With the Dunett test the 72 h-NOEC and 72 h-LOEC for the growth rate was estimated to be 11.7 mg/l and 12.6 mg/l resp.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

27.03.2001 (11)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	activated sludge
Exposure period	:	3 hour(s)
Unit	:	mg/l
EC50	:	842
Analytical monitoring	:	no
Method	:	other: Commission Directive 88/302/EEC; Official Journal of the EC L 133, Part C: Biodegradability: Test for inhibition of oxygen consumption
Year	:	2000
GLP	:	yes
Test substance	:	other TS: 99.5 %
Remark	:	Because of the rapid hydrolysis the test substance was added to water in different weights, treated 3-4 hours by ultrasound and stirred overnight before testing. The test vessel with 1000 mg/l direct weight resulted in a 3 h-EC36. The 3 h-EC50 estimated by Probit analysis gave a value of 842 mg/l.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

27.03.2001 (11)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 746 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	other: undiluted
Doses	:	
Method	:	other: 4 dose levels; 14 day oberservation period
Year	:	1964
GLP	:	no
Test substance	:	other TS: no further information
Remark	:	NO. OF ANIMALS: 5/dose ORIGINAL VALUE: 0.71 ml/kg (density: approx. 1.05 g/cm3 at 25 oC) MORTALITY: 5/5 (2 ml/kg); 5/5 (1 ml/kg); all deaths occurred within 4 hours after application; no deaths after 0.5 and 0.25 ml/kg CLINICAL SIGNS: soon after dosing all animals appeared to be extremly sluggish BODY WEIGHT: 9/10 gained weight during the observation period GROSS EXAMINATION: congestion throughout the abdominal viscera
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

23.10.2000 (12) (13)

Type	:	LD50
Value	:	= 959 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	other: oil
Doses	:	
Method	:	other: 7 dose levels; 14 days oberservation period
Year	:	1970
GLP	:	no
Test substance	:	other TS: chemical pure Desmodur H
Remark	:	NO. OF ANIMALS: 15/dose ORIGINAL VALUE: 0.913 ml/kg (density: approx. 1.05 g/cm3 at 25 oC) MORTALITY: 15/15 (2 ml/kg); 14/15 (1.5 ml/kg);11/15 (1 m l/kg); 5/15 (0.75 ml/kg); all deaths occurred within the 1 day; no deaths after 0.5; 0.25 and 0.1 ml/kg CLINICAL SIGNS: soon (30 minutes - 2 hours after) after dosing all animals appeared to be extremly sluggish; duration of clinical signs: max. 7 days BOD Y WEIGHT: no data

GROSS EXAMINATION: no data

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
23.10.2000 (14)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	.124 mg/l
Species	:	rat
Strain	:	
Sex	:	male/female
Number of animals	:	
Vehicle	:	other: no
Doses	:	
Exposure time	:	4 hour(s)
Method	:	OECD Guide-line 403 "Acute Inhalation Toxicity"
Year	:	1997
GLP	:	yes
Test substance	:	other TS: purity: 99.5 %
Remark	:	Nose-only exposure to vapour NO. OF ANIMALS: 5/concentration/sex Analytical monitoring of the vapour test atmosphere CONCENTRATIONS: 0.055, 0.107, 0.120 or 0.151 mg/l confidence interval (95%) = 0.111-0.140 mg/l No gender specific susceptibility, therefore, males and females were evaluated together for the LC50-calculation
Result	:	Concentration-dependent signs indicative for respiratory tract irritation (maximum duration up to day 28); gross necropsy revealed less collapses, dark-red lungs with serous mucus in trachea, lung associated lymph nodes were enlarged NO(A)EL: < 0.055 mg/l
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

23.10.2000 (15)

Type	:	other: sensory irritation study
Value	:	
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	.5 hour(s)
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	
Remark	:	Concentrations between 0.00077 - 0.039 mg/l caused within the first five minutes an inhibition of respiration in the sensory irritation study; afterwards tolerance was developed The RD50 (50 % inhibition of respiration) was 0.00993 mg/l
Reliability	:	(2) valid with restrictions

Flag	:	Critical study for SIDS endpoint
23.10.2000		(16)
Type	:	other: sensory irritation study
Value	:	
Species	:	rat
Strain	:	
Sex	:	female
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	3 hour(s)
Method	:	
Year	:	
GLP	:	yes
Test substance	:	other TS: purtiy: 100 %
Result	:	The RD50 for the last hour of a 3-hour exposure was 1.69 ppm (0.0118 mg/l); the no-observable-effect-level was >= 0.10 ppm (0.0007 mg/l)
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint
09.04.2001		(17)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	= 599 mg/kg bw
Species	:	rabbit
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: 24-hour skin contact (occlusive); 14-day observation period
Year	:	1964
GLP	:	no
Test substance	:	other TS: no further information
Remark	:	NO. OF ANIMALS: 4/dose ORIGINAL VALUE: 0.566 ml/kg (density: approx. 1.05 g/cm3 at 25 oC) MORTALITY: 3/4 (0.80 ml/kg); 1/4 (0.4 ml/kg); all deaths occurred within 24 hours after application CLINICAL SIGNS: no data LOCAL EFFECTS: no data BODY WEIGHT: 3 of the survivors lost weight or gained at a subnormal rate
Reliability	:	(2) valid with res trictions
Flag	:	Critical study for SIDS endpoint
23.10.2000		(12) (13)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	
Exposure	:	Occlusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	corrosive
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	
GLP	:	no
Test substance	:	no data
Remark	:	CONCENTRATION: undiluted 4 hours after patch removal: 6/6 showed an erythema (grade 4) and oedemda (grade 4); 24 hours after patch removal: 6/6 showed induration and necrois of the application site; irreversible within 8 days
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

