SIDS Initial Assessment Report

For

SIAM 20

Paris, France, 19-22 April 2005

1. Chemical Name:	**4,4´-Methylenedicyclohexyl diisocyanate**
2. CAS Number:	**5124-30-1**
3. Sponsor Country:	Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn
4. Shared Partnership with:	-
5. Roles/Responsibilities of the Partners:	-
• Name of industry sponsor /consortium	Bayer AG, Germany Contact person: Dr. Burkhardt Stock D-51368 Leverkusen Gebäude 9115
• Process used	OECD/ICCA - The BUA Peer Review Process: see next page
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	by ICCA-Initiative
7. Review Process Prior to the SIAM:	last literature search (update): 4 October 2004 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 8 November 2004 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms OECD/ICCA
8. Quality check process:	IUCLID was used as a basis for the SIDS dossier. All data were checked and validated by BUA. A final evaluation of the human health part has been performed by the Federal Institute for Risk Assessment (BfR) and of the ecotoxicological part by the Federal Environment Agency (UBA).
9. Date of Submission:	Deadline for circulation: 21 January 2005
10. Date of last Update:	Last literature search: IUCLID Chapters 1-4: 2003-08-13, Chapter 3.2.1 2004-07-27, Chapter 5: 2003-01-22;

11. Comments:

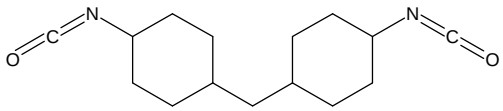
OECD/ICCA - The BUA* Peer Review Process

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

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4), i.e. reliability not assignable)
- Review 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.	5124-30-1
Chemical Name	4,4´-Methylenedicyclohexyl diisocyanate
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

4,4´-Methylenedicyclohexyl diisocyanate is of low oral and dermal acute toxicity with an oral LD_{50} (rat) of 9900 mg/kg bw and a dermal LD_{50} (rabbit) > 10,000 mg/kg. Toxic symptoms after oral administration included severe diarrhea, loss of appetite and increasing weakness. Assessment of the acute inhalation toxicity data indicates that exposure to respirable aerosols of 4,4´-methylenedicyclohexyl diisocyanate confined predominantly to the respiratory tract. Clinical signs (salivation, bradypnea, stridor) indicated respiratory distress. A haemorrhagic lung edema was considered to be causative for mortality. An animal study according to OECD TG 403 gives a LC_{50} (4 h, rat) of 434 mg/m^3.

4,4´-Methylenedicyclohexyl diisocyanate is moderately to severely irritant to the skin of rabbits (OECD TG 404). Irritant effects were observed after instillation of 4,4´-methylenedicyclohexyl diisocyanate into the eyes of rabbits (OECD TG 405). The repeated dose studies indicate that 4,4´-methylenedicyclohexyl diisocyanate causes irritation of the respiratory tract.

Animal data are not uniform however they frequently provide evidence of a skin sensitizing potential of 4,4´-methylenedicyclohexyl diisocyanate. Human case reports describe allergic contact dermatitis due to 4,4´-methylenedicyclohexyl diisocyanate exposure. Although no validated animal model is available to assess the potential for respiratory sensitization or asthma in humans animal data support to some extent the hypothesis that respiratory hypersensitivity may be induced by 4,4´-methylenedicyclohexyl diisocyanate.

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure. A subacute inhalation study (1, 6 and 36 mg/m^3; 6 hours/day on five days/week for 4 weeks) with rats (OECD TG 412) indicates the respiratory tract to be the target organ of respirable 4,4´-methylenedicyclohexyl diisocyanate aerosol. The reported NOAEL for effects governed by respiratory tract irritation is 1 mg/m^3; the LOAEL is 6 mg/m^3 (i.e. histopathological changes in nasal passages, larynx and bronchi). The results of a reproduction/developmental toxicity screening test (OECD TG 421) corresponds to the results of the subacute study.

4,4´-Methylenedicyclohexyl diisocyanate did not induce gene mutations in bacteria (OECD TG 471) and demonstrated no potential to induce chromosome aberrations in Chinese hamster V79 cells *in vitro* (OECD TG 473) either with or without metabolic activation.

Data from an inhalative reproduction/developmental toxicity screening test according to OECD TG 421 with rats (1, 6 and 36 mg/m^3) did not reveal substance related impairment of reproduction up to a 4,4´-methylenedicyclohexyl diisocyanate concentration of 6 mg/m^3. A slightly reduced fertility index was observed at an exposure level (36 mg/m^3) that was associated with parental toxicity. NOAELs were considered to be 1 mg/m^3 in males and females for general toxicity. NOAEL for reproductive toxicity is 6 mg/m^3.

Pre-natal inhalation toxicity testing in rats (OECD°TG°421) indicates the absence of selective toxicity to the development at levels up to 36°mg/m^3. No findings indicate any specific developmental effects such as live birth index, viability index and apparent malformation. The reported $NOAEL_{(developmental)}$ for 4,4´-methylenedicyclohexyl diisocyanate in a developmental toxicity study according to OECD TG 414 (1, 6 and

36 mg/m³) is 6 mg/m³/day. At the 36 mg/m³ level that caused clear maternal respiratory tract toxicity ($NOAEL_{(maternal)}$ = 1 mg/m³) increased incidences of ventricular septal defects of the heart and slight dilation of lateral brain ventricles were observed, which lay marginally above the upper or within the normal range of scattering of the rat strain used respectively.

Environment

4,4'-Methylenedicyclohexyl diisocyanate is a slightly yellowish, moisture/water sensitive liquid with a melting point of 15 °C. 4,4'-Methylenedicyclohexyl diisocyanate has a relative density of 1.07 at 25 °C, a boiling point of 167 - 168 °C (at 2 hPa), and a vapor pressure of 2.13 x 10^{-5} hPa at 25 °C [Directive 92/69/EEC, A.4]. A water solubility and a log K_{OW} are not determinable due to the instability of 4,4'-methylenedicyclohexyl diisocyanate in water. The flash point of 4,4'-methylenedicyclohexyl diisocyanate is 200 °C [DIN 51758], the ignition point is 225 °C and the viscosity is approximately 30 mPa x s at 25 °C [DIN ISO EN 3219/A.3]. The calculated half-life of 4,4'-methylenedicyclohexyl diisocyanate in air due to indirect photodegradation is about 15.0 h.

4,4'-Methylenedicyclohexyl diisocyanate hydrolyses rapidly in the presence of water, the major product in the aqueous phase is methylene bis(4-cyclohexylamine). In water, a half-life for 4,4'-methylenedicyclohexyl diisocyanate of approximately 2 hours was determined experimentally. Due to the rapid hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate, a transport of the substance between environmental compartments is unlikely. Consequently, a calculation of the Henry Law Constant and of the distribution between the environmental compartments according to the Mackay fugacity model level 1 is not suitable.

However, several aquatic toxicity tests have been undertaken with 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products. Because of the rapid hydrolysis the assessment of the substance should be based on the hydrolysis products and not on 4,4'-methylenedicyclohexyl diisocyanate. The hydrolysis product methylenebis-p-cyclohexylamine was assessed by the EU PBT Working Group. The hydrolysis product was not classified as a PBT substance.

4,4'-Methylenedicyclohexyl diisocyanate is not readily biodegradable.

Due to the rapid hydrolysis 4,4'-methylenedicyclohexyl diisocyanate is neither persistent in the water compartment nor bioaccumulative. The calculated K_{oc}-value indicates that 4,4'-methylenedicyclohexyl diisocyanate may strongly adsorb to soil but due to its rapid hydrolysis any emission to the terrestrial compartment would be affected by humidity and therefore, geoaccumulation of 4,4'-methylenedicyclohexyl diisocyanate is not expected to occur.
Concerning the toxicity of 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products towards aquatic species, reliable experimental results of tests with fish, *Daphnia*, and algae are available (* = determined as TOC and back-calculated to parent substance, n = nominal concentration).

Danio rerio (fish):	96 h-LC_{50} > 8.1 mg/l*,	[Directive 92/69/EEC, C.1]
Daphnia magna (aq. invertebrate):	48 h-EC_{50} > 8.3 mg/l*,	[Directive 92/69/EEC, C.2]
Scenedesmus subspicatus (algae):	72 h-E_rC_{50} > 5 mg/l*,	[Directive 92/69/EEC, C.3]
Activated sewage sludge (bacteria):	3 h-EC_{50} = 191 mg/l (n),	[Directive 88/302/EEC, Part C

(corresponds to the OECD TG 209)].

It has to be considered that the toxicity observed in the reported aquatic studies was caused both by the 4,4'-methylenedicyclohexyl diisocyanate as well as by the hydrolysis products due to the instability of the test substance.
Based on the acute aquatic toxicity data on three trophic levels (fish, *Daphnia*, algae), the Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000 applied to the lowest acute effect concentration. The lowest 72 h-E_rC_{50}-value of > 5 mg/l obtained for the alga species *Scenedesmus subspicatus* was used to derive a $PNEC_{aqua}$ of > 5 µg/l.

Exposure

Commercial 4,4'-methylenedicyclohexyl diisocyanate manufacturing starts with hydrogenated methylenedianiline (methylenebis-p-cyclohexylamin) which is phosgenated. The global production capacity of 4,4'-methylenedicyclohexyl diisocyanate is 10 000 - 20 000 tonnes/a, with most of it in the USA. In Germany, the only producer has a manufacturing capacity of 1000 - 5000 tonnes/a of 4,4'-methylenedicyclohexyl diisocyanate.

4,4'-Methylenedicyclohexyl diisocyanate is an intermediate in the chemical industry, used for the manufacture of binders or hardeners for coating materials or adhesives (60 %), prepolymers (20 %), and for other applications, e.g. for the production of elastomers (20 %). 4,4'-Methylenedicyclohexyl diisocyanate is not used for "Do It Yourself" applications or in other consumer products. 4,4'-Methylenedicyclohexyl diisocyanate is registered as a component in approximately 50 industrial products listed in the Danish, Finnish, and Swedish Product Registers with a consumption of about 30 tonnes/a in 2000 and 2001 (last years of record). 4,4'-Methylenedicyclohexyl diisocyanate is confidentially listed in the Norwegian Product Register. There is no registration for a consumer product. The main use category is "non-dispersive use". For 4,4'-methylenedicyclohexyl diisocyanate the Swiss Product Register lists 34 industrial products (with concentrations of up to 100 % 4,4'-methylenedicyclohexyl diisocyanate), but no consumer product.

By the producer in Germany, 4,4'-methylenedicyclohexyl diisocyanate is manufactured and processed (including filling) in closed systems at the same industrial site. To the customers most of the 4,4'-methylenedicyclohexyl diisocyanate is transported in ISO containers, and to a minor part, in drums.

During 4,4'-methylenedicyclohexyl diisocyanate manufacturing and processing, virtually no 4,4'-methylenedicyclohexyl diisocyanate (< 25 kg/a) is emitted into the atmosphere from the Bayer plants. Waste from the manufacturing and processing of 4,4'-methylenedicyclohexyl diisocyanate is disposed off in an incinerator for hazardous wastes. Due to wastewater-free manufacturing and processing, and to rapid hydrolysis, no emissions into the aquatic environment are expected.

Surveys of the workplaces have been performed also according to German Technical Guidance TRGS 402, TRGS 430, and TRGS 900 by the producer in Germany. To protect workers from exposure, several precautionary and protective measures are taken, e.g., sampling takes place in a widely closed system. In Germany for occupational settings, the maximum permissible concentration for 4,4'-methylenedicyclohexyl diisocyanate is 0.054 mg/m³. At the producer in Germany, all exposure data were below the maximum permissible concentration.

No environmental monitoring data have been identified. Traces of 4,4'-methylenedicyclohexyl diisocyanate (up to 2 $\mu g/m^3$) were detected as a thermolytic degradation product during joint welding of polyurethane floor covering in a small room with no ventilation.

The exposure of consumers to 4,4'-methylenedicyclohexyl diisocyanate is unlikely to occur, because no consumer product is known to contain 4,4'-methylenedicyclohexyl diisocyanate. An exposure via the environment is also unlikely to occur because there are virtually no emissions of 4,4'-methylenedicyclohexyl diisocyanate, and 4,4'-methylenedicyclohexyl diisocyanate released to environment would rapidly be degraded by photooxidants and water.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (severe irritation of skin, eye and respiratory tract, sensitization of skin and predicted to be a respiratory tract sensitizer because it is a diisocyanate). Based on data presented by the Sponsor country (relating to production by one producer which accounts for approximately 5 % to 50 % of global production and relating to the use pattern in several OECD countries), occupational exposure is anticipated to be low and there are no known consumer uses. Therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The chemical (including its hydrolysis products) possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for approximately 5 % to 50 % of global production and relating to the use pattern in several OECD countries), exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

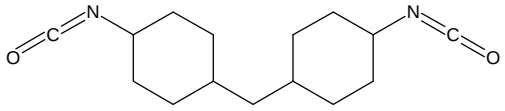
CAS Number: 5124-30-1

Substance name: 4,4´-methylenedicyclohexyl diisocyanate (EINECS name)

IUPAC Name: 1,1´-Methylenebis(4-isocyanatocyclohexane)

Molecular Formula: $C_{15}H_{22}N_2O_2$

Structural Formula:



Molecular Weight: 262.35 g/mol

Synonyms: Cyclohexane, 1,1’-methylenebis-(4-isocyanato)- (CAS name)
Desmodur W (Product of Bayer MaterialScience AG)
Hylene W
Hydrogenated MDI
H_{12}MDI
Methylene bis(4-cyclohexylisocyanate)
4,4’-Dicyclohexylmethanediisocyanate
4,4’-Diisocyanatodicyclohexylmethane
4,4’-Methylenebis(cyclohexyl isocyanate)
Bis(4-isocyanatocyclohexyl)methane
Dicyclohexylmethane-4,4'-diisocyanate
Methylenebis(1,4-cyclohexylene) diisocyanate
Methylene bis(4-isocyanatocyclohexane)
Methylenedi-1,4-cyclohexylene isocyanate
Methylenedi-4-cyclohexylene diisocyanate

1.2 Purity/Impurities/Additives

A typical composition of 4,4’-methylenedicyclohexyl diisocyanate was specified by Dieterich and Uhlig (2002) with a purity of 92 % 4,4’-methylenedicyclohexyl diisocyanate and the corresponding isomeric composition:

- *cis*,*cis*-isomer 14 %
- *cis*,*trans*-isomer 58 %
- *trans*,*trans*-isomer 20 %
- others 8 % (2,4'-methylenedicyclohexyl diisocyanate).