09.05.2001 (18)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	100 other: ul
Exposure time	:	.5 minute(s)
Comment	:	other: rinsing of the eyes
Number of animals	:	6
Vehicle	:	
Result	:	corrosive
Classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	
GLP	:	no
Test substance	:	no data
Remark	:	CONCENTRATION: undiluted 1 hour to 8 days after instillation corneal opacity, irritation of the iris, conjunctival redness and chemosis were observed in all animals; examination of the eyes was difficult due to swelling
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

09.05.2001 (18)

5.3 SENSITIZATION

Type	:	Buehler Test
Species	:	guinea pig
Number of animals	:	20

Vehicle	:	no data
Result	:	sensitizing
Classification	:	
Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1996
GLP	:	no data
Test substance	:	no data
Remark	:	induction: 10 % challenge: 1 % positive allergic reaction: 100 %
Flag	:	Critical study for SIDS endpoint

09.04.2001 (19)

Type	:	Buehler Test
Species	:	guinea pig
Number of animals	:	20
Vehicle	:	petrolatum
Result	:	sensitizing
Classification	:	
Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1998
GLP	:	no data
Test substance	:	other TS: purity 99.0 %
Remark	:	induction: 1 % challenge: 0.1 % positive allergic reaction: 14/20
Flag	:	Critical study for SIDS endpoint

09.04.2001 (20)

Type	:	Guinea pig maximization test
Species	:	guinea pig
Number of animals	:	20
Vehicle	:	other: soy bean oil or a mixture of soy bean oil / 2-butanone 1:2
Result	:	sensitizing
Classification	:	
Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1981
GLP	:	no data
Test substance	:	no data
Remark	:	induction: 1 % i.d., 10 % top challenge: 0.3 % positive allergic reaction: 18/20
Flag	:	Critical study for SIDS endpoint

09.04.2001 (21)

Type	:	Guinea pig maximization test
Species	:	guinea pig
Number of animals	:	17
Vehicle	:	petrolatum
Result	:	sensitizing
Classification	:	
Method	:	other
Year	:	1983
GLP	:	no
Test substance	:	other TS: purity 99 %

Remark : induction: 10 % i.d., undiluted i.d.
challenge: 1 % and 0.3 %
positive allergic reaction: 16/17
Flag : Critical study for SIDS endpoint
09.04.2001 (22)

Type : Mouse ear swelling test
Species : mouse
Number of animals : 10
Vehicle : other: acetone
Result : sensitizing
Classification :
Method : other
Year : 1986
GLP : no data
Test substance : no data

Remark : induction: 5 %
challenge: 0.5 %
positive reaction: 67 %
Flag : Critical study for SIDS endpoint
09.04.2001 (23)

Type : Mouse ear swelling test
Species : mouse
Number of animals : 6
Vehicle : other: acetone
Result : sensitizing
Classification :
Method : other
Year : 1996
GLP : no data
Test substance : no data

Remark : induction: 0.03 - 250 ug
challenge: 100 ug HDI
Flag : Critical study for SIDS endpoint
09.04.2001 (24)

Type : Mouse ear swelling test
Species : mouse
Number of animals :
Vehicle : other: acetone
Result : sensitizing
Classification :
Method : other
Year : 1987
GLP : no data
Test substance : other TS: purity > 98 %

Remark : NUMBER OF ANIMALS: 4-5
Flag : Critical study for SIDS endpoint
09.04.2001 (25)

Type : Mouse local lymphnode assay
Species : mouse
Number of animals : 4

Vehicle :
Result : sensitizing
Classification :
Method :
Year :
GLP : no data
Test substance :

Remark : Vehicle: acetone: olive oil (4:1)
Flag : Critical study for SIDS endpoint
23.10.2000 (26)

Type : Patch-Test
Species : human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year :
GLP : no data
Test substance :

Remark : Positive reaction in an occupationally exposed worker who suffered from contact dermatitis and had respiratory symptoms
Test substance : 1 % HDI solved in petrolatum
Flag : Critical study for SIDS endpoint
23.10.2000 (27)

Type : Patch-Test
Species : human
Number of animals :
Vehicle :
Result :
Classification :
Method : other
Year :
GLP : no data
Test substance :

Remark : 6/6 workers that suffered from occupational contact dermatitis reacted positive, while all of the 20 control patients were negative
Test substance : 99 % pure HDI was diluted to 1 % in petrolatum
Flag : Critical study for SIDS endpoint
(28) (29)

Type : Patch-Test
Species : human

Remark : 0/92 emoloyers in a Swedish aircraft plant with present or previous skin desease was reported to be positive with HDI
Flag : Critical study for SIDS endpoint
21.10.1998 (30)

Type : other
Species : human

Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	

Remark : Standard skin prick testing in healthy workers; none of the 20 tested workers reacted positive
Test substance : Albumin conjugated HDI
Flag : Critical study for SIDS endpoint

(31)

Type	:	other
Species	:	human
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	

Remark : Standard skin prick test in five healthy - sporadically to isocyanates exposed - volunteers; none reacted positive
Test substance : Conjugated HDI, prepolymeric HDI (Desmodur)
Flag : Critical study for SIDS endpoint

(32)

Type	:	other: Lung Sensitization
Species	:	guinea pig
Number of animals	:	
Vehicle	:	other: see remark
Result	:	
Classification	:	
Method	:	other: see remark
Year	:	
GLP	:	yes
Test substance	:	other TS: purity: 99.5 %