The commercial product of 4,4’-methylenedicyclohexyl diisocyanate also contains 2,4’-methylenedicyclohexyl diisocyanate (Bayer MaterialScience AG, 2004a).

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties of **4,4'-methylenedicyclohexyl diisocyanate**

Property	Value	Reference	IUCLID
Substance type	Organic compound	Bayer MaterialScience AG, 2004b	1.1.1
Physical state	Slightly yellowish liquid with slight lachrymatory odour	Bayer MaterialScience AG, 2004b	1.1.1
Melting point	15 °C**	Dieterich and Uhlig, 2002	2.1
Boiling point	167 - 168 °C (at 2 hPa)	GIAP, 1969	2.2
Relative density	1.07 at 25 °C	NIOSH, 2004	2.3
Vapour pressure	2.13 x 10^{-5} hPa at 25 °C	Bayer AG, 1994a	2.4
Partition coefficient n-octanol/water (K_{ow})	Calculation is not suitable due to hydrolysis*		2.5
Water solubility	Hydrolysis*	NIOSH, 2004	2.6.1
Flash point	200 °C	Bayer AG, 1979	2.7
Ignition point	225 °C	Zhuravlev, 1976	2.8
Viscosity	ca. 30 mPa x s at 25 °C	Bayer MaterialScience AG, 2004b	2.13

*In water, 4,4'-methylenedicyclohexyl diisocyanate hydrolyses with a half-life of approximately 2 h (Bayer AG, 1999) **For the mixture reported by Dieterich and Uhlig (2002) in Chapter 1.2. Melting point may vary according to exact isomeric composition.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Commercial 4,4'-methylenedicyclohexyl diisocyanate manufacturing starts with hydrogenated methylenedianiline (4,4'-methylenebis(cyclohexylamine), CAS 1761-71-3) which is generally known as H_{12}MDA or PACM. PACM is a mixture of three isomers, *trans*,*trans*-, *cis*,*trans*-, and *cis*,*cis*-PACM which is obtained by catalytic hydrogenation of methylenedianiline (MDA). PACM is phosgenated (Six and Richter, 2003):

$NH_2\text{-}C_6H_4\text{-}CH_2\text{-}C_6H_4\text{-}NH_2 + 2\ COCl_2 \rightarrow OCN\text{-}C_6H_{10}\text{-}CH_2\text{-}C_6H_{10}\text{-}NCO + 4\ HCl$

During phosgenation hydrochloric acid is stripped and recycled to yield chlorine for the phosgene production. The isocyanate is dried and distilled. The reaction product consists of 92 % 4,4'-methylenedicyclohexyl diisocyanate with 14 % *cis*,*cis*-isomer, 58 % *cis*,*trans*-isomer, and 20 % *trans*,*trans*-isomer (Dieterich and Uhlig, 2002), the 2,4´-isomers accounting for the remaining approx. 8 % (Bayer MaterialScience AG, 2004a). Since the *trans*,*trans*-4,4'-methylenedicyclohexyl diisocyanate is solid in the pure state [melting point 83 °C (Dieterich and Uhlig, 2002)], to obtain a liquid diisocyanate product in the subsequent phosgenation, the amount of *trans*,*trans*-4,4'-methylenebis(cyclohexylamine) has to be reduced to less than 20 % (selective hydrogenation and/or crystallisation) (Six and Richter, 2003).

The global production capacity of 4,4'-methylenedicyclohexyl diisocyanate is 10,000 - 20,000 tonnes/a, with most of it in the USA (Bayer MaterialScience AG, 2004a). In Germany, Bayer MaterialScience AG (2004a) is the only producer and has a manufacturing capacity of 1000 - 5000 tonnes/a of 4,4'-methylenedicyclohexyl diisocyanate.

4,4'-Methylenedicyclohexyl diisocyanate is used as an intermediate in several industries, e.g. the chemical industry and coatings industry. 4,4'-Methylenedicyclohexyl diisocyanate is used as a monomer and is industrially processed to polymers with e.g. polyols in the coatings industry to produce e. g. binders, prepolymers, and elastomers. 4,4'-Methylenedicyclohexyl diisocyanate is supplied to the chemicals industry, mainly coatings industry, but is not distributed to consumers. It is used for the manufacture of

- Binders or hardeners for coating materials or adhesives (60 %)
- Prepolymers (20 %)
- Others, e.g. for the production of elastomers (20 %) (Bayer MaterialScience AG, 2004a).

4,4'-Methylenedicyclohexyl diisocyanate is not used for "Do it Yourself" applications or in other consumer products (Bayer MaterialScience AG, 2004a). Consistently, 4,4'-methylenedicyclohexyl diisocyanate is registered as a component in approximately 50 industrial products in the Danish, Finnish, and Swedish Product Registers with a consumption of about 30 metric tonnes/a in 2000 and 2001 (last years of record). It is used as an intermediate for the manufacture of rubber and plastic products, industrial paints, chemical products, construction and transport equipment. There is no registration for a consumer product. It is confidentially listed in the Norwegian Product Register. The main use category is "non-dispersive use" (SPIN, 2004).

The Swiss Product Register (2004) lists 34 industrial products (with concentrations of up to 100 % 4,4'-methylenedicyclohexyl diisocyanate), but no consumer product containing 4,4'-methylene-dicyclohexyl diisocyanate.

2.2 Environmental Exposure and Fate

When 4,4'-methylenedicyclohexyl diisocyanate is released to water, degradation occurs through hydrolysis (*cf.* Chapter 2.2.3). A half-life of approximately 2 hours was determined for 4,4'-methylenedicyclohexyl diisocyanate (Bayer AG, 1999). The hydrolysis product 4,4'-methylenebis(cyclohexylamine) was assessed by the EU PBT Working Group (2003). The hydrolysis product was not classified as a PBT (persistent, bioaccumulative, toxic) substance.

2.2.1 Sources of Environmental Exposure

Environmental information from manufacturing and processing of 4,4'-methylenedicyclohexyl diisocyanate is available for the Bayer plants in Germany. Both plants are at the same industrial site (Bayer MaterialScience AG, 2004a).

Since phosgene (precursor) and 4,4'-methylenedicyclohexyl diisocyanate (product) react violently with traces of water, the synthesis is performed in a closed, water-free system (Bayer MaterialScience AG, 2004a).

The exhausts from manufacturing and processing are connected to a thermal exhaust purification plant. Amine and isocyanate tanks are secured with activated carbon filters. The product is automatically filled into special metal drums or ISO containers (20 feet containers) using suction devices and widely closed systems (*cf.* Chapter 2.3.1). Thus, according to the current Official

Emission Declaration of the year 2000, Bayer emitted virtually no 4,4'-methylenedicyclohexyl diisocyanate (< 25 kg/a) into the atmosphere during manufacturing and processing (Bayer MaterialScience AG, 2004a).

Waste from the manufacturing and processing is incinerated in an incinerator for hazardous wastes (Bayer MaterialScience AG, 2004a).

Due to the water sensitivity of precursors and product, 4,4'-methylenedicyclohexyl diisocyanate is manufactured in closed system virtually free of water. Water is used only in the case of maintenance (after the system has been eluted with solvent), to flush the system to ensure hydrolysis of phosgene. Due to this procedure, the wastewater does not contain 4,4'-methylenedicyclohexyl diisocyanate. However, all wastewater from manufacturing and processing is led into a Bayer-owned wastewater treatment plant (hydraulic retention times > 1 d), where 4,4'-methylenedicyclohexyl diisocyanate would be hydrolyzed (*cf.* Chapter 2.2.3). No additional information is available from other companies (Bayer MaterialScience AG, 2004a). However, there is no doubt that rules were abided to and regulations are strictly met in the Sponsor country.

2.2.2 Photodegradation

There are no experimental data on the stability of 4,4'-methylenedicyclohexyl diisocyanate in the atmosphere. A half-life of about 15 hours is estimated due to reaction with photochemically produced hydroxyl radicals, considering a mean OH concentration of 0.5×10^6 OH radicals/cm³ as a 24 h-average (Bayer Industry Services, 2004a) (*cf.* Table 2). However, the AOPWIN program used for this estimate does not take into account that 4,4'-methylenedicyclohexyl diisocyanate is sensitive to hydrolysis e.g. in aerosols with aquatic phases.

Table 2 Photodegradation of 4,4'-methylenedicyclohexyl diisocyanate (IUCLID 3.1.1)

Parameter	Method	Result	Reference
Indirect photodegradation in air	Calculation for 24 h-day, 500,000 OH/cm^3, Rate constant = 25.8×10^{-12} cm^3/(molecule x s)	$t_{1/2}$ = 15 h	Bayer Industry Services, 2004a

2.2.3 Stability in Water

4,4'-Methylenedicyclohexyl diisocyanate hydrolyzes rapidly in the presence of water. A half-life for 4,4'-methylenedicyclohexyl diisocyanate hydrolysis of approximately 2 hours was determined experimentally (Bayer AG, 1999).

In this study performed in accordance with the GLP-requirements, 1 g/l 4,4'-methylenedicyclohexyl diisocyanate dissolved in an acetonitrile/water-mixture was investigated at 23 °C. The decrease of NCO-content was observed in this solution during the study period. For this purpose the concentration of 4,4'-methylenedicyclohexyl diisocyanate was determined by means of capillary gas chromatography using flame ionization detection at continuous time intervals (*cf.* Table 3).

The rapid hydrolysis means that 4,4'-methylenedicyclohexyl diisocyanate discharged into the environment will be abiotically degraded.

A preliminary test according to the OECD TG 111 was carried out with 4,4'-methylenedicyclohexyl diisocyanate to determine the resulting products from the reaction with water. A solution of 2.64 g/l was incubated in demineralized, unbuffered water at 50 °C during 5 days under continuous stirring (Bayer Industry Services, 2004b).

In the aqueous phase the three isomers of 4,4'-methylenebis(cyclohexylamine) were identified with GC- and HPLC-MS. Additionally, the HPLC-analysis showed to a minor extent traces of a trimeric diamine compound; this was bound by urea-groups. Insoluble droplets obtained during hydrolysis testing adhered to the glass wall. They were analyzed with IR spectroscopy and were found to contain urea components (polymeric urea) and encapsulated traces of isocyanate-groups (Bayer Industry Services, 2004b). This hydrolysis product is more or less inert and - because of its macromolecular size - not bioavailable. In addition, this substance is formed only in the case of high isocyanate concentration which does not correspond to environmental conditions (EU PBT Working Group, 2003).

Table 3 Hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate (IUCLID 3.1.2)

Test substance	Procedure	Result	Reference
4,4'-methylenedi-cyclohexyl diisocyanate	50 % acetonitrile, 50 % water Determination of NCO-content using GC analysis with FID detection	$t_{1/2}$ = 1.97 hours at 23 °C; Rate constant k_{obs} = 9.78 x 10^{-5} 1/s	Bayer AG, 1999

2.2.4 Transport between Environmental Compartments

In the aquatic environment, 4,4'-methylenedicyclohexyl diisocyanate will undergo hydrolysis (Bayer AG, 1999). Due to the rapid hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate, a transport of the substance between environmental compartments is unlikely.

A calculation of the Henry Law Constant and also of the distribution between the environmental compartments according to the Mackay fugacity model level 1 is not suitable due to the hydrolyzing properties of 4,4'-methylenedicyclohexyl diisocyanate.

For the hydrolysis product, 4,4'-methylenebis(cyclohexylamine), a Henry Law Constant of 0.00046 Pa-m3/mole is obtained by the Bond method and of 0.016 Pa-m3/mole by the vapor pressure/water solubility equation (US EPA, 2005). The Mackay results are compiled in Table 4. The predominant environmental compartment of the hydrolysis product is water (98 %) (EU PBT Working Group, 2003).

Table 4 Input parameters and results **for 4,4'-methylenebis(cyclohexylamine)** of the Mackay Fugacity Model Level I (IUCLID 3.3.2)

Input Parameters	Value
Molar mass	210.36 g/mol
Temperature	20 °C
Vapour pressure	0.033 Pa
Water solubility	5800 g/m^3
log K_{ow}	2.03
Melting point	320 °C

Compartment	Calculated distribution
Water	98.256 %
Air	0.041 %
Sediment	0.823 %
Soil	0.880 %
Aquatic Biota	0.001 %

2.2.5 Biodegradation

Based on the available experimental biodegradation test result for 4,4'-methylenedicyclohexyl diisocyanate, the substance is classified as not readily biodegradable (*cf.* Table 5). No test on inherent biogradability is available.

In a GLP-study which was conducted according to Directive 92/69/EEC C.4-D (Manometric Respirometry Test), the biodegradation of 4,4'-methylenedicyclohexyl diisocyanate was investigated with a test substance concentration of 100 mg/l (no toxicity to bacteria observed). Within the test period of 28 days, a degradation of 0 % was determined for 4,4'-methylenedicyclohexyl diisocyanate (Bayer AG, 2000a).

In a GLP-study which was conducted according to OECD TG 301F, the biodegradation of 4,4'-methylenedicyclohexyl diisocyanate was tested at an initial concentration of 12 mg/l because a preliminary test at 100 mg/l indicated that the substance was toxic to bacteria present in the sewage sludge. This difference of toxicity between the two tests, both performed with an inoculum from a domestic sewage sludge, is presumably due to changes in sludge properties. Within the test period of 28 days, a degradation of 0 % was determined for 4,4'-methylenedicyclohexyl diisocyanate (Bayer AG, 1992).

Table 5 Biodegradation of 4,4'-methylenedicyclohexyl diisocyanate (IUCLID 3.5)

Inoculum	Procedure	Result	Reference
Aerobic predominantly domestic sewage	Directive 92/69/EEC, C.4-D	0 % degradation after 28 days	Bayer AG, 2000a
Domestic activated sludge	OECD TG 301F	0 % degradation after 28 days	Bayer AG, 1992

The biodegradability of the hydrolysis product, 4,4'-methylenebis(cyclohexylamine), was calculated with the EPIWIN BIOWIN (v4.02) Program. Four out of six estimation methods predict fast biodegradation, with an ultimate biodegradation timeframe of weeks (US EPA, 2005). The EU PBT Working Group (2003) assessed biodegradation tests on the hydrolysis product 4,4'-methylenebis(cyclohexylamine). These tests show that 4,4'-methylenebis(cyclohexylamine) is at least inherently biodegradable.

2.2.6 Bioaccumulation

Measured bioconcentration factors (BCF) for 4,4'-methylenedicyclohexyl diisocyanate are not available.