Remark : VEHICLE: Vapor exposure
METHOD: A standard approach was used that included either three intradermal injections (one per day) or 5x3 hrs inhalation exposures, including one additional intradermal injection, followed by inhalation challenge with the hapten, acetylcholine and conjugate by inhalation.
Result : The study provides clear evidence that HDI is a respiratory sensitizer in the guinea pig bioassay. These findings lend support the conclusion that succesful induction and elicitation of allergic respiratory hypersensitivity can be achieved either by intradermal and by inhalation induction exposure.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
25.10.2000

(33)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	3 hours daily
Frequency of treatm.	:	5 consecutive days followed by 2 non-exposure days, a sixth day of exposure
Post exposure period	:	4 days
Doses	:	1.17 ppm (0.0081 mg/l)
Contrd group	:	
Method	:	
Year	:	
GLP	:	yes
Test substance	:	other TS: purity: 100 %
Result	:	A cumulative effect on baseline respiratory rate was observed with no change in the extent of the respiratory response during exposure
Reliability	:	(2) valid w ith restrictions
Flag	:	Critical study for SIDS endpoint

09.05.2001 (34)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	other: head only vapor inhalation
Exposure period	:	3 weeks
Frequency of treatm.	:	5 h/d, 5 d/week
Post exposure period	:	2 weeks
Doses	:	0, 0.0048, 0.0175, 0.1500 and 0.300 ppm (analytically confirmed overall mean HDI concentrations)
Control group	:	yes, concurrent no treatment
NOAEL	:	= .005 ppm
LOAEL	:	= .0175 ppm
Method	:	other: see remark
Year	:	1984
GLP	:	yes
Test substance	:	other TS: purity 99,83 %
Remark	:	METHOD: other: 10 animals/sex/level; animals of each test level were split into two groups; animals of group 1 were sacrificed after the last exposure, and animals of group 2 were allowed to recover for 13 days and then sacrificed for gross necropsy and tissue collection NOMINAL CONCENTRATIONS: 0, 0.005, 0.020, 0.200 and 0.300 ppm (nominal concentrations) DEVITATION IN THE EXPOSURE REGIMEN: Originally only three exposure concentration levels were planned. Since microscopic pathological changes at the highest level were not clear,a fourth exposure level of 0.3 ppm was added. No controls wer used for 0.3 ppm. The objective of this test level was to study the microscopic pathological changes of the respiratory system at a concentration where a definite effect is seen.

MICROSCOPIC CHANGES: The changes described above appeared to occur in a dose-related manner in the nasal cavity only. The incidence of changes in the larynx and trachea was increased in exposed groups, but severity of the changes did not increase with concentration. A consultant pathologist who reviewed the slides of the nasal cavity characterized the changes primarily as inflammatory and concluded that only 0.15 and 0.3 ppm were effect levels

Result : 0.300 ppm: no mortality; severe irritation of eyes and noses during exposure and at one hour post-exposure; no effect on body weights, no biologically significant effects on hematology, blood chemistry and urinalyses; decrease in the liver and kidney absolute and relative weights (females); decrease in the relative and absolute kidney weights (males); in the recovery group only relative and absolute weights in female livers, relative kidney weights in females and relative liver weights in males; no gross lesions
MICROSCOPIC CHANGES: hemorrhage, inflammatory exudate and epithelial changes in the nasal cavity (80 to 90% of the animals were affected with moderate severity); focal accumulations of mixed inflammatory cells in submucosa and a minimal to mild hyperplasia of the epithelium in the larynx and trachea; no recovery in males
0.1500 ppm: no mortality; severe irritation of eyes and noses during exposure and at one hour post-exposure; no effect on body weights; no biologically significant effects on hematology, blood chemistry and urinalyses; no effects organ weights; no gross lesions
MICROSCOPIC CHANGES: hemorrhage, inflammatory exudate and epithelial changes in the nasal cavity (50 to 70% of the animals were affected with moderate severity) ; focal accumulations of mixed inflammatory cells in submucosa and a minimal to mild hyperplasia of the epithelium in the larynx and trachea; recovery is suggested
0.0175 ppm: no mortality; irritation of eyes and noses during exposure and at one hour post-exposure; no effect on body weights; no biologically significant effects on hematology, blood chemistry and urinalyses; no effects on organ weights; no gross lesions
MICROSCOPIC CHANGES: the changes in the nasal cavity were minimal to mild in severity, and were similar to the control even though the incidence was slightly higher; recovery is suggested.
0.005 ppm: no mortality; irritation of eyes and noses during exposure and at one hour post-exposure; no effect on body weights; no biologically significant effects on hematology, blood chemistry and urinalyses; no effects on organ weights; no gross lesions
MICROSCOPIC CHANGES: the changes in the nasal cavity were minimal to mild in severity, and were similar to the control.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.04.2001 (35)