4,4'-Methylenedicyclohexyl diisocyanate hydrolyzes rapidly in the presence of water with a half life of approximately 2 hours. Therefore a risk estimation regarding the bioaccumulation potential of 4,4'-methylenedicyclohexyl diisocyanate on the basis of a log K_{ow}, determined by QSAR, is misleading. A calculated theoretical log K_{ow} value reflects the undissociated molecule without influence of water.

According to the EU Technical Guidance Document a substance is regarded as potentially bioaccumulative if the log K_{ow} exceeds 3 and the half life time in water exceeds 12 hours. This is not the case for 4,4'-methylenedicyclohexyl diisocyanate. The substance is not persistent in water due to the rapid hydrolysis. Therefore it is not bio-available. Possible hydrolyzation products are less lipophilous. On the basis of these information it can not be expected that bioaccumulation of 4,4'-methylenedicyclohexyl diisocyanate occurs (Bayer Industry Services, 2003).

The hydrolysis product, 4,4'-methylenebis(cyclohexylamine) is also not bioaccumulative (EU PBT Working Group, 2003). With a measured log K_{ow} (OECD 107) of 2.03, and calculated log K_{ow} values of 2.55 (CLOGP3 program) (EU PBT Working Group, 2003) and 3.26 (EPIWIN BCF Program (v2.15)) (US EPA, 2005), log BCF values of 0.863 (BCF = 7), 1.264 (BCF = 18), and 1.814 (BCF = 65) were calculated, respectively.

2.2.7 Geoaccumulation

There are no experimental data on the geoaccumulation potential of 4,4'-methylenedicyclohexyl diisocyanate, because the substance hydrolyzes rapidly in aqueous environment.

The distribution of 4,4'-methylenedicyclohexyl diisocyanate between the organic phase of soil or sediments and the porewater was calculated using QSAR. With the PCKOC program (v 1.66), a K_{oc}-value of 3.8×10^5 was calculated for 4,4'-methylenedicyclohexyl diisocyanate (Bayer Industry Services, 2004a). For the hydrolysis product, 4,4'-methylenebis(cyclohexylamine), a K_{oc} of 672 is obtained (US EPA, 2005) (*cf.* Table 6).

Table 6 Geoaccumulation properties of 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis product (IUCLID 3.3.1)

Compound	Method	Result	Reference
4,4'-methylenedicyclohexyl diisocyanate	Soil organic carbon-water distribution coefficient calculated with PCKOCWIN, v.1.66	$K_{oc} = 3.762 \times 10^5$, log $K_{oc} = 5.575$	Bayer Industry Services, 2004a
4,4'-methylenebis(cyclohexylamine)	Soil organic carbon-water distribution coefficient calculated with PCKOCWIN, v.1.66	$K_{oc} = 672$	US EPA, 2005

According to Litz (1990) 4,4'-methylenedicyclohexyl diisocyanate should be regarded as a substance with very high geoaccumulation properties. However, geoaccumulation in soil will be affected by humidity due to its rapid hydrolysis.

It is therefore concluded that geoaccumulation of 4,4'-methylenedicyclohexyl diisocyanate is unlikely to occur. The hydrolysis product has only a small to medium tendency for geoaccumulation.

2.2.8 Environmental Monitoring

No data have been identified.

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational exposure to 4,4'-methylenedicyclohexyl diisocyanate is most likely to occur through inhalation and dermal routes.

Workplaces

At the Bayer manufacturing site, some 4,4'-methylenedicyclohexyl diisocyanate is also used in the production of powder coatings. During this processing 4,4'-methylenedicyclohexyl diisocyanate is converted into a polymeric resin (Bayer MaterialScience AG, 2004a). Workplaces where 4,4'-methylenedicyclohexyl diisocyanate is manufactured and processed include (*cf.* Chapter 2.1)

- the synthesis of phosgene from carbon monoxide and chlorine supplied via pipelines from other manufacturers in the Bayer integrated industrial site and
- the synthesis of 4,4'-methylenedicyclohexyl diisocyanate from phosgene and PACM, and finally
- the isolation and filling of 4,4'-methylenedicyclohexyl diisocyanate , and
- the processing of 4,4'-methylenedicyclohexyl diisocyanate.

4,4'-Methylenedicyclohexyl diisocyanate is manufactured in closed systems (*cf.* Chapters 2.1 and 2.2.1).

To the customers most of the 4,4'-methylenedicyclohexyl diisocyanate is transported in ISO containers, and (a minor part) in drums (Bayer MaterialScience AG, 2004a).

Precautionary measures at the workplace

In accordance with the principles of Responsible Care and Sustainable Development, at Bayer the exposure of workers is reduced to the lowest technically practicable level (Bayer MaterialScience AG, 2004a).

Surveys of the Bayer workplaces are performed according to German Technical Guidances TRGS 402 (1997), TRGS 430 (2004), and TRGS 900 (2004). This includes regular surveys in the production plant for any possible exposure to phosgene, an organic solvent, and 4,4'-methylenedicyclohexyl diisocyanate under all relevant work situations, and application of appropriate control measures. In the processing plant, 4,4'-methylenedicyclohexyl diisocyanate is monitored (Bayer MaterialScience AG, 2004a).

To protect workers from exposure, several precautionary and protective measures are taken. E.g., sampling takes place in a widely closed system. For filling in ISO containers the workers have to wear full protective clothing and gas filter masks. Repair and maintenance work is only carried out on parts of the manufacturing system, which have been emptied. Prior to repair and maintenance the relevant components are flushed with solvent and water to remove residual substances. Special written permits are required which include a detailed description of the protective measures depending on the work to be done (e.g., full protective clothing and gas filter masks (classification ABEK)) (Bayer MaterialScience AG, 2004a).

Down stream users of 4,4'-methylenedicyclohexyl diisocyanate are informed by way of a material safety data sheet on the recommended safety measures (see above) (Bayer MaterialScience AG, 2004a).

Potential exposure at the workplace

In Germany for occupational settings, the maximum permissible concentration for 4,4'-methylene-dicyclohexyl diisocyanate is 0.054 mg/m³ according to TRGS 900.

The main process to manufacture 4,4'-methylenedicyclohexyl diisocyanate is by a phosgenation process. Thus special safety measures are taken to prevent any risk of exposure. These measures include a continuous phosgene monitoring coupled with an automatic water/ammonia spray system for abatement. Since 4,4'-methylenedicyclohexyl diisocyanate is closely associated with phosgene during manufacturing, these measures are also suited to ensure that neither the environment nor the workers are exposed to 4,4'-methylenedicyclohexyl diisocyanate. In the processing area, where 4,4'-methylenedicyclohexyl diisocyanate is used to manufacture powder coatings, 17 4,4'-methylenedicyclohexyl diisocyanate measurements (8 total shift and 9 short term measure-ments) were made between 1994 and 2001. All results were below the maximum permissible concentration (Bayer MaterialScience AG, 2004a).

Thermal degradation products formed during grinding and welding of certain polyurethanes were reported to include 4,4'-methylenedicyclohexyl diisocyanate. Traces of 4,4'-methylenedicyclohexyl diisocyanate (up to 2 µg/m^3) were detected as a thermolytic degradation product during joint welding of polyurethane floor covering in a small room with no ventilation in a car repair shop (Henriks-Eckerman et al., 2002).

4,4'-Methylenedicyclohexyl diisocyanate (which was used for the manufacturing of water pipes equipped with water flow measuring devices), was not detectable with a limit of detection of < 0.0006 mg/sample (< 0.0022 µg/l) in workplace air of an US plant (Lewis, 1980).

2.3.2 Consumer Exposure

4,4'-Methylenedicyclohexyl diisocyanate is exclusively used as an intermediate in chemical processes. A direct use of this substance is not known (Bayer MaterialScience AG, 2004a). Consistently, there is no registration of a consumer product containing 4,4'-methylenedicyclohexyl diisocyanate in the Danish, Finnish, Swedish (SPIN, 2004), and Swiss Product Register (2004). 4,4'-Methylenedicyclohexyl diisocyanate is confidentially listed in the Norwegian Product Register (SPIN, 2004), but since the main use category is "non-dispersive use", it is assumed that the confidential registration is also for industrial use only.

The exposure of consumers to 4,4'-methylenedicyclohexyl diisocyanate is unlikely to occur via consumer products, because no consumer product is known to contain 4,4'-methylenedicyclohexyl diisocyanate (Bayer MaterialScience AG, 2004a). An exposure of consumers to 4,4'-methylene-dicyclohexyl diisocyanate via the environment is also unlikely to occur because there are virtually no emissions of 4,4'-methylenedicyclohexyl diisocyanate, and 4,4'-methylenedicyclohexyl diisocyanate released to environment would rapidly be degraded by photooxidants (*cf.* Chapter 2.2.2) and water (*cf.* Chapter 2.2.3).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There are no data available (With regard to information on the fate of 4,4´-methylenedicyclohexyl diisocyanate in aqueous systems see chapter 2.2.3).

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

The acute inhalation toxicity of 4,4´-methylenedicyclohexyl diisocyanate (purity > 99.2 %) was studied by Bayer AG (1995a) by exposing Wistar rats in seven groups, each containing 5 males and 5 females. The method used was essentially that of OECD TG 403. Each group was nose only exposed to concentrations of the aerosol of the test substance. After exposure (4 hours) the animals were observed for two weeks. The actual mean concentrations of 4,4´-methylenedicyclohexyl diisocyanate were 151, 388, 418, 552, 730, 865 and 1352 mg/m^3. The test substance aerosol exhibited a particle-size indicating that this aerosol was of adequate respirability (90 % of the particle mass was ≤ 3 µm; mass median aerodynamic diameter (MMAD) ≈ 1.4 µm; geometric standard deviation (GSD) ≈ 1.8 µm). Rats exposed to ≥ 151 mg/m^3 experienced signs of respiratory tract distress (i.e. salivation, bradypnea, stridor). Exposure to concentrations of ≥ 388 mg/m^3 caused mortality, which occurred on the exposure day through post exposure day 4. Gross necropsy findings (less collapsed lungs including a hemorrhagic lung edema, red secretions in the nose, pale liver with lobular pattern, pale spleen and kidneys) were observed only in the rats which died during the observation period The LC_{50} (4 h) stated in this study (Bayer AG, 1995a) is 434 mg/m^3 with confidence limits (95 %) of 355 - 533 mg/m^3 both sexes combined.

Another study report (Mobay Chemical Corp., 1985) documented that the four-hour LC_{50} of 4,4´-methylenedicyclohexyl diisocyanate (purity technical grade, no further data) to male rats was 295 mg/m^3 with 95 % confidence interval of 221 to 380 mg/m^3, and to female rats it was 307 mg/m^3 with 95 % confidence interval of 268 to 327 mg/m^3. The no-observed-effect level was less than 113 mg/m^3. The animals were exposed, by heads only, to 4,4´-methylenedicyclohexyl diisocyanate aerosol and observed for two weeks after the exposure. The data on particle size distribution showed that the mass median aerodynamic diameter (MMAD) of all concentration groups were ≤ 2 µm but the geometric standard deviation (GSD) was in the range of 2.4 to 5.5. Differences in the analytical method for the determination of the chamber concentration between this study and the study conducted by Bayer ten years after (Bayer AG, 1995a) may account for marginal discrepancy of the LC_{50}-values. Due to the analytical method the airborne concentration measured were probably lesser than the actual one because the test substance partly would have been captured by reaction with filter material and/or humidity. Nevertheless the qualitative data of both studies are in agreement. All compound-exposed animals exhibited nasal and ocular irritation during exposure and post-exposure and the gross lesions observed were mainly in the nose and lung.

Dermal

In an early acute dermal toxicity study done by Monsanto Co. (1966) 1 rabbit/dose was used in 6 dose groups with alternating sex. 4,4´-Methylenedicyclohexyl diisocyanate (purity not specified) was applied as 50 % solution in corn oil or undiluted at the dose levels of 1000, 1580, 2510 and 3980 mg/kg bw or 6,310 and 10,000 mg/kg bw throughout a 24-hour exposure period. The test site was covered. There were no deaths. Transient reduction of activity and appetite was observed in animals at the two high dosage levels. No LD_{50} could be obtained from this study, and it was therefore > 10 g/kg bw.

Oral

An early acute oral toxicity study was conducted on rats with 4,4´-methylenedicyclohexyl diisocyanate (purity not specified) in doses up to 12,600 mg/kg bw (administered as 50 % solution in corn oil). Mortality occurred at ≥ 7940 mg/kg bw and the LD_{50} was determined to be 9900 mg/kg bw. Toxic symptoms included severe diarrhea, loss of appetite and increasing weakness. At autopsy liver discoloration and renal hyperemia were recorded (Monsanto Co., 1966).

Conclusion

4,4´-Methylenedicyclohexyl diisocyanate is of low oral and dermal acute toxicity with an oral LD_{50} (rat) of 9900 mg/kg bw and a dermal LD_{50} (rabbit) > 10,000 mg/kg. Toxic symptoms after oral administration included severe diarrhea, loss of appetite and increasing weakness. Assessment of the acute inhalation toxicity data indicates that exposure to respirable aerosols of 4,4´-methylene-dicyclohexyl diisocyanate confined predominantly to the respiratory tract. Clinical signs (salivation, bradypnea, stridor) indicated respiratory distress. A hemorrhagic lung edema was considered to be causative for mortality. An animal study according to OECD TG 403 gives a LC_{50} (4 h, rat) of 434 mg/m^3.

3.1.3 Irritation

Skin Irritation

Studies in Animals

In two well-conducted (but non-GLP) studies according to OECD TG 404 4,4´-methylene-dicyclohexyl diisocyanate (liquid and solid test sample, no data on purity) was applied under occlusive dressings for 4 hours to the intact but shaved skin of a group of 6 male albino New Zealand rabbits (Bayer AG, 1981 a, b)). Skin irritation was assessed after 4, 24, 48, 72 hours and 8 days using the Draize scale. The calculation of the primary irritation index was based on the scores of the 24 and 72 hours reading times for erythema and edema formation. In these studies 4,4´-methylenedicyclohexyl diisocyanate was considered as moderately irritating to the skin with an irritation index of 4.2 (liquid sample) and 3.6 (solid sample) of max 8.0 (3.1 - 5.0 = moderately irritating). At the end of the post observation period (8 days) surface skin scaling was observed.