Type :
Species : rat
Sex : male/female
Strain : Fischer 344

Route of admin.	:	other: vapor inhalation
Exposure period	:	approx. 13 weeks
Frequency of treatm.	:	6 h/day, 5 d/week
Post exposure period	:	no
Doses	:	0, 0.01, 0.04 and 0.14 ppm (analytically confirmed overall mean HDI concentrations)
Control group	:	yes, concurrent no treatment
LOAEL	:	= .01 ppm
Method	:	OECD Guide-line 413 "Subchronic Inhalation Toxicity: 90-day Study"
Year	:	1988
GLP	:	yes
Test substance	:	other TS: purity 99,83 %
Remark	:	NOMINAL CONCENTRATIONS: 0, 0.01, 0.04, and 0.16 ppm DEVIATION IN THE EXPOSURE REGIMEN: The variation in the number of exposure days (66 to 69) was a result of different rats beeing sacrificed over a period of four days. During this last week allrats not removed fo r necrospy were still exposed. CLINICAL SIGNS: rhinorrhea and ocular opacity were not considered to be compound related HISTOPATHOLOGIC LESIONS: hyperplasie and/or squamous metaplasia of the respiratory epithelium; keratin was often present covering the metaplastic epithelium in the mid- and high-dose rats; mucous cell hyperplasia predominantly of respiratory epithelium and inflammatory cell infiltrate principally within subepithelial tissues
Result	:	0.14 ppm: no mortality; ocular irritation (includes lacrimation); no effects on body weights, on clinical chemistry, hematology, urinalyses; gross pathology and organ to body weight ratios; histopathological lesions in the cranial nasal cavity anterior to the nasal papilla of both sexes (for details see the remark field) 0.04 ppm: no mortality; ocular irritation (includes lacrimation); no effects on body weights, on clinical chemistry, hematology, urinalyses; gross pathology and organ to body weight ratios. histopathological lesions in the cranial nasal cavity anterior to the nasal papilla of both sexes (for details see the remark field) 0.01 ppm: no mortality; ocular irritation (includes lacrimation); no effects on body weights, on clinical chemistry, hematology, urinalyses; gross pathology and organ to body weight ratios; histopathological lesions in the cranial nasal cavity anterior to the nasal papilla of both sexes (for details see the remark field); the lesions were minor and were seen in only a few animals
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

25.10.2000 (36)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	other: whole body vapor inhalation
Exposure period	:	2 years
Frequency of treatm.	:	6 h/day, 5 d/week
Post exposure period	:	
Doses	:	0, 0.005, 0.025 and 0.175 ppm (nominal concentrations)

Control group	:	yes, concurrent no treatment
NOAEL	:	= .005 ppm
Method	:	other: OECD Guide-line 453
Year	:	1989
GLP	:	yes
Test substance	:	other TS: purity 99,83 %

Remark :

Analytically confirmed overall mean HDI
CONCENTRATIONS: 0, 0.005, 0.025, and 0.164 ppm
EXPOSURE REGIMEN: Seperate groups of 10 rats/sex/level were exposed under the same exposure regime for one year (satellite group)
EXPERIMENTAL DESIGN: the exposure was conducted under dynamic conditions, the air control animals were sham-exposed (conditioned room air) under comparable conditions
HISTOPATHOLOGY: emphasis was placed on the standardization of trimming procedures of the nasal cavity; removal of mandible, tongue and associated structures, coronal nasal sections were made from the followingareas:
Level I vestibule
Level II posterior to incisor teeth
Level III prepapilla
Level IV incisive papilla
Level V first palatal ridge
Level VI second palatal ridge
Level VII first molar teeth (second molar tetth in satellite animals)
HISTOPATHOLOGIC LESIONS:
Nasal cavity:
Level I: There was increased incidence of epithelial hyperplasia or thickening with hyperkeratosis and erosion at 0.175 ppm. Septal epithelial thickness did not statistically differ between control and exposed males. In females, hyperkeratosis of the epithelium was increased in all exposed groups while epithelial hyperplasia was more frequent in 0.005 ppm and 0.025 ppm exposed groups. There was a statistically significant difference in septal epithelial thickness between control and 0.005 ppm and 0.025 ppm (but not 0.175 ppm) exposed females in the nasal vestibule.
Level II: There was prominent, minmal to mild, hyperkeratosis and erosion in both sexes exposed to 0.175 ppm of HDI. In 0.175 ppm males, the erosion was often more severe leading to ulceration. Females receiving 0.025 ppm also demonstrated increased hyperkeratosis. Squamous metaplasia genrally affecting the turbinate tips, septum, and lateral walls was extensive in 0.175 ppm rats while a combination of epithelial hyperplasia/metaplasia or mucus secretory cell hyperplasia was most prevalent in 0.005 ppm and 0.025 ppm rats o f both sexes. Inflammatin was observed in 0.025 ppm and 0.175 ppm male and female rats an was slightly more severe in the 0.175 ppm exposure groups. Thickness of the epithelium (regardless of morphologic type) covering the nasal septum, dorsal and ventral turbinates and lateral walls was statistically different from controls at all exposure levels in females and at the 0.025 ppm and 0.175 ppm levels in males.
Level III: There was decreased squamous metaplasia

(compared hyperplasia/metaplasia in 0.175 ppm rats. Epithelial hyperplasia without metaplastic change was notably increased in 0.025 ppm and 0.175 ppm males and 0.025 ppm females. Hyperkeratosis was present in some 0.175 ppm rats of both sexes. Mucus secretory cell hyperplasia was increased at all exposure levels in both sexes. At this third section, hyaline droplet degeneration of epithelium along the dorsal septum and dorsal meatus was prominent in 0.005 ppm and 0.025 ppm females as wll as 0.025 ppm males. Non-specific inflammation was observed in groups exposed to 0.025 ppm and 0.175 ppm. Epithelial erosion or ulceration was present in a few animals particularly at 0.1175 ppm.

Level IV: Hyaline droplet degeneration was seen in both sexes with increased incidence in all exposed groups as compared to controls, but this change was more prevalent and was graded more extensively in groups exposed to 0.025 ppm. There was notable olfactory epithelium degeneration in 0.175 ppm males and females with narrowing or atrophy and occasional focal erosion or ulceration. Epithelial hyperplasia of 0.025 ppm females and mucus secretroy cell hyperplasia of all exposure groups in males and females were present. Inflammation was observed in 0.025 ppm abd 0.175 ppm males and females.

Level V/VI: In controls, there wæs considerable minimal to mild background levels of epithelial cell mucus and hyaline droplet, degeneration particularly along the nasal turbinate scrolls, adjacent to the septum and pharyngeal duct. There was increased amounts of muscus and hyaline material after exposure to all concentration of HDI as compared with controls. Epithelial hyperplasia, usually along the septum, was seen in 0.025 ppm females while dorsal septal erosion, often associated with metaplastic change to a squamous epithelium, was seen in 0.175 ppm males. Degeneration of the olfactory epithelium was prominent in the 0.175 ppm exposure group of both sexes. Inflammation was observed in 0.025 ppm and 0.175 ppm males and females.