In a study performed according to OECD TG 404 4,4´-methylenedicyclohexyl diisocyanate was considered as severely irritating to the skin after 4 hours semi-occlusive exposure (Bayer AG, 1994b). According to the guideline for reasons of animal welfare, due to the expected irritant potency of the test substance in the test only one animal was used. The scores according to the Draize scale of the 24, 48 and 72 hours reading times were used in calculating respective mean value. The mean value for erythema/eschar formation was 2.7 of max. 4 and the mean value for edema formation was 1.3 of max. 4. After 14 days the epidermis of the exposed skin area had become partially detached.

In 1996 the primary dermal irritation/corrosion potential of 4,4´-methylenedicyclohexyl diiso-cyanate was evaluated when applied to the skin of 3 rabbits under semi-occlusive conditions for exposure periods of 3-minutes, 1-hour, and 4-hours (Bayer Corporation, 1996). For this purpose the undiluted test material was applied to three separate areas on the intact skin on each animal´s back. In this well conducted GLP-study no evidence of corrosion was observed at any of the test sites for any of the exposure periods. Based on these results, the test material was not considered to be a corrosive material. Dermal irritation was evident at all exposure sites and was characterized by very slight to well-defined erythema (scores of 1 to 2 according to the Draize scale of max. 4) and very slight to slight edema (scores of 1 to 2 according to the Draize scale of max. 4). By day 21 all signs of edema had subsided and only one animal was noted with very slight erythema at all exposure sites. However, on day 21, areas of thickened skin were observed at some or all of the exposure sites for two animals. There were no remarkable signs of clinical toxicity and/or ill health noted during the course of this study.

Eye Irritation

Studies in Animals

In two studies according to OECD TG 405 4,4´-methylenedicyclohexyl diisocyanate (liquid and solid test sample) was instilled into the conjunctival sac of each eye of 6 male albino New Zealand rabbits (Bayer AG, 1981 c, d). The right eye was rinsed with saline 30 seconds after instillation and the left eye remained unrinsed. Eye irritation was assessed using the Draize scale. In these studies 4,4´-methylenedicyclohexyl diisocyanate was considered to be not irritating to the eye with an irritation index (24 - 72 hour) of 3.0 (liquid sample, with/without rinsing) and 0.4 (solid sample, with rinsing) and 6.3 respectively (solid sample, without rinsing) (0-10 = not irritating). However, the individual findings at the various observation times (24, 48, 72 hours) showed that irritation of the conjunctivae was evident for both test samples and both test procedures (with/without rinsing). Signs of irritation were characterized by redness and chemosis scored 1 to 2. By day 8 all signs of irritation had subsided for the animals, which have been treated with the solid sample. Slight effects

on the conjunctivae (score 1-2) at the end of the observation period were still observed in 3/6 rabbits treated with the liquid test material. Corneal opacity was restricted to 3/6 (solid/liquid, with rinsing) and 2/6 (solid, without rinsing) animals and was reversible within 72 hours at the latest.

Respiratory Tract Irritation

Studies in Animals

Based on 'regulatory' acute toxicity studies (*cf.* Chapter 3.1.2) no conclusions can be drawn regarding the respiratory irritating properties of 4,4´-methylenedicyclohexyl diisocyanate. The same applies for the studies that determined the 4,4´-methylenedicyclohexyl diisocyanate concentration causing a 50 % decrease in respiratory rate (RD_{50}) for mice (Mobay Chemical Corp., 1984; Weyel and Schaffer, 1985). This test system is restricted to vapors (= upper tract irritant). It is irrelevant for aerosols for which the deposit pattern strongly depends on the generation of the test atmosphere. For aerosols irritation of the respiratory tract is apparently more dependent on the specific site receiving the highest fraction of the dose rather than the total airborne concentration. However, the repeated dose studies (see 3.1.5 and 3.1.8) do indicate that 4,4´-methylenedicyclohexyl diisocyanate causes irritation of the respiratory tract.

Conclusion

4,4´-methylenedicyclohexyl diisocyanate is moderately to severe irritant to the skin of rabbits (OECD TG 404). Irritant effects were observed after instillation of 4,4´-methylenedicyclohexyl diisocyanate into the eyes of rabbits (OECD TG 405). The repeated dose studies indicate that 4,4´-methylenedicyclohexyl diisocyanate causes irritation of the respiratory tract.

3.1.4 Sensitisation

Studies in Animals

Skin

4,4´-Methylenedicyclohexyl diisocyanate, was assessed for sensitizing properties using a modified Guinea pig maximization test of Magnusson and Kligman by Bayer AG (1984). 4,4´-Methylenedicyclohexyl diisocyanate, 10 % in paraffin oil and Freund's Complete Adjuvant were injected intracutaneously on days 0 and 7 in 20 Guinea pigs. Dermal provocation applications of 0.03 and 0.1 % 4,4´-methylenedicyclohexyl diisocyanate in paraffin oil were made on day 21 (6 hours) and on day 35 (6 hours). Two negative control groups (one control group for each challenge) of 10 animals were treated with Freund's Complete Adjuvant and paraffin oil. 4,4´-Methylene-dicyclohexyl diisocyanate was not considered to be a skin sensitizer in this test.

This negative test result was confirmed by the findings of the same laboratory using the Guinea pig maximization test of Magnusson and Kligman, which comply mostly with OECD TG 406 (Bayer AG, 1985). 4,4´-Methylenedicyclohexyl diisocyanate, 1 % in paraffin oil and Freund's Complete Adjuvant were injected intracutaneously on day 0 in 20 Guinea pigs. The topical induction was done on day 7 with 10 % 4,4´-methylenedicyclohexyl diisocyanate for 48 hours. Dermal provo-cation applications of 0.001 and 0.01 % 4,4´-methylenedicyclohexyl diisocyanate in paraffin oil were made on day 21 (24 hours, occlusive). A negative control group of 10 animals was treated with Freund's Complete Adjuvant and paraffin oil.

The fact that slightly irritating test concentrations were applied for the challenge in both studies does not invalidate the findings that 4,4´-methylenedicyclohexyl diisocyanate is not a skin sensitizer in the Guinea pig maximization test.

Positive results were reported for 4,4´-methylenedicyclohexyl diisocyanate in the Buehler Assay (American Cyanamid Company 1984; Zissu, Binet and Limasset, 1998), mouse ear swelling test (Stadler and Karol, 1985; Thorne et al., 1987), the local lymph node assay (Dearman, Basketter and Kimber, 1992; Dearman, Spence and Kimber, 1992).

Stadler and Karol (1984) dealt with the relationship between inhalation of 4,4´-methylene-dicyclohexyl diisocyanate and the development of dermal sensitivity. For this purpose mice and guinea pigs were exposed to an aerosol (4,4´-methylenedicyclohexyl diisocyanate in acetone) for 2 hours/day on 3 consecutive days. Both species exhibited contact sensitivity upon subsequent dermal challenge whereas caution must be exercised because nose-only exposure system has an unavoidable contribution of dermal involvement.

Respiratory Tract

In an unpublished report of Bayer AG (1995b), sensitization of 8 guinea pigs with a single intradermal injection of 4,4´-methylenedicyclohexyl diisocyanate (100 µl, 0.13% solution in olive oil) followed after four weeks by inhalation challenge with the 4,4´-methylenedicyclohexyl diisocyanate hapten (30 min, 68 ± 3.6 mg/m^3) was examined. No immediate-onset responses were observed. Gross pathological examinations showed roughly the same incidence of lung changes in all Guinea pigs of this study. The histopathological assessment of the degree of eosinophilia re-vealed an increased influx of eosinophilic granulocytes in animals sensitized with 4,4´-methylene-dicyclohexyl diisocyanate. Because eosinophils are known to play a critical role in pathogenesis of asthma and of other hyperresponsive airway diseases the study provided evidence that 4,4´-methylenedicyclohexyl diisocyanate is a weak respiratory sensitizer in guinea pigs.

In another set of studies, the Murine Local Lymph Node Assay (LLNA) and Mouse IgE Test were used for the identification of respiratory allergens, frequently associated with specific IgE antibody (Dearman, Basketter and Kimber, 1992; Dearman, Spence and Kimber, 1992). These data suggest that 4,4´-methylenedicyclohexyl diisocyanate appears not to induce respiratory sensitization. In another study no pulmonary sensitivity was detected in any of 12 guinea pigs sensitized by topical exposure to 4,4´-methylenedicyclohexyl diisocyanate (Karol and Magreni, 1982).

Although some animal studies have been published for this endpoint, none are considered as validated assays to assess the potential for respiratory sensitization or asthma in humans.

Studies in Humans

Skin

In humans, case reports have demonstrated skin effects usually attributable to occupational exposure to 4,4´-methylenedicyclohexyl diisocyanate (Emmett, 1976; Malten, 1977; King, 1980; Israeli, Smirnov and Sculsky, 1981; Hoffman 1982; White, 1982; White, Stewart and Rycroft, 1983; Thompson and Belisito, 1997; Frick et al., 2003). Some of these cases were subsequently determined to be cases of dermal sensitization as confirmed by patch testing.

Respiratory Tract

There are no data available.

Conclusion

Animal data are not uniform however they frequently provide evidence of a skin sensitizing potential of 4,4´-methylenedicyclohexyl diisocyanate. Human case reports describe allergic contact dermatitis due to 4,4´-methylenedicyclohexyl diisocyanate exposure. Although no validated animal model is available to assess the potential for respiratory sensitization or asthma in humans, animal

data support to some extent the hypothesis that respiratory hypersensitivity may be induced by 4,4´-methylenedicyclohexyl diisocyanate.

3.1.5 Repeated Dose Toxicity

Studies in Animals

No repeated-dose toxicity studies are available for the oral and dermal route of exposure.

Inhalation

A subacute 4-week inhalation study with 4,4´-methylenedicyclohexyl diisocyanate according to the OECD TG 412 was performed with male and female Wistar rats (Bayer MaterialScience AG, 2004d). The rats were exposed under dynamic directed-flow nose-only exposure conditions for 6 hours/day on 5 days a week to 0, 1, 6 and 36 mg/m^3 (= target concentration). The mean actual exposure concentrations (= analytical concentration) were 1.057, 6.022 and 33.83 mg/m^3). Throughout the groups the mass median aerodynamic diameter (MMAD) was in the range of 1.0-1.2 µm (the geometric Standard deviation ≈2) and therefore was highly respirable to rats. Mortality did not occur up to the highest concentration tested. No clinical effects were recorded for the rats exposed to 1 mg/.m^3 At 6 mg/m^3 in most rats (7/10 males and 7/10 females) a borderline response, such as nasal discharge (wet nose), was observed whilst at 36 mg/m^3 in all rats respiratory tract irritation occurred (bradypnea, labored breathing patterns, irregular breathing patterns, tachypnea, nasal discharge, stridor, nostrils: red encrustations). The rats of this group experienced a mild hypothermia. No dose dependent effect on body weights was observed. There was no evidence of adverse hematological effects. Clinical-chemistry and urinalysis were without pathological findings. There were relative to body weight significantly elevated lung weights (app. 12 %) in rats of the high-level exposure group. No statistically significant or conclusive changes of the other absolute or relative organ weights were observed. Histopathological changes were restricted to the nasal cavities, pharynx, larynx, bronchi and lungs, which became unequivocal evident at 36 mg/m^3 and which occurred at 6 mg/m^3 in borderline intensity. All findings are suggestive of a direct local irritant mechanism at the location of initial deposition of aerosol. The laryngeal squamous epithelial metaplasia, which was observed at all exposure concentrations is considered to be a rather rat-specific response and causally related to adaptive rather than adverse effects. Therefore 1 mg/m^3 constitutes a no-observed-adverse-effect-level (NOAEL) for effects governed by respiratory tract irritation (histopathological changes in nasal passages, pharynx, bronchi and lung).

4,4´-Methylenedicyclohexyl diisocyanate has been examined in Wistar rats in a reproduction / developmental Toxicity Screening Test according to OECD TG 421 (for details and exposure period see Chapter 3.1.8; Bayer MaterialScience AG, 2004e). The rats were exposed nose-only daily for 6 hours/day to nebulized 4,4´-methylenedicyclohexyl diisocyanate in concentrations of 0, 1, 6 and 36 mg/m^3 (= target concentrations). In all exposure groups, the aerosol was highly respirable to rats, i.e., the average mass median aerodynamic diameter (MMAD) was ≈ 1 µm, the geometric standard deviation (GSD) was ≈ 2. No test substance-related effects on the appearance, health or behavior were observed in the F_0 parental animals up to 36 mg/m^3 except for clear signs of respiratory tract irritation (changes in breathing behavior) at 36 mg/m^3. At 6 mg/m^3 only serous nasal discharge and red encrusted nostrils were noted in F0 rats. One male of the high dose group was found dead during the premating period and one female of the high dose group has to be killed in moribund condition. Body weight gain was reduced in both sexes at 36 mg/m^3 at some time points. Transient reduced food consumption was restricted to the males of the high dose group. The absolute and relative lung weights were significantly elevated (14 and 18 %, respectively) at 36 mg/m^3 in male rats. Thus the NOAEL of the subacute study (= 1 mg/m^3) corresponds to these findings.

Conclusion

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure. A subacute inhalation study (1, 6 and 36 mg/m^3; 6 hours/day on five days/week for 4 weeks) with rats according to the OECD TG 412 indicates the respiratory tract to be the target organ of respirable 4,4´-methylenedicyclohexyl diisocyanate aerosol. The reported NOAEL for effects governed by respiratory tract irritation is 1 mg/m^3; the LOAEL is 6 mg/m^3 (i.e. histopathological changes in nasal passages, larynx and bronchi). The results of the reproduction/developmental toxicity screening test (OECD TG 421) corresponds to the results of the subacute study.

3.1.6 Mutagenicity

In vitro Studies

4,4´-Methylenedicyclohexyl diisocyanate did not induce gene mutations in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, TA 100 and TA 102 in an Ames test under GLP, and according to OECD TG 471 (Bayer MaterialScience AG, 2005). Concentrations of up to 50 µg/plate (with S9-mix) and 16 µg/plate (without S9-mix) were used. 4,4´-Methylenedicyclohexyl diisocyanate showed a strain-specific cytotoxicity, starting at 1.6 µg/plate. Appropriate reference mutagens were used as positive controls and showed the expected results throughout all tested strains.

A previous Ames test (DuPont De Nemours, 1977) which does not comply with the current guideline also gave no evidence for a genotoxic potential of 4,4´-Methylenedicyclohexyl diisocyanate in bacteria. Deficiencies of this Ames test from 1977 compared to today´s guideline are the number and kind of tester strains, the missing independent repeat experiment and the limited documentation.