Level VII: Epithelial changes were similar to those of the previous two sections and only prominent changes were noted in addition to those observations. Thus the obersevations were less frequent and principal lesions consisted of degeneration of the dorsal olfactory epithelium of the ethmoid turbinates in 0.175 ppm males and hyaline droplet degereration in 0.005 ppm females.

Lungs:

There were generally minimal to mild, focal to multifocal lesions coded as epithelialization (alveolar lining cell proliferatin), interstitial pneumonia (septal thickening, alveolar cellular content and increased alveolar lining cell prominence), or alveolar macrophage accumulation (histiocyte cells in alveolar space). When considered individually or combined there was an exposure-related incidence of these lesions in rats of both sexes exposed to 0.025 ppm or 0.175 ppm of HDI.

SATELLITE OBSERVATIONS: no statistically significant terminal body weight differences between control and exposed rats of either sex in the satellite group. Nonneoplastic or neoplastic lesions were similar but less developed than those in terminal sacrifice animals; there was no early dose-related onset of neoplastic gross tissue changes;

		lesions were restricted to histopathologic alteration of nasal mucosa; after one year 0.005 ppm is considered to be a NOEL since the changes observed occurred only in one sex, were qualitatively similar to those seen in controls and did not show any concentration-dependent increase in degree.
Result	:	0.005 ppm: no effect on mortality rate; ocular irritation (includes lacrimation); no effects on body weights, on clinical chemistry, hematology, urinalyses; gross pathology and no significant effects on organ weights; histopathological lesions in the nasal cavity; no associated exposure-related lesions were observed in the trachea, larynx or nasal lacrimal duct (for details see the remark field) 0.025 ppm: no effect on mortality rate; ocular irritation (includes lacrimation); no effects on body weights, on clinical chemistry, hematology, urinalyses; gross pathology and no significant effects on organ weights; histopathological lesions in the nasal cavity and lungs; no associated exposure-related lesions were observed in the trachea, larynx or nasal lacrimal duct (for details see the remark field) 0.175 ppm: no effect on mortality rate;transient ocular irritation in males; no lesions of the eye detected by ophthalmoscopic examination; slight body weight decrease in females during the second year of exposure; hematologic effects in females (associated with slight anemia); no effects on dinical chemistry, urinalyses; gross pathology and no significant effects on organ weights; histopathological lesions in the nasal cavity and lungs; no associated exposure-related lesions were observed in the trachea, larynx or nasal lacrimal duct (for details see the remark field)
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
13.12.2001		(37) (38)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	other: whole body vapor inhalation
Exposure period	:	male: 28 days; female: 50 days
Frequency of treatm.	:	6 hours/day; 7 days/week
Post exposure period	:	4 days (female)
Doses	:	0, 0.005, 0.050 or 0.300 ppm (nominal concentrations)
Control group	:	yes, concurrent no treatment
NOAEL	:	.005 ppm
LOAEL	:	.05 ppm
Method	:	other: OECD Guide-line 422
Year	:	1999
GLP	:	yes
Test substance	:	other TS: purity: 99,7% -99.6%
Remark	:	Analytically confirmed overall (for the entire study) mean HDI CONCENTRATIONS: 0.005, 0.053 and 0.299 ppm EXPOSURE PERIOD: during a 4-day lactation phase the exposure to HDI was also discontinued for the dams. Deviation in the exposure regimen of the females: some of

		the females were exposed through gestation day 19, otherswere exposed through gestation day 18 only, and others were exposed through gestation day 18 and again on gestation day 20. In order to assess the impact of the deviation on the study the tissues from the respiratory tract of all females were examined microscopically. The results of these examinations did not indicate any differences between the females differentially exposed
Result	:	0.300 ppm: microscopic effects in the nasal cavity of both sexes (epithelial hyperplasia, squamous metaplasia, chronic-active inflammation, degeneration of the olfactory epithelium); no effects on hematology, clinical chemistry, organ weights and neurologic parameters 0.050 ppm: similar microscopic effects, albeit to a lesser extent than in the 0.300 ppm exposure group; no effects on hematology, clinical chemistry, organ weights and neurologic parameters 0.005 ppm: No histopathological findings; no effects on hematology, clinical chemistry, organ weights and neurologic parameters For clinical signs and body weight in parental animals (NOAEL Parental) and pups (NOAEL F1 Offspring) see chapter 5.8 ("Toxicity to Reproduction)
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

25.10.2000 (39) (40)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	S. typhimurium TA 100, TA 1537 and TA 98
Test concentration	:	no data
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: without modifications as described by Ames, B.N. et al., Mutat. Res. 31, 347-364 (1975)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: purity: synthetic grade from Merck-Schuchardt dissolved in DMSO
Remark	:	METABOLIC ACTIVATION: liver microsome fraction S-9 mix from rats receiving 0.1% sodium phenobarbital in the drinking water one week before they were killed METHOD: plates containing the same dose and compound were placed in polyethylene bags which were sealed
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

26.10.2000 (41)

Type	:	Bacterial reverse mutation assay
System of testing	:	S. typhimurium TA 98, TA 100, TA 1535 and TA 1537
Test concentration	:	6, 12, 20, 25, 50 and 150 uL per desiccator
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative

Method	:	other: see remark field
Year	:	1998
GLP	:	yes
Test substance	:	other TS: purity: 99.5. %
Remark	:	METABOLIC ACTIVATION: Aroclor 1254-induced male rat liver S9 was used. METHOD: The test system was exposed to the test substance via the desiccator methodology, a modification of the plate incorporation methodology originally described by Ames et al., Mutat. Res. 31, 347-364 (1975) and updated by Maron and Ames, Mutat. Res. 113, 173-215 (1983). The desiccator methodology has been shown to be an effective method for detecting the genotoxic activity of volatile and gaseous test substances (Wagner et al., Environ. Mol. Mutagen. 19, 68 (1992)). Deviation from the original study protocol: The independent repeat assay was not performed because technical difficulties in dosing the test article using the desiccator methodology make further testing unwarranted. The test article exposure was reduced to approx. 8 hours. After this exposure period, the plates were removed from the desiccator and incubated with the lids replaced such that the total incubation time was approx. 48 to 72 hours RESULT: No precipitate was observed but toxicity generally observed at >= 6uL per desiccator, with non-uniform toxicity over at least 25% of the surface of each affected plate. Th enon-uniform toxicity did not appear to be a function of the location or orientation of the plates in the desiccators. The non-uniform toxicitx profile appears to be unique to HDI. In addition, no mutagenic activity was observed in locations on the plates where the background lawns were nontoxic (normal).
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

02.11.2000 (42) (43)

Type	:	HGPRT assay
System of testing	:	CHO cells
Test concentration	:	see remark field
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: see remark field
Year	:	1998
GLP	:	yes
Test substance	:	other TS: purity: 99.5 %
Remark	:	METABOLIC ACTIVATION: Aroclor 1254-induced male rat liver S9 was used METHOD: The assay was performed according to a protocol developed from published methodologies (Hsie et al., Mutat. Res. 86, 193-214 (1981); O´Neill et al., Mutat. Res. 45, 91-101 (1977); Wagner et al., Environ. Mol. Mutagen. 19, 68 (1992)). The desiccator methodology has been shown to be an effective method for detecting the genotoxic activity of volatile and gaseous test substances (Wagner et al. (1992). CONCENTR ATIONS: initial assay: 1.0 up to 5 mL (-S9) and 1.0 up to 10 mL (+S9); independent repeat assay: 1.0 up to 10 mL

(+/-S9)
DEVIATION FROM THE PROTOCOL: negative controls exhibited mutant frequencies > 25% per 10 to the sixth clonable cells in the initial and the repeat assay; therefore this deviation was not considered to have any adverse impact on the conclusion or integrity of the study. Exposure time was increased from 5 hours to 7.5 hours.
CONCURRENT CYTOTOXICITY: initial assay: no toxicity, i.e., cloning efficiency <=50%, at any dose level (relative cloning efficiency was 121% and 78% at the highest dose tested without and with metabolic activation, respectively); independent repeat assay: no toxicity, i.e., cloning efficiency <=50%, at any dose level (relative cloning efficiency was 74% and 114% at the highest dose tested without and with metabolic activation, respectively)

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
02.11.2000 (44) (43)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male/female
Strain : CD-1
Route of admin. : other: whole body vapor inhalation
Exposure period : once for 6 hours
Doses : 0.15, 0.75 and 1.5 ppm (nominal concentrations)
Result :
Method : other: the protocol complies with OECD Guide-line 474
Year : 1998
GLP : yes
Test substance : other TS: purity: 99.5 %

Remark : ANALYTICAL CONCENTRATIONS: 0.14, 0.80 and 1.47 ppm
Result : TOLERATION BY THE ANIMALS: no animals died; increased activity was the only sign observed during the exposures in all treated groups; all animals in the 2 highest exposure groups that were on study until Day 3 had lost weight compared to their pretest weight; no macroscopic changes were observed at necropsy in any dose group
RATIO OF POLYCHROMATIC ERYTHROCYTES TO TOTAL ERYTHROCYTES:
reductionof 2 to 17% in test substancetreated males at 48 hours (at 0.15 ppm 17%; at 0.75 ppm 8% and at 1.5 ppm 2%)
MICRONUCLEATED POLYCHROMATIC ERYTHROZYTES: no significant increase was observed in male and female mice at 24, or 48 hours
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
02.11.2000 (45) (43)

5.7 CARCINOGENICITY

Species : rat
Sex : male/female

Strain	:	Fischer 344
Route of admin.	:	inhalation
Exposure period	:	2 years
Frequency of treatm.	:	6 h/day, 5 d/week
Post exposure period	:	no
Doses	:	0.035; 0.175 or 1.2 mg/m3 (0.005; 0.025 or 0.175 ppm)
Result	:	
Control group	:	yes, concurrent vehicle
Method	:	other: Test guidelines: EPA/TSCA, subpart D, 798.3320 (1988); OECD No. 453 (1981); MAFF/Japan, 59 NohSan No. 4200 (1985)
Year	:	
GLP	:	yes
Test substance	:	
Remark	:	see also chapter 5.4
Result	:	no increase of tumor incidences at any concentration
Flag	:	Critical study for SIDS endpoint

(38)

5.8.1 TOXICITY TO FERTILITY

Type	:	other: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	other: whole body vapor inhalation
Exposure period	:	male: 28 days; female: 50 days
Frequency of treatm.	:	6 hours/day, 7 days/week
Premating exposure period		
Male	:	14 days
Female	:	14 days
Duration of test	:	54 days
No. of generation studies	:	
Doses	:	0, 0.005, 0.050 or 0.300 ppm (nominal concentrations)
Control group	:	yes, concurrent no treatment
Method	:	other: OECD Guide-line 422
Year	:	1999
GLP	:	yes
Test substance	:	other TS: purity:99.7% -99.6%
Remark	:	Analytically confirmed overall (for the entire study) mean HDI CONCENTRATIONS: 0.005, 0.053 and 0.299 ppm EXPOSURE PERIOD: during a 4-day lactation phase the exposure to HDI was also discontinued for the dams. Deviation in the exposure regimen of the females: some of the females were exposed through gestation day 19, others were exposed through gestation day 18 only, and others were exposed through gestation day 18 and again on gestation day 20. In order to assess the impact of the deviation on the study the tissues from the respiratory tract of all females were examined microscopically. The results of these examinations did not indicate any differences between the females differentially exposed. NOAEL PARENTAL:

		The NOEL for clinical signs during premating and mating phases, for both and females, was 0.300 ppm. The NOEL for effects on body weight during premating and mating phases was 0.050 ppm for the females and 0.300 ppm for the males. The NOEL for maternal clinical signs and for effects on maternal body weight during gestationphase was 0.300 ppm. The NOEL for maternal clinical signs and for effects on maternal body weight and food consumption during the lactation phase was 0.300 ppm. NOAEL F1 OFFSPRING: The NOEL for pup clinical signs and for effects on pup body weight during lactation phase were 0.300 ppm.
Result	:	There were no statistically significant effects on the mating, fertility, or gestation indices. There were no effects observed on the days to insemination, gestation length, or total number of implantation sites. The NOEL for effects on reproductive parameters was 0.300 ppm. There were no statistically significant effects on litter size, total number of pups born, sex distribution, mean weight of viable pups, mean number of viable pups or number of stillborn pups. No statistically significant effects were observed on the live birth, viability, lactation, or birth indices. The NOEL for effects on litter parameters was 0.300 ppm. The pathology findings, including hematology, clinical chemistry, organ weights, gross and microscopic evaluations, and the neurotoxicological evaluations are presented in chapter 5.4 ("Repeated Dose Toxicity").
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

25.10.2000 (39) (40)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	other: whole body vapor inhalation
Exposure period	:	days 0 through 19 of gestation
Frequency of treatm.	:	daily 6 hours
Duration of test	:	20 days
Doses	:	0, 0.005, 0.050 or 0.300 ppm (nominal concentrations)
Control group	:	yes, concurrent no treatment
NOAEL maternal tox.	:	.005 ppm
NOAEL teratogen.	:	.3 ppm
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1999
GLP	:	yes
Test substance	:	other TS: purity:99.7% -99.6%
Remark	:	Analytically confirmed overall (for the entire study) mean HDI CONCENTRATIONS: 0.005, 0.052 and 0.308 ppm
Result	:	0.300 ppm: no mortality; no clinical signs; no test compound related effects on maternal body weight, uterine weight, and net body weight; microscopic changes within the nasal

cavity;
No effects on reproductive parameters; no embryotoxicity; no litter effects; no fetal external, visceral, and skeletal malformations
0.050 ppm: no mortality; no clinical signs; no test compound related effects on maternal body weight, uterine weight, and net body weight; microscopic changes within the nasal cavity (to a lesser extent compared to the 0.300 ppm exposure group)
No effects on reproductive parameters; no embryotoxicity; no litter effects; no fetal external, visceral, and skeletal malformations
0.005 ppm: no mortality; no clinical signs; no test compound related effects on maternal body weight, uterine weight, and net body weight; no microscopic changes within the nasal cavity
No effects on reproductive parameters; no embryotoxicity; no litter effects; no fetal external, visceral, and skeletal malformations

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
13.12.2001 (46)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Remark : Three male volunteers were shortly exposed to HDI (insufficiently reported study). 0.007 mg/m3 (0.001 ppm) was not smelled; 0.035 mg/m3 (0.005 ppm) was smelled by 1/3 man and 0.07 mg/m3 (0.01 ppm) by all; at 0.14 mg/m3 (0.02 ppm) HDI was clearly perceptible and led to a slight irritation in two volunteers; 0.7 mg/m3 (0.1 ppm) had an acrid odor and led to clear irritation of eyes and throat.
Flag : Critical study for SIDS endpoint
(14)

Remark : Case reports as well as systematic examinations of occupationally exposed workers described as main symptoms asthmatic reactions, bronchial hyperreactivity, alveolitis, changes in several parameters of lung function and the occurrence of IgG or IgE antibodies against HDI bound to human serum albumin. In most of the cases the exposure occurred to spray applications of polyurethane coatings that based on HDI prepolymers and had an average residual monomer content of <= 0.5 %; additionally during production and processing the workers were exposed (for details see cited references).
Flag : Critical study for SIDS endpoint
02.11.2000 (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (31) (67) (68) (69) (70) (71) (72) (73) (74) (75) (76) (77) (78)

Remark : Several cases of cross reactivity between different isocyanates (HDI, TDI, MDI etc.) were reported in exposed workers.
Flag : Critical study for SIDS endpoint
(79) (80) (81) (82) (68) (83) (71) (72) (77)

Remark : Biomonitoring:
In an inhalation trail five healthy male non-smokers (age 36 to 50 years; four out of five were exposed in former times) were exposed to an average HDI concentration of 0.025 mg/m3 for 7.5 h; the absorbed dose/person was estimated to be about 0.1 mg; in the hydrolysed urine 0.0018 to 0.014 mg of the related 1,6-hexamethylene diamine (HDA) was determined within 28 h corresponding to 11 to 21 % of the absorbed HDI concentration; HDA elimination was rapid and the half life was in the range of 1.1 to 1.4 h; HDA was not detectable in the plasma (detection limit: 0.0005 mg/l).
Flag : Critical study for SIDS endpoint
(32)