4,4´-Methylenedicyclohexyl diisocyanate was tested in the chromosome aberration assay with Chinese hamster V79 cells *in vitro* according to OECD TG 473 (Bayer MaterialScience AG, 2004f). None of the cultures treated with 4,4´-methylenedicyclohexyl diisocyanate in the absence and in the presence of S9 mix up to cytotoxic concentrations (4.5 µg/ml without S9 mix and 12 mg/ml with S9 mix) showed biologically relevant or statistically significant increased numbers of aberrant metaphases. The positive controls induced clastogenic effects.

In vivo Studies

There are no data available.

Conclusion

4,4´-Methylenedicyclohexyl diisocyanate did not induce gene mutations in bacteria (OECD TG 471) and demonstrated no potential to induce chromosome aberrations in Chinese hamster V79 cells mammalian cells *in vitro* (OECD TG 473) either with or without metabolic activation

3.1.7 Carcinogenicity

There are no data available.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

In a reproduction/developmental toxicity screening test according to OECD TG 421 (Bayer MaterialScience AG, 2004e) Wistar rats (12 animals/sex/dose) were exposed to 4,4´-methylene-dicyclohexyl diisocyanate aerosol. The rats were exposed nose-only daily for 6 hours/day to concentrations of 0, 1, 6 and 36 mg/m^3 (= target concentrations). F_0 male and female rats were exposed for 2 weeks (premating exposure period), which was continued during the approximately 2 week mating period. Males were exposed for at least 28 days (prior to necropsy) whereas the exposure of the F_0 females continued during the pregnancy up to day 19 post coitum (p.c.). Exposure of the F_0 females was suspended up to the day of necropsy on day 4 - 6 p.p. (post partum), i.e., the time points at which F_1 pups were sacrificed. In all exposure groups, the aerosol was highly respirable to rats, i.e., the average mass median aerodynamic diameter (MMAD) was ≈ 1 µm, the geometric standard deviation (GSD) was ≈ 2. Clinical signs as changes in breathing behavior and/or serous nasal discharge were documented for F_0 animals of the 6 and 36 mg/m^3 groups. One male of the high dose group was found dead during the premating period and one female of the high dose group had to be killed in moribund condition. No effect on body weights gain, food consumption and necropsy findings, were observed at ≤ 6 mg/m^3. Significant increases of absolute and relative weights of the lungs were detected at 36 mg/m^3 in male rats. No effects of 4,4´-methylene-dicyclohexyl diisocyanate on reproductive parameters such as insemination index, gestation index and length and the number of implantation sites were described. At 36 mg/m^3 a slightly reduced fertility index was noted (0, 1, 6, 36 mg/m^3: fertility index: 91.7, 81.8, 83.8, 66.7* % (*= $p > 0.05$)). No remarkable clinical signs were seen in any F_1 pubs during the 4 day lactation period and body weight gain was comparable to the control animals. In the testes of both groups evaluated (control and high concentration F_0 animals) tubular degeneration (mainly multi/focal) was seen in the majority of animals. In the epididymides, spermatic debris and oligospermia occurred in almost all rats. These histopathological findings are concordant with the results of the spermatological evaluation of all animals (no or very low sperm motility and high percentage of abnormal sperms in control rats and in all concentration groups). Nevertheless the findings seen in the testes are not substance-related because they were found also in the control animals and they are dose in-dependent. Mechanical stress on the epididymides and testes caused by the narrowness of exposure restrainers seems to be responsible for the effects seen in all 4,4´-methylenedicyclohexyl diiso-cyanate and air exposed animals.

Based on these findings, the NOAELs were considered to be 1 mg/m^3 in males and females for general toxicity. Due to a slightly reduced fertility index at 36 mg/m³, 6 mg/m^3 is the NOAEL for reproductive toxicity in rats.

Developmental Toxicity

No effects of 4,4´-methylenedicyclohexyl diisocyanate on developmental parameters such as live birth index and viability index and no apparent malformation were found in pups of a reproduction/developmental toxicity screening test according to OECD TG 421 in which Wistar rats (12 animals/sex/dose) have been exposed daily for 6 hours/day during two weeks before mating until day 19 of gestation to nebulized 4,4´-methylenedicyclohexyl diisocyanate in concentrations of 0, 1, 6 and 36 mg/m^3 (= target concentrations; Bayer MaterialScience AG, 2004e).

The prenatal toxicity of 4,4´-methylenedicyclohexyl diisocyanate in pregnant Wistar rats was additionally investigated by aerosol inhalation according to OECD TG 414 (Bayer MaterialScience AG, 2004g). Mated female rats (at least 27/dose) were exposed nose-only to target concentrations

of 0, 1, 6 and 36 mg/m^3 for 6 h/day from day 6 to day 19 p.c.. Particle size determination of the aerosol yielded MMADs within the respirable range (≈ 1 µm, the geometric standard deviation (GSD) ≈ 2). Exposure to 4,4´-methylenedicyclohexyl diisocyanate aerosols caused no premature death. Clinical signs of respiratory tract irritation (i.e. decreased respiratory rates, labored breathing, irregular respiration and sounds consistent with rhinitis) became apparent at 36 mg/m^3. Furthermore, rough fur, serous nasal discharge, reddish encrusted nostrils, occurred in the 36 mg/m^3 group. From a pilot inhalation study (Bayer MaterialScience AG, 2004c) it is known that at this exposure concentration also the lung weights were significantly increased. At 6 mg/m^3 only single females evidenced clinical signs of beginning respiratory irritation. Reduction in food consumption occurred at 36 mg/m^3, which was accompanied by a delay of body weight development during the treatment period (approximately 24 % below controls) and during gestation (approximately 15 % below controls). Gross-pathologically no treatment-related findings in the dams occurred at any concentration. The gestation rate, appearance of placentas, placental weights, postimplantation loss, number of live fetuses, fetal sex distribution, and fetal weights were unaffected by treatment up to and including the concentration of 36 mg/m^3. With regard to the results on malformation a marginally increased incidence of ventricular septal defects of the heart (three fetuses out of three litters, 1.2 % of total fetuses) occurred at the 36 mg/m^3 level, which lay only marginally above the upper normal range (0.9 % affected fetuses) of scattering of the rat strain used.

The incidence and type of external or visceral deviations were unaffected by treatment at levels up to and including 6 mg/m^3. A statistically significantly increased incidence of slight dilation of lateral brain ventricles occurred at 36 mg/m^3. A treatment related effect for this anomaly is unlikely, as the incidence is normally broadly scattering between unaffected study groups, and because the value (11.3 % affected fetuses, 56.5 % affected litters) lay within the range of historical control data and data of different unaffected study groups of the rat strain used (up to 12.7 % affected fetuses, up to 65.0 % affected litters).

Nevertheless, a NOAEL of 6 mg/m^3 was determined in this study with regard to developmental toxicity.

Conclusion

Data from an inhalative reproduction/developmental toxicity screening test according to OECD TG 421 with rats (1, 6 and 36 mg/m^3) did not reveal substance related impairment of reproduction up to a 4,4´-methylenedicyclohexyl diisocyanate concentration of 6 mg/m^3. A slightly reduced fertility index was observed at an exposure level (36 mg/m^3) that was associated with parental toxicity. NOAELs were considered to be 1 mg/m^3 in males and females for general toxicity. NOAEL for reproductive toxicity is 6 mg/m^3.

Pre-natal inhalation toxicity testing in rats (OECD°TG°421) indicates the absence of selective toxicity to the development at levels up to 36 mg/m^3. No findings indicate any specific developmental effects such as live birth index, viability index and apparent malformation. The reported NOAEL$_{(developmental)}$ for 4,4´-methylenedicyclohexyl diisocyanate in a developmental toxicity study according to OECD TG 414 (1, 6 and 36 mg/m^3) is 6 mg/m^3/day. At the 36 mg/m^3 level that caused clear maternal respiratory tract toxicity (NOAEL$_{(maternal)}$ = 1 mg/m^3) increased incidences of ventricular septal defects of the heart and slight dilation of lateral brain ventricles were observed, which lay marginally above the upper or within the normal range of scattering of the rat strain used respectively.

3.1.9 Experience with human exposure

Eleven of 15 workers of a plant which has in 1981 established a new process to prevent glass bottles from cracking by coating the bottles with polyurethane (4,4´-methylenedicyclohexyl diisocyanate was used as monomer) suffered from several signs of an intoxication (Israeli, Smirnov and Sculsky, 1981). All workers dealt for the first time with 4,4´-methylenedicyclohexyl diisocyanate. The onset of the symptoms was observed 4 - 7 days after the exposure (no further details available) and all workers recovered within 10 - 14 days. With the symptoms which were recorded allergic and non-allergic skin reactions predominated (11/11). Six workers suffered from vertigo with or without headaches and four developed a decrease of the obstructive lung function, tachycardia and hypotension (EKG normal). The occupational hygiene with regard to ventilation was described as insufficient but no air monitoring has been done.

Additional information relating to experience with human exposure is presented in Chapters 2.3 and 3.1.4.

3.2 Initial Assessment for Human Health

4,4´-Methylenedicyclohexyl diisocyanate is of low oral and dermal acute toxicity with an oral LD_{50} (rat) of 9900 mg/kg bw and a dermal LD_{50} (rabbit) > 10,000 mg/kg. Toxic symptoms after oral administration included severe diarrhea, loss of appetite and increasing weakness. Assessment of the acute inhalation toxicity data indicates that exposure to respirable aerosols of 4,4´-methylene-dicyclohexyl diisocyanate confined predominantly to the respiratory tract. Clinical signs (salivation, bradypnea, stridor) indicated respiratory distress. A hemorrhagic lung edema was considered to be causative for mortality. An animal study according to OECD TG 403 gives a LC_{50} (4 h, rat) of 434 mg/m^3.

4,4´-Methylenedicyclohexyl diisocyanate is moderately to severely irritant to the skin of rabbits (OECD TG 404). Irritant effects were observed after instillation of 4,4´-methylenedicyclohexyl diisocyanate into the eyes of rabbits (OECD TG 405). The repeated dose studies indicate that 4,4´-methylenedicyclohexyl diisocyanate causes irritation of the respiratory tract.

Animal data are not uniform however they frequently provide evidence of a skin sensitizing potential of 4,4´-methylenedicyclohexyl diisocyanate. Human case reports describe allergic contact dermatitis due to 4,4´-methylenedicyclohexyl diisocyanate exposure. Although no validated animal model is available to assess the potential for respiratory sensitization or asthma in humans animal data support to some extent the hypothesis that respiratory hypersensitivity may be induced by 4,4´-methylenedicyclohexyl diisocyanate.

No results from repeated-dose toxicity tests are available for the oral and dermal route of exposure. A subacute inhalation study (1, 6 and 36 mg/m^3; 6 hours/day on five days/week for 4 weeks) with rats (OECD TG 412) indicates the respiratory tract to be the target organ of respirable 4,4´-methylenedicyclohexyl diisocyanate aerosol. The reported NOAEL for effects governed by respiratory tract irritation is 1 mg/m^3; the LOAEL is 6 mg/m^3 (i.e. histopathological changes in nasal passages, larynx and bronchi). The results of a reproduction/developmental toxicity screening test (OECD TG 421) corresponds to the results of the subacute study.

4,4´-Methylenedicyclohexyl diisocyanate did not induce gene mutations in bacteria (OECD TG 471) and demonstrated no potential to induce chromosome aberrations in Chinese hamster V79 cells *in vitro* (OECD TG 473) either with or without metabolic activation.

Data from an inhalative reproduction/developmental toxicity screening test according to OECD TG 421 with rats (1, 6 and 36 mg/m^3) did not reveal substance related impairment of

reproduction up to a 4,4´-methylenedicyclohexyl diisocyanate concentration of 6 mg/m^3. A slightly reduced fertility index was observed at an exposure level (36 mg/m^3) that was associated with parental toxicity. NOAELs were considered to be 1 mg/m^3 in males and females for general toxicity. NOAEL for reproductive toxicity is 6 mg/m^3.

Pre-natal inhalation toxicity testing in rats (OECD°TG°421) indicates the absence of selective toxicity to the development at levels up to 36°mg/m^3. No findings indicate any specific developmental effects such as live birth index, viability index and apparent malformation. The reported $NOAEL_{(developmental)}$ for 4,4´-methylenedicyclohexyl diisocyanate in a developmental toxicity study according to OECD TG 414 (1, 6 and 36 mg/m^3) is 6 mg/m^3/day. At the 36 mg/m^3 level that caused clear maternal respiratory tract toxicity ($NOAEL_{(maternal)}$ = 1 mg/m^3) increased incidences of ventricular septal defects of the heart and slight dilation of lateral brain ventricles were observed, which lay marginally above the upper or within the normal range of scattering of the rat strain used respectively.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The inherent property of 4,4'-methylenedicyclohexyl diisocyanate is to hydrolyze in an aquatic environment. In the following the toxicity of 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products is reported. Because of the rapid hydrolysis the assessment of the substance should be based on the hydrolysis products and not on 4,4'-methylenedicyclohexyl diisocyanate. Tests were conducted according to the GLP requirements and specially laid down test conditions.

Acute Toxicity Test Results

Concerning the acute toxicity of 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products towards aquatic species, experimental results for the three trophic levels (*cf.* Table 7) are available. QSAR (EcoSar, version 0.99) calculations showed substantially lower EC/LC_x values for the main hydrolysis product, 4,4'-methylenebis(cyclohexylamine).

A static acute test with *Danio rerio* (formerly *Brachydanio rerio*) was conducted according to the German UBA-proposal of 1984, which is in most parts equivalent to OECD TG 203. The test solutions were treated in water with ultra-turrax at 8000 rpm for 60 seconds, before the animals were added. Based on nominal concentration of 4,4'-methylenedicyclohexyl diisocyanate a 96 h-LC_{50} of 1.2 mg/l (nominal) was obtained (Bayer AG, 1992). However, this test has not been taken into account for the assessment of 4,4'-methylenedicyclohexyl diisocyanate. The aquatic half-life of this isocyanate is approximately 2 hours. Possible aquatic emissions of the substance would enter a wastewater treatment plant with a hydraulic retention time of several hydrolysis half-lives, which means that virtually all isocyanate would hydrolyze before it enters environmental waters. Thus, for assessment, not the isocyanate, but its hydrolysis product have to be tested. The hydrolysis product, 4,4'-methylenebis(cyclohexylamine), is the predominant form of the test substance in the following tests:

Before beginning of the following studies with *Danio rerio* (formerly *Brachydanio rerio*), *Daphnia magna* and *Scenedesmus subspicatus* pre-treatments were performed with 4,4'-methylenedicyclohexyl diisocyanate according to the recommendation mentioned in the "OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures" in order to accelerate the solution procedure. For that purpose the solutions of the test substance were prepared at a nominal concentration that were 5fold higher than the maximum water solubility found for

4,4'-methylenedicyclohexyl diisocyanate in preliminary tests. The solutions were treated in water with ultra-turrax 60 s/8000 rpm, afterwards stirred for 24 hours on a magnetic stirrer and finally filtered. Because of the short half-life of 4,4'-methylenedicyclohexyl diisocyanate, testing with the degradation products is required and has been conducted as seen in this test. Filtration removed additional insoluble hydrolysis products. Substance concentrations (mainly the soluble hydrolysis product 4,4'-methylenebis(cyclohexylamine)) were determined as TOC and back-calculated to the parent compound.