Remark : Biomonitoring:
One volunteer was exposed to an average HDI concentration of 0.03 mg/m3 for 7.5 h and the absorbed HDI amount was estimated to be around 0.1 mg; in the hydrolysed urine 0.01 mg HDA was detected within 28 h corresponding to around 10 % of the absorbed HDA; HDA half life was about 1.4 h and more than 90 % were excreted via the urine within the first four h.
Flag : Critical study for SIDS endpoint
(84)

Remark : Biomonitoring:
Exposure of five volunteers to HDI (0.15 to 0.33 mg/m3) lasting 15 min. led to detectable amounts of HDA in the hydrolysed urine; the highest HDA concentration was noted after 30 min. (around 0.0185 mg/mmol creatinine) while after 6 to 8 h less than 0.0003 mg HDA/mmol creatinine was detectable (with one exception).
Flag : Critical study for SIDS endpoint
(85)

Remark : 41 male car painters (age: 20 to 64; 58 % smokers) with an average of 7 year employment that were e xposed to HDI concentrations of about 0.001 mg/m3 (paint with 0.5 to 1 % unreacted HDI and 40 to 50 % HDI biuret trimer in the hardener) with brief peaks had an increased incidence in eye, nose and throat irritation and chronic bronchitis but no differences in spirometry was noted in comparison to controls (car painters and mechanics without HDI exposure). Closing volume in relation to vital capacity was increased suggesting a "small airways disease" on Monday before work and tended to increase during work week.

Flag : Critical study for SIDS endpoint
(86)

Remark : 81 workers (age: 21 to > 50 years; 57 % smokers) engaged in the production of HDI showed normal lung functions (cross-sectional analysis) though the 20 ppb TLV was occasionally exceeded.

Flag : Critical study for SIDS endpoint
(87)

Remark : 36 male car painters (average age of 39.8 years, 55 % smokers, mean employment of 16.5 years) participated in a follow-up study with measurement of lung function and exposure measurement. The mean HDI exposure was 0.0015 mg/m3 and the mean HDI biuret trimer (HDI-BT) exposure 0.09 mg/m3. The smoking car painters had greater yearly reduction in forced vital capacity, forced expiratory volume and closing volume compared to smoking controls, while the nonsmoking car painters showed no differences in lung volumes in comparison to nonsmoking controls. The impairment correlated with the frequency of high peak exposure to HDI-BT but not with the mean exposure to diisocyanates.

Flag : Critical study for SIDS endpoint
(88)

Remark : In a prospective evaluation of 150 workers exposed to HDI and its trimer during 18 months specific IgG- and IgE-antibodies against HDI bound to human serum albumin were found in 13 and 5 % of the exposed group resp.. However, there was insufficient evidence about the relationship between antibody titer and clinical disease.

Flag : Critical study for SIDS endpoint
(89)

Remark : An examination of 11 workers with occupational asthma after HDI exposure indicated that people with a heterozygous alpha1 antitrypsin phenotype tend to bronchial hyperreactivity in contrast to people with homozygous alpha1 antitrypsin phenotype.

Flag : Critical study for SIDS endpoint
(90)

Remark : The results of a 2.5-year follow-up of workers in a polyurethane molding process with combined exposure to isocyanate and organic solvents indicate that long-term exposure to isocyanates may contribute to impaired pulmonary function.

Flag : Critical study for SIDS endpoint
21.10.1998
(91)

Remark : Peripheral blood mononuclear cells of workers (n=19) with confirmed diisocyanate-induced occupational asthma can be

stimulated in vitro with DHI-HSA antigens to produce basophil-activating histamine releasing factors and monocyte chemoattractant protein 1.

Flag : Critical study for SIDS endpoint
21.10.1998 (92)

Remark : Biomonitoring: There was a linear association of HDI air concentration (0.30 to 97.7 ug/m3) with urinary HDA (1.36 to 27.7 ug/g creatinine) liberated by acid hydrolysis from its conjugates in post shift samples of 19 men.

Flag : Critical study for SIDS endpoint
22.10.1998 (93)

Remark : The apoptosis seems to increase in white blood cells of isocyanate-workers after inhalation of HDI (5 ppb for 15 minutes followed by 10 ppb for 105 minutes; number of HDI-exposed workers unknown).

Flag : Critical study for SIDS endpoint
21.10.1998 (94)

Remark : Biomonitoring: Three volunteers were each exposed to 11.9, 20.5 and 22.1 ug HDI/m3 for 2 hours. After hydrolys is under alkaline conditions the average urinary excretion of HDA was 39 %. The average urinary elimination half-time for HDA was 2.5 h. No HDA could be found in hydrolysed plasma.

Flag : Critical study for SIDS endpoint
21.10.1998 (95)

Remark : Biomonitoring:
Urine samples were taken from sprayers wearing personal protective equipment and spraying in booths or with local exhaust ventilation, from bystanders, and from unexposed subjects. HDA was detected in four sprayers and one bystander out of 22 workers. No HDA was detected in the urine of unexposed subjects.

Flag : Critical study for SIDS endpoint
02.11.2000 (96)

Remark : This pilot study documents HDI contamination on a number of surfaces in auto body shops. In addition, it has been shown evidence of substantial epicutaneous exposure to HDI in auto body shop workers and the inadequacy of latex gloves in exposures.

Flag : Critical study for SIDS endpoint
02.11.2000 (97)

5.11 ADDITIONAL REMARKS

Type : other

Remark : revision: 10/00

Flag : Critical study for SIDS endpoint
25.10.2000

Type : other

Remark : An overall perspective of the toxicology of hexamethylene diisocyanate is given in some comprehensive publications

Flag : Critical study for SIDS endpoint
26.10.2000 (98) (99)

Type : other

Remark : An overall perspective of the sensitization potential

Flag : Critical study for SIDS endpoint
02.11.2000 (100)

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