Acute toxicity to fish (*Danio rerio*) has been investigated in a limit test under static conditions according to Directive 92/69/EEC, C.1. A concentration of 30 mg/l 4,4'-methylenedicyclohexyl diisocyanate was pretreated before start as described above. A 96 h-LC50 of > 8.1 mg/l (determined as TOC and back-calculated to parent substance) was observed (Bayer AG, 2000b). At this concentration level 10 % mortality was detected, however, in a range finding test no mortality occurred at the highest concentration tested of 6 mg/l (nominal).

The hydrolysis product, 4,4'-methylenebis(cyclohexylamine), has a low ecotoxicity (LC_{50} (fish) = 38 mg/l) and was not classified as a PBT substance (EU PBT Working Group, 2003).

With the invertebrate *Daphnia magna* one acute static limit test in accordance with Directive 92/69/EEC, C.2, is available. For a test period of 48 hours an EC_0 value of ≥ 8.3 mg/l (determined as TOC and back-calculated to parent substance) was determined. At this concentration no mortality was observed. A start concentration of 45 mg/l 4,4'-methylenedicyclohexyl diisocyanate was treated for 24 h in the same way as described above (Bayer AG, 2000c).

Concerning the algal toxicity, a 72-hour test with *Scenedesmus subspicatus* was performed. According to Directive 92/69/EEC, C.3, the growth inhibition of the alga species was investigated with test substance concentrations in the range of 0.08 to 5 mg/l. The proceeding for preparation of the stock solution was in the same way as described above (stirring and filtration). A 72 h-E_rC_{50} of > 5 mg/l (determined as TOC and back-calculated to parent substance) was determined. As the test concentrations for the determination of the NOEC and LOEC were below the detection limit of the TOC determination (2 mg/l), the test results of the algal toxicity study refer to nominal concentrations. The arithmetic means of the TOC determination of the highest test concentration (5 mg/l) exhibited an expected recovery rate (90 %) of the test substance based on organic C (Bayer AG, 2000d).

Because of the short half-live of, testing with the degradation product is required for assessment. The results of the aquatic toxicity testing on fish, *Daphnia* and algae of virtually completely hydrolyzed 4,4'-methylenedicyclohexyl diisocyanate are compiled in Table 7 (all studies compiled in this Table have a reliability of 1).

Table 7 Acute toxicity of hydrolyzed 4,4'-methylenedicyclohexyl diisocyanate to fish, *Daphnia* and algae

Species	Test type	Result	Reference	IUCLID
Brachydanio rerio (fish)	Static, 96 h	LC_{50} > 8.1 mg/l* (10 % mortality rate)	Bayer AG, 2000b	4.1
Daphnia magna (crustacean)	Static, 48 h	EC_{50} > 8.3 mg/l*	Bayer AG, 2000c	4.2
Scenedesmus subspicatus (algae)	Static, 72 h	E_rC_{50} > 5 mg/l* NOEC (cell density) = 0.31 mg/l (n) LOEC (cell density) = 0.63 mg/l (n)	Bayer AG, 2000d	4.3

*determined as TOC and back-calculated to the parent compound
(n) nominal concentration

Chronic Toxicity Test Results

Chronic data for aquatic toxicity of 4,4'-methylenedicyclohexyl diisocyanate are not available.

Determination of $PNEC_{aqua}$:

Since there are acute test results available for 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products from three trophic levels, an assessment factor of 1000 was applied for the derivation of the $PNEC_{aqua}$ according to the EU Technical Guidance Document. The lowest acute tested concentration level was 5 mg/l for the alga species *Scenedesmus subspicatus*: 72 h-E_rC_{50} > 5 mg/l (nominal) (Bayer AG, 2000d). This value was used to calculate the

$PNEC_{aqua}$ > 5 µg/l

Toxicity to Microorganisms

Regarding the toxicity to microorganisms, an oxygen consumption inhibition test according to Commission Directive 88/302/EEC, Part C (corresponds to the OECD TG 209) with activated sewage sludge during 3 hours was performed and an EC_{50} of 191 mg/l (nominal) was determined (Bayer AG, 2000e). Before testing a pre-treatment was performed with the test substance according to the recommendation mentioned in the OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures. 4,4'-Methylenedicyclohexyl diisocyanate was directly weighted into water, treated by ultrasound for 3 - 4 hours and stirred overnight. This led to the nearly complete hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate and to the formation of the hydrolysis product, 4,4'-methylenebis(cyclohexylamine).

The EU PBT Working Group (2003) reports that the hydrolysis product, 4,4'-methylenebis(cyclohexylamine), has a low ecotoxicity (EC_3 (bacteria) = 80 mg/l).

By an oxygen consumption inhibition test according to ISO 8192 with activated sewage sludge during 3 hours, an EC_{50} of 19 mg/l (nominal) was determined under conditions which were not relevant for assessment (Bayer AG, 1992).

Microbial toxicity of the hydrolysis products of 4,4'-methylenedicyclohexyl diisocyanate is presented in Table 8.

Table 8 Toxicity of hydrolyzed 4,4'-methylenedicyclohexyl diisocyanate to microorganisms

Species	Endpoint	Parameter	Effects	Reference	IUCLID
Activated sludge	Inhibition of respiration	3 h-EC_{50}	191 mg/l (n)	Bayer AG, 2000e	4.4

(n) nominal concentration

4.2 Terrestrial Effects

No data available.

4.3 Other Environmental Effects

No data available.

4.4 Initial Assessment for the Environment

4,4'-Methylenedicyclohexyl diisocyanate is a slightly yellowish, moisture/water sensitive liquid with a melting point of 15 °C. 4,4'-Methylenedicyclohexyl diisocyanate has a relative density of 1.07 at 25 °C, a boiling point of 167 - 168 °C (at 2 hPa), and a vapor pressure of 2.13 x 10^{-5} hPa at 25 °C [Directive 92/69/EEC, A.4]. A water solubility and a log K_{OW} are not determinable due to the instability of 4,4'-methylenedicyclohexyl diisocyanate in water. The flash point of 4,4'-methylenedicyclohexyl diisocyanate is 200 °C [DIN 51758], the ignition point is 225 °C and the viscosity is approximately 30 mPa x s at 25 °C [DIN ISO EN 3219/A.3]. The calculated half-life of 4,4'-methylenedicyclohexyl diisocyanate in air due to indirect photodegradation is about 15.0 h.

4,4'-Methylenedicyclohexyl diisocyanate hydrolyses rapidly in the presence of water, the major product in aqueous phase is 4,4'-methylenebis(cyclohexylamine). In water, a half-life for 4,4'-methylenedicyclohexyl diisocyanate of approximately 2 hours was determined experimentally. Due to the rapid hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate, a transport of the substance between environmental compartments is unlikely. Consequently, a calculation of the Henry Law Constant and of the distribution between the environmental compartments according to the Mackay fugacity model level 1 is not suitable.

However, several aquatic toxicity tests have been undertaken with 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products. Because of the rapid hydrolysis the assessment of the substance should be based on the hydrolysis products and not on 4,4'-methylenedicyclohexyl diisocyanate. The hydrolysis product 4,4'-methylenebis(cyclohexylamine) was assessed by the EU PBT Working Group. The hydrolysis product was not classified as a PBT substance.

4,4'-Methylenedicyclohexyl diisocyanate is not readily biodegradable.

Due to the rapid hydrolysis 4,4'-methylenedicyclohexyl diisocyanate is neither persistent in the water compartment nor bioaccumulative. The calculated K_{oc}-value indicates that 4,4'-methylenedicyclohexyl diisocyanate may strongly adsorb to soil but due to its rapid hydrolysis any emission to the terrestrial compartment would be affected by humidity and therefore, geoaccumulation of 4,4'-methylenedicyclohexyl diisocyanate is not expected to occur.

Concerning the toxicity of 4,4'-methylenedicyclohexyl diisocyanate and its hydrolysis products towards aquatic species, reliable experimental results of tests with fish, *Daphnia*, and algae are

available (* = determined as TOC and back-calculated to parent substance, n = nominal concentration).

Danio rerio (fish):	96 h-LC_{50} > 8.1 mg/l*,	[Directive 92/69/EEC, C.1]
Daphnia magna (aq. invertebrate):	48 h-EC_{50} > 8.3 mg/l*,	[Directive 92/69/EEC, C.2]
Scenedesmus subspicatus (algae):	72 h-E_rC_{50} > 5 mg/l*,	[Directive 92/69/EEC, C.3]
Activated sewage sludge (bacteria):	3 h-EC_{50} = 191 mg/l (n),	[Directive 88/302/EEC, Part C (corresponds to the OECD TG 209)].

It has to be considered that the toxicity observed in the reported aquatic studies was caused both by the 4,4'-methylenedicyclohexyl diisocyanate as well as by the hydrolysis products due to the instability of the test substance.

Based on the acute aquatic toxicity data on three trophic levels (fish, *Daphnia*, algae), the Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000 applied to the lowest acute effect concentration. The lowest 72 h-E_rC_{50}-value of > 5 mg/l obtained for the alga species *Scenedesmus subspicatus* was used to derive a $PNEC_{aqua}$ of > 5 µg/l.

5 RECOMMENDATIONS

Human Health:

The chemical possesses properties indicating a hazard for human health (severe irritation of skin, eye and respiratory tract, sensitization of skin and predicted to be a respiratory tract sensitizer because it is a diisocyanate). Based on data presented by the Sponsor country (relating to production by one producer which accounts for approximately 5 % to 50 % of global production and relating to the use pattern in several OECD countries), occupational exposure is anticipated to be low and there are no known consumer uses. Therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environmental:

The chemical (including its hydrolysis products) possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country (relating to production by one producer which accounts for approximately 5 % to 50 % of global production and relating to the use pattern in several OECD countries), exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country. The chemical is currently of low priority for further work.

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S I D S

Dossier

Existing Chemical	**:**	ID: 5124-30-1
CAS No.	**:**	5124-30-1
EINECS Name	**:**	4,4'-methylenedicyclohexyl diisocyanate
EC No.	**:**	225-863-2
Molecular Weight	**:**	262.35 g/mol
Molecular Formula	**:**	C15H22N2O2

Producer related part

Company	**:**	Bayer AG
Creation date	**:**	08.12.1994

Substance related part

Company	**:**	Bayer AG
Creation date	**:**	08.12.1994
Status	**:**	
Memo	**:**	
Printing date	**:**	09.11.2006
Revision date	**:**	12.02.1997
Date of last update	**:**	09.11.2006
Number of pages	**:**	131
Chapter (profile)	**:**	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	**:**	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	**:**	Flags: without flag, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, 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

IUPAC Name : 1,1´-methylenebis(4-isocyanatocyclohexane)
Smiles Code : O=C=NC(CCC(C1)CC(CCC(N=C=O)C2)C2)C1
Molecular formula : C15 H22 N2 O2
Molecular weight : 262.35 g/mol
Petrol class :

Remark : IUPAC name was generated by ICS naming system (http://by-cis.bayer-ag.com:81/icsweb/naming/naming_single)
Flag : Critical study for SIDS endpoint
02.01.2006 (93)

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : liquid
Purity : 100 % w/w
Colour : light yellowish
Odour : slight lachrymatory odour

Remark : 100 % purity relates to the usuable components of the product (isomers of 4,4'-methylenedicyclohexyl diisocyanate and 2,4'-methylenedicyclohexyl diisocyanate)
Flag : Critical study for SIDS endpoint
22.11.2004 (32)

Remark : As long as not otherwise stated, the isomers mixture of 92 % 4,4´-isomers and 8 % 2,4´-isomers is meant
Result : The approximate isomeric composition of the pure industrial product is:
4,4'-methylenedicyclohexyl diisocyanate (in total 92 %)
- cis,cis-isomer 14 %
- cis,trans-isomer 58 %
- trans,trans-isomer 20 %
- others 8 % (2,4'-methylenedicyclohexyl diisocyanate)

Flag : Critical study for SIDS endpoint
14.12.2005 (45)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1,1-Methylenebis(4-isocyanatocyclohexane)

Flag : Critical study for SIDS endpoint
10.09.2004 (4) (45)

4,4'-Dicyclohexylmethanediisocyanate

Flag : Critical study for SIDS endpoint
10.09.2004 (4)

4,4'-Diisocyanatodicyclohexylmethane

Flag : Critical study for SIDS endpoint
10.09.2004 (45)

4,4'-Methylenebis(cyclohexyl isocyanate)

Flag : Critical study for SIDS endpoint
10.09.2004 (4)

Bis(4-isocyanatocyclohexyl)methane

Flag : Critical study for SIDS endpoint
10.09.2004

Cyclohexane, 1,1'-methylenebis(4-isocyanato)-

Remark : CAS name
Flag : Critical study for SIDS endpoint
16.09.2004 (4)

Desmodur W

Flag : Critical study for SIDS endpoint
(45)

Dicyclohexylmethane-4,4'-diisocyanate

Flag : Critical study for SIDS endpoint
10.09.2004 (4)

H12MDI

Flag : Critical study for SIDS endpoint
10.09.2004 (84)

Hydrogenated MDI

Flag : Critical study for SIDS endpoint
10.09.2004 (4)

Hylene W

Flag : Critical study for SIDS endpoint
25.11.2004

Methylene bis(4-isocyanatocyclohexane)

Flag : Critical study for SIDS endpoint
10.09.2004

Methylenebis(1,4-cyclohexylene) diisocyanate

Flag : Critical study for SIDS endpoint
10.09.2004

Methylenedi-1,4-cyclohexylene isocyanate

Flag : Critical study for SIDS endpoint
10.09.2004

Methylenedi-4-cyclohexylene diisocyanate

Flag : Critical study for SIDS endpoint
10.09.2004 (4)

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name :
Molecular formula :
Value :

Remark : no impurities reported
22.11.2004

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 1000 - 5000 tonnes produced in 2003

Remark : The global production capacity of 4,4'-methylenedicyclohexyl diisocyanate is 10,000-20,000 tonnes/a, with most of it in the USA. In Germany, Bayer MaterialScience AG is the only producer and has a manufacturing capacity of 1,000-5,000 tonnes/a of 4,4'-methylenedicyclohexyl diisocyanate.

Flag : Critical study for SIDS endpoint
22.11.2004 (31)

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 system 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 water (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)

1.6.2 CLASSIFICATION

Classified	:	as in Directive 67/548/EEC
Class of danger	:	irritating
R-Phrases	:	(36/37/38) Irritating to eyes, respiratory system and skin
Specific limits	:	

Classified	:	as in Directive 67/548/EEC
Class of danger	:	sensitizing
R-Phrases	:	(42/43) May cause sensitization by inhalation and skin contact
Specific limits	:	

Classified	:	as in Directive 67/548/EEC
Class of danger	:	toxic
R-Phrases	:	(23) Toxic by inhalation
Specific limits	:	

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use	:	type
Category	:	Non dispersive use
Flag	:	Critical study for SIDS endpoint

22.11.2004 (85)

Type of use	:	industrial
Category	:	Chemical industry: used in synthesis
Remark	:	Used for the manufacture of rubber and plastic products, industrial paints, chemical products, construction and transport equipment
Flag	:	Critical study for SIDS endpoint

22.11.2004 (85)

Type of use : use
Category : Intermediates

Remark : 4,4'-Methylenedicyclohexyl diisocyanate is registered as a component in approximately 50 industrial products in the Danish, Finnish, and Swedish Product Registers with a consumption of about 30 tonnes/a in 2000 and 2001 (last years of record). There is no registration for a consumer product. It is confidentially listed in the Norwegian Product Register. The main use category is "non-dispersive use".
Flag : Critical study for SIDS endpoint
22.11.2004 (85)

Type of use : use
Category : Intermediates

Remark : The Swiss Product Register lists 34 industrial products (with concentrations of up to 100 % 4,4'-methylenedicyclohexyl diisocyanate), but no consumer product containing 4,4'-methylenedicyclohexyl diisocyanate.
The following industrial product categories were reported:
auxiliary material; cleaning agent; glue, surfacer, cement; sealing mass; hardener; paints, dyes, lacquers; plastic molding
Flag : Critical study for SIDS endpoint
22.11.2004 (89)

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 : MAK (DE)
Limit value : .054 mg/m3
Short term exposure limit value
Limit value :
Time schedule : 8 hour(s)
Frequency : times

Remark : Mean for 8 h shift
Flag : Critical study for SIDS endpoint
22.11.2004 (32)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : other: Bayer AG

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

Remark : Identification no. 6724.
Class of danger: according to VwVwS Appendix 3

21.12.2004 (32)

1.8.4 MAJOR ACCIDENT HAZARDS

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

Remark : Reported in Appendix II Nr. 4 c; III Teil 2 Kat. 2; IV Kat. 2 ("giftige Stoffe")

23.06.1998

1.8.5 AIR POLLUTION

Classified by : other: Bayer AG
Labelled by :
Number : other: TA-Luft 5.2.5 organic substances
Class of danger : I

22.11.2004 (32)

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

Type : degradation product in water
CAS-No : 1761-71-3
EC-No : 217-168-8
EINECS-Name : 4,4'-methylenebis(cyclohexylamine)
IUCLID Chapter : 3.1.2

16.09.2004 (29)

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 : 1
Date of search : 13.08.2003

16.09.2004

Type of search : Internal and External
Chapters covered : 2
Date of search : 13.08.2003

16.09.2004

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 13.08.2003

Remark : Last literature search for Chapter 3.2.1 27-JUL-2004
16.09.2004

Type of search : Internal and External
Chapters covered : 5
Date of search : 22.01.2003

Remark : Human Health: last literature search January 22, 2003: CAS number search in external and internal databases, e.g. Biosis, Embase, Toxline, Scisearch

14.09.2004

1.13 REVIEWS

2.1 MELTING POINT

Value : 15 °C
Sublimation :
Method : other: no data
Year : 2004
GLP : no data
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, purity: 92 %

Result : The melting point of the isomeric mixture of 4,4'-methylenedicyclohexyl diisocyanate (cis, cis-isomer: 14 %; cis, trans-isomer: 58 % and trans, trans-isomer: 20 %, 8 % 2,4-isomers) is 15 °C.
The melting point of 4,4'-methylenedicyclohexyl diisocyanate is 83 °C.
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
19.09.2004 (45)

Value : < -10 °C
Sublimation :
Method : other: no data
Year : 2004
GLP : no data
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : Freezing point. No information supplied on the isomeric composition of the substance
Reliability : (2) valid with restrictions
Data from handbook or collection of data
19.09.2004 (78)

Value : 49.8 °C
Sublimation :
Method : other: no data
Year : 1975
GLP : no
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, purity not below 99.9 %

Remark : A sample of 4,4'-methylenedicyclohexyl diisocyanate having a melting point of 49.8 +/- 0.2 °C was used for different investigations concerning physicochemical properties.
No information supplied on the isomeric composition of the substance
Reliability : (2) valid with restrictions
Basic data given
22.11.2004 (99)

Value : = 78 °C
Sublimation :
Method : other: no data
Year : 1971
GLP : no
Test substance : other TS: trans, trans-4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Result : The solidification point of crystalline trans,trans-4,4'-methylenedicyclohexyl diisocyanate is 78 °C
Reliability : (2) valid with restrictions

Basic data given
04.11.2005 (40) (74)

Value : = 80 °C
Sublimation :
Method : other: no data
Year : 1968
GLP : no
Test substance : other TS: trans, trans-4,4'-Diisocyanatodicyclohexylmethane, no purity specified

Remark : trans,trans-4,4'-Methylenedicyclohexyl diisocyanate is prepared by reacting a carbon dioxide-4,4'-methylenebis(cyclohexylamine)-adduct (contains 95% w/w of the trans,trans-isomer) with phosgene
Reliability : (2) valid with restrictions
Basic data given
10.05.2004 (5) (40)

Value : 81.5 - 82 °C
Sublimation :
Method : other: no data
Year : 1965
GLP : no
Test substance : other TS: trans, trans-4,4'-Methylenedicyclohexyl diisocyanate, purity: 98%

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
04.11.2005 (40)

Value : ca. 25 °C
Sublimation :
Method : other: no data
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : Point of solidification
Reliability : (4) not assignable
Manufacturer data without proof
23.11.2004 (32)

Value : 19 - 23 °C
Sublimation :
Method : other: no data
Year : 2004
GLP : no data
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : No information given on isomeric composition of mixture
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
19.09.2004 (92)

Value : 60 - 71 °C
Sublimation :
Method : other: no data
Year : 1977
GLP : no
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : No information given on isomeric composition of mixture
Reliability : (4) not assignable
Manufacturer data without proof
19.09.2004 (6)

2.2 BOILING POINT

Value : 167 - 168 °C at 2 hPa
Decomposition :
Method : other: no data
Year : 1969
GLP : no
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : No information given on isomeric composition of mixture. The British patent 1.173.890 is the English (British) version of the French patent 1.578.808
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
19.09.2004 (60) (81) (88)

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

Remark : Not measurable (decomposition) at standard pressure
Reliability : (4) not assignable
Manufacturer data without proof
02.11.2005 (32)

Value : 155 - 160 °C at .67 hPa
Decomposition :
Method : other: no data
Year : 1965
GLP : no
Test substance : other TS: trans, trans-4,4'-Methylenedicyclohexyl diisocyanate, purity: 92 %

Reliability : (2) valid with restrictions
Basic data given
04.11.2005 (40)

2.3 DENSITY

Type :
Value : 1.07 at 25 °C
Method : other: no data
Year : 2004
GLP : no data
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : No information supplied on the isomeric composition of the substance
Reliability : (2) valid with restrictions
Data from handbook or collection of data

Flag : Critical study for SIDS endpoint
19.09.2004 (78)

Type : density
Value : 1.0058 g/cm³ at 55 °C
Method : other: no data
Year : 1975
GLP : no
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, purity not below 99.9 %

Remark : The method of determination of the density was described in an earlier report which is not available (Zhuravleva EZ and Melent'eva TI, All-Union Scientific and Technical Conference on the Chemistry and Technology of Production, Processing, and Applications of Polyurethanes and Intermediates for their Production, February 10-13, 1971, Vladimir. Abstracts of Papers [in Russian] (1970), p. 17).
Result : The temperature dependence of the density of 4,4'-methylenedicyclohexyl diisocyanate was determined:

t [°C]	density [g/m3]
55	1.0058
60	1.0024
65	0.9990
70	0.9954
75	0.9920
80	0.9884

In the temperature range studied the density of the diisocyanate decreases linearly with increase of temperature
Reliability : (2) valid with restrictions
Basic data given
19.09.2004 (99)

Type : density
Value : ca. 1.07 g/cm³ at 25 °C
Method : other: DIN EN ISO 2811
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Manufacturer data without proof
23.11.2004 (32)

Type : density
Value : 1.029 g/cm³ at 70 °C
Method : other: no data
Year : 1977
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Manufacturer data without proof
23.11.2004 (6)

Type : density
Value : 1.07 g/cm³ at 20 °C
Method : other: no data
Year : 2004
GLP : no data
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : No information supplied on the isomeric composition of the substance
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
19.09.2004 (92)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .0000213 hPa at 25 °C
Decomposition :
Method : Directive 92/69/EEC, A.4
Year : 1994
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Vapour pressure at different temperatures:
1.22*10E-05 hPa at 20 °C,
2.13*10E-05 hPa at 25 °C,
3.00*10E-04 hPa at 50 °C
Reliability : (2) valid with restrictions
Non-GLP guideline study
Flag : Critical study for SIDS endpoint
23.11.2004 (16) (32)

Value : .0013 hPa at 25 °C
Decomposition :
Method : other (measured): no data
Year : 2004
GLP : no data
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : No information supplied on the isomeric composition of the substance
Reliability : (2) valid with restrictions
Data from handbook or collection of data
19.09.2004 (78)

Value : .000436 hPa at 53.7 °C
Decomposition :
Method :
Year : 1975
GLP : no
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, purity not below 99.9 %

Method : The vapour pressure was measured by Knudsen's effusion method with the aid of diaphragms having orifices 4.10E-04 and 17.49E-04 cm2 in area and Clausing coefficients 0.8060 and 0.8956.
Remark : No information supplied on the isomeric composition of the substance
Result : The temperature dependence of the vapour pressure of 4,4'-methylenedicyclohexyl diisocyanate was determined:

t [°C]	vapour pressure [hPa]
53.7	0.000436
75.7	0.002782
85.9	0.006158
99.6	0.016945

		110.6 0.037437 114.3 0.046516 130.1 0.128883
Reliability	:	(2) valid with restrictions Basic data given
22.11.2004		(99)
Value	:	.4 hPa at 138 °C
Decomposition	:	
Method	:	other (measured): no data
Year	:	1977
GLP	:	no
Test substance	:	other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified
Remark	:	No information supplied on the isomeric composition of the substance
Result	:	Vapour pressure at different temperatures: 0.400 hPa at 138 °C; 5.866 hPa at 189 °C 0.533 hPa at 140 °C; 12.66 hPa at 210 °C 0.667 hPa at 145 °C; 29.33 hPa at 232 °C 1.467 hPa at 160 °C; 71.99 hPa at 245 °C 3.333 hPa at 178 °C; Estimated to be 1013 hPa at 360 °C
Reliability	:	(4) not assignable Manufacturer data without proof
19.09.2004		(6)
Value	:	.0013 hPa at °C
Decomposition	:	
Method	:	other (measured): no data
Year	:	2004
GLP	:	no data
Test substance	:	other TS:4,4'-Methylenedicyclohexyl diisocyanate, no purity specified
Remark	:	No information supplied on the isomeric composition of the substance
Reliability	:	(4) not assignable Data from non peer-reviewed handbook or collection of data
31.10.2005		(92)
Value	:	.00058 - .00172 hPa at 25 °C
Decomposition	:	
Method	:	other (calculated): EPIWIN MPBPWIN v1.41
Year	:	2005
GLP	:	no
Test substance	:	other TS: 4,4'-Methylenebis(cyclohexylamine)
Result	:	Vapor pressure estimations using a boiling point of 320.00 °C (user entered): 0.000438 mm Hg = 0.00058 hPa (Antoine Method) 0.000671 mm Hg (Modified Grain Method) 0.00129 mm Hg = 0.00172 (Mackay Method) Selected vapor pressure 0.000671 mm Hg = 0.00089 hPa (Modified Grain Method)
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint
22.12.2005		(94)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	at °C
pH value	:	
Method	:	other (calculated): Fragment
Year	:	2004
GLP	:	
Test substance	:	other TS: 4,4'-Methylenedicyclohexyl diisocyanate
Method	:	This endpoint can not be determined experimentally due to rapid hydrolysis. Fragment method calculation TYPE | NUM | FRAGMENT | COEFF | VALUE Frag | 9 | -CH2- | 0.4911 | 4.4199 Frag | 4 | -CH | 0.3614 | 1.4456 Frag | 2 | -N=C=O | 0.0100**| 0.0200 Const | | | 0.2290 log Kow = 6.1145 **An estimated coefficient was used
Remark	:	The calculation of log Kow for 4,4'-methylenedicyclohexyl diisocyanate is unsuitable. A calculated theoretical log Kow value reflects the undissociated molecule without influence of water. 4,4'-Methylenedicyclohexyl diisocyanate hydrolyzes rapidly in the presence of water with a half life of approximately 2 hours (cf. Chapter 3.1.2, stability in water)
Result	:	Log Kow (version 1.66 estimate): 6.11 NOTE: Isocyanates hydrolyze....estimate questionable! In water, 4,4'-methylenedicyclohexyl diisocyanate hydrolyzes with a half-life of approximately 2 h.
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

31.10.2005 (93)

Partition coefficient	:	octanol-water
Log pow	:	2.03 - 2.55 at °C
pH value	:	
Method	:	other (calculated)
Year	:	2003
GLP	:	no data
Test substance	:	other TS: 4,4'-Methylenebis(cyclohexylamine)
Result	:	For 4,4'-methylenebis(cyclohexylamine) a measured log Kow (OECD 107) of 2.03 and calculated log Kow (QSAR) = 2.55 were determined
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

22.12.2005 (58)

Partition coefficient	:	octanol-water
Log pow	:	3.26 at 25 °C
pH value	:	
Method	:	other (calculated): EPIWIN KOWWIN Program (v1.67)
Year	:	2005
GLP	:	no
Test substance	:	other TS: 4,4'-Methylenebis(cyclohexylamine)

Test condition	:	LOGKOW Fragment method: 9 -CH2- [aliphatic carbon] (0.4911) 4.4199 4 -CH [aliphatic carbon] (0.3614) 1.4456 2 -NH2 [aliphatic attach] (-1.4148) -2.8296 Equation constant 0.2290 log Kow = 3.2649
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

22.12.2005 (94)

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	:	
Deg. product	:	
Method	:	other: no data
Year	:	2004
GLP	:	no data
Test substance	:	other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified
Remark	:	No information supplied on the isomeric composition of the substance
Result	:	4,4'-Methylenedicyclohexyl diisocyanate hydrolyzes in water with a half live of 2 hours (cf. Chapter 3.1.2 of this IUCLID)
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
Flag	:	Critical study for SIDS endpoint

19.09.2004 (78)

Solubility in	:	Water
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	4,4'-Methylenedicyclohexyl diisocyanate is insoluble in water. It hydrolyzes in contact with water and forms carbon dioxide
Reliability	:	(4) not assignable Manufacturer data without proof

23.11.2004 (32)

Solubility in	:	Water
Value	:	at °C

pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: no data
Year	:	2004
GLP	:	no data
Test substance	:	other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified
Remark	:	No information supplied on the isomeric composition of the substance
Result	:	4,4'-Methylenedicyclohexyl diisocyanate is insoluble/reactive in water
Reliability	:	(4) not assignable Data from non peer-reviewed handbook or collection of data

31.10.2005 (41) (92)

Solubility in	:	Water
Value	:	5 - 5.8 g/l at 20 °C
pH value	:	11.5
concentration	:	5 g/l at 20 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: no data
Year	:	2000
GLP	:	no data
Test substance	:	other TS: 4,4'-Methylenebis(cyclohexylamine), no purity reported
Result	:	Data from IUCLID
Source	:	Data from Bayer AG and Huels AG
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

22.12.2005 (58)

Solubility in	:	Water
Value	:	1146 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: calculated: EPIWIN WSKOW v1.41
Year	:	2005
GLP	:	no
Test substance	:	other TS: 4,4'-Methylenebis(cyclohexylamine)
Remark	:	4,4'-Methylenebis(cyclohexylamine) is expected not to hydrolyse in aquaeous solution due to lack of hydrolyzable groups (expert judgement)
Result	:	With the WSKOW Program (v1.41), a water solubility of 1146 mg/l is calculated.

With the ECOSAR Program (v0.99h), a water solubility of 207.6 mg/l is calculated.
With the Water Sol Progam (v1.01), a water solubility of 16055 mg/l is obtained

Test condition : Equation used to make water solubility estimate:
Log S (mol/l) = 0.693-0.96 log Kow-0.0092(Tm-25)-0.00314 MW + Correction (Amine, aliphatic 0.838)
log Kow used by water solubility estimate: 3.26
Melting Pt (Tm) = 15.00 °C (Tm = 25 °C used for all liquids)

Reliability : (2) valid with restrictions
Accepted calculation method

22.12.2005 (94)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : 200 °C
Type :
Method : other: DIN 51758
Year : 1979
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
23.11.2004 (7)

Value : > 201.7 °C
Type :
Method : other: no data
Year : 2004
GLP : no data
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : No information supplied on the isomeric composition of the substance
Reliability : (2) valid with restrictions
Data from handbook or collection of data
19.09.2004 (78)

Value : 199 °C
Type :
Method : other: no data
Year : 1976
GLP : no
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, purity not below 99.9 %

Remark : The experimental technique and the method used for the calculation were described in an earlier report which is not available (Monakhov VT, Methods for Investigating the Fire Hazards of Substances [in Russian], Izd. "Khimiya", Moscow (1972)).
No information supplied on the isomeric composition of the substance

Result : The experimentally determined flash point of 4,4'-methylenedicyclohexyl diisocyanate was 199 °C and the calculated flash point was 223 °C. The results of the determinations were reduced to normal atmospheric pressure

Test condition : The test was performed in an open crucible.
Reliability : (2) valid with restrictions
Basic data given
22.11.2004 (98)

Value : ca. 200 °C
Type :
Method : other: DIN EN 22719
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Manufacturer data without proof
23.11.2004 (32)

Value : 210 °C
Type :
Method : other: no data
Year : 1977
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Manufacturer data without proof
23.11.2004 (6)

Value : 201.7 °C
Type :
Method : other: no data
Year : 2004
GLP : no data
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : No information supplied on the isomeric composition of the substance
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
22.12.2005 (41)

Value : > 110 °C
Type :
Method : other: no data
Year : 2004
GLP : no data
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Remark : No information supplied on the isomeric composition of the substance
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
22.12.2005 (92)

2.8 AUTO FLAMMABILITY

Value : 225 °C at
Method : other: no data
Year : 1976
GLP : no
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, purity not below 99.9 %

Remark	:	The experimental technique and the method used for the calculation were described in an earlier report which is not available (Monakhov VT, Methods for Investigating the Fire Hazards of Substances [in Russian], Izd. "Khimiya", Moscow (1972)). No information supplied on the isomeric composition of the substance
Result	:	The experimentally determined ignition point of 4,4'-methylenedicyclohexyl diisocyanate was 225 °C and the calculated ignition point was 226 °C. The results of the determinations were reduced to normal atmospheric pressure.
Test condition	:	The test was performed in an open crucible
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint
22.11.2004		(39) (98)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Value	:	ca. 30 - mPa s (dynamic) at 25 °C
Result	:	
Method	:	other: DIN ISO EN 3219/A.3
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable Manufacturer data without proof
Flag	:	Critical study for SIDS endpoint
23.11.2004		(32)
Value	:	12.658 - mPa s (dynamic) at 55 °C
Result	:	
Method	:	other: no data
Year	:	1975
GLP	:	no
Test substance	:	other TS: 4,4'-Methylenedicyclohexyl diisocyanate, purity not below 99.9 %
Remark	:	The method of determination of the viscosity was described in an earlier report which is not available (Zhuravleva EZ and Melent'eva TI, All-Union Scientific and Technical Conference on the Chemistry and Technology of Production, Processing, and Applications of Polyurethanes and Intermediates for their Production, February 10-13, 1971, Vladimir. Abstracts of Papers [in Russian] (1970), p. 17). No information supplied on the isomeric composition of the substance

Result : The temperature dependence of the viscosity of 4,4'-methylenedicyclohexyl diisocyanate was determined:

t [°C]	viscosity [mPaxs]
55	12.658
60	10.452
65	8.674
70	7.220
75	6.005
80	4.890

Reliability : (2) valid with restrictions
Basic data given

19.09.2004 (99)

Value : 6.3 - mm2/s (static) at 70 °C
Result :
Method : other: measured not specified
Year : 1977
GLP : no
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, no purity specified

Result : At 70 °C: 6.3 mm2/s
At 80 °C: 5.1 mm2/s
At 90 °C: 4.1 mm2/s
Reliability : (4) not assignable
Manufacturer data without proof

19.09.2004 (6)

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Conc. of substance	:	at 25 °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	.000000000026 cm³/(molecule*sec)
Degradation	:	50 % after 15 hour(s)
Deg. product	:	
Method	:	other (calculated): EPIWIN AOPWIN v1.91, 2000
Year	:	2004
GLP	:	
Test substance	:	other TS: 4,4'-Methylenedicyclohexyl diisocyanate
Remark	:	The EPIWIN AOPWIN v1.91 program does not take into account that 4,4'-methylenedicyclohexyl diisocyanate is sensitive to hydrolysis e.g. in aerosols with aquatic phases
Result	:	A half-life of about 15.0 h based on a 24-hour day is estimated due to reaction with photochemically produced hydroxyl radicals (OH concentration: 0.5E+6 radicals/cm³)
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

04.11.2005 (28)

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: Decrease of NCO-Content in Water, followed by GC-analysis
Year	:	1999
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	1 g of the test substance was dissolved in acetonitrile and filled up to 100 ml. 10 ml of this solution were pipetted, 40 ml of acetonitrile added (see remark) and filled up with water to 100 ml. This solution was injected into the gas chromatography system every 20 min.
Remark	:	The preparations with a lower content of acetonitrile were cloudy due to the low water solubility of the test substance. The determination of the concentration change in such an inhomogenous solution gives wrong results. For this reason the lowest concentration of acetonitrile required to obtain a clear solution was chosen. The solution of the test substance in acetonitrile was stable over measurement time.
Result	:	The half-time of the test substance in water was determined to be approximately 2 hours at 23 °C (t1/2 = 1.97 hours). The rate constant kobs was 9.78E-05 1/s.
Test condition	:	The content of test substance was determined by means of capillary gas chromatography and flame ionisation detection (GC-FID) under the

following conditions:
Chromatographic column: fused silica capillary, length: 30 m, internal diameter: 0.32 mm, film thickness: 0.25 µm;
Stationary phase: HP 1; Carrier gas: helium;
Split: 30 ml/min; Pressure: 0.6 bar;
Temperature programm:

Temp [°C]	Time [min]	Ramp [K/min]
180	0	10
260	1	-

Detector temperature: 250 °C;
Sample injection: split injection;
Injection volume: 2 µl;
Quantification was performed by area comparison

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
Flag : Critical study for SIDS endpoint
23.11.2004 (20)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Degradation : 100 % after 5 day(s) at pH and °C
Deg. product : yes
Method : OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year : 2004
GLP : yes
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate, > 99.5 % purity
Deg. products : 1761-71-3 217-168-8 4,4'-methylenebis(cyclohexylamine)

Remark : The aim of this study was to determine the degradation products formed when 4,4'-methylenedicyclohexyl diisocyanate reacts with water.
Result : - The aqueous phase contained 3 isomers of 4,4´-methylenedicyclohexyl diisocyanate; they were identified by GC and HPLC (CAS 1761-71-3).
- Additionally, HPLC showed traces of a trimeric diamine. The monomers were connected by urea-groups.
- The insoluble droplets adhered to the glass wall were analysed with IR-Spectroscopy. They contained urea components (polyurea) as well as traces of isocyanate-groups. The polymeric urea compounds encapsulated isocyanate groups which slows down the complete hydrolysis of the isocyanate groups.
Test condition : - Preliminary test only performed in demineralized water
- 2.64 g of the test substance were dissolved in 10 ml acetonitrile. 1 ml of this solution was diluted to 100 ml with demineralized water. The final solution was thus 0.01 mol/l (2.64 g/l). Incubation was at 50 °C during 5 days under continuous stirring.
- Water was not buffered for the preliminary test.
- The solution was extracted with methylene chloride after adjusting the solution at pH 11 and then analysed with GC-MS, HPLC-MS and IR-spectroscopy.
Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions
Flag : Critical study for SIDS endpoint
04.11.2005 (29)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

Type of measurement	:	concentration at contaminated site
Media	:	air
Concentration	:	
Method	:	LC/UV
Method	:	The thermal degradation products of polyurethanes (PURs) and exposure to isocyanates were studied by stationary and personal measurements in 5 different occupational environments (car repair shop, machining of PUR coating, injection moulding, welding of district heating pipes, and installation of PUR floor covering) from September 1999 until November 2000
Remark	:	During grinding and welding thermal degradation products of certain polyurethanes were reported to include 4,4'-methylenedicyclohexyl diisocyanate. In the air samples taken during joint welding of PUR floor covering and samples taken in the breathing zone of a floor covering layer who was welding floor covering on his knees in a small room with no ventilation small amounts of 4,4'-methylenedicyclohexyl diisocyanate were detectable (limit of detection <0.6 mg/m3).
Result	:	Traces of 4,4'-methylenedicyclohexyl diisocyanate (up to 2 µg/m3) were detected as a thermolytic degradation product during joint welding of polyurethane floor covering in a small room without ventilation in a car repair shop
Test condition	:	- Isocyanates were collected on glass fiber filters impregnated with 1-(2-methoxyphenyl)piperazine (2MP) and via the n-dibutylamine impinger method - Derivatives analyzed by LC with UV (250 nm) and electrochemical detection - Limit of quantification < 0.02-0.1 µg per sample depending on isocyanate (not indicated which is valid for 4,4´-methylenedicyclohexyl diisocyanate)
Test substance	:	4,4'-Methylenedicyclohexyl diisocyanate, purity 100 %, from Tokyo Kasei Organic Chemicals, Tokyo, used as external standard for quantification
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint
22.11.2004		(62)

Type of measurement	:	concentration at contaminated site
Media	:	air
Concentration	:	< .0022 µg/l
Method	:	HPLC
Result	:	4,4'-Methylenedicyclohexyl diisocyanate was not detectable
Test condition	:	- US plant manufacturing water pipes with equipment to measure flow rate - Asbestos type insulation coated the inside of a significant part of the plant buildings - Several chemicals were handled in the plant, e.g. 4,4'-methylenedicyclohexyl diisocyanate, haloorganics, and epichlorohydrin - 3 samples taken in September and October, 1979 - Isocyanate absorbed in nitro reagent in impinger, air flow rate 1 l/min - Analysis by NIOSH method N420 (modified), via HPLC, - Limit of detection: 0.0006 mg/sample (<0.0022 µg/l)
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint
26.11.2004		(71)

Type of measurement	:	concentration at contaminated site

Media : air
Concentration : < .02 - .03 µg/l
Method : GC

Remark : Author states that it is not clear whether the measurements are valid because reactions of 4,4'-methylenedicyclohexyl diisocyanate may have occured in the sampling solution before measurements
No sensitizing effects of 4,4'-methylenedicyclohexyl diisocyanate were found in approximately 200 workers of this US manufacturing plant
Result : 4,4'-Methylenedicyclohexyl diisocyanate was not detectable
Test condition : - US plant manufacturing data processing and control equipment was monitored
- Several chemicals were handled in the plant, e.g. 4,4'-methylenedicyclohexyl diisocyanate, haloorganics, cyanide, and nitric acid
- 5 samples taken on May 7, 1975 (NIOSH survey)
- Air sampling volume of 294-475 l/sample
- Isocyanate absorbed in unspecified solution
- GC
- Limit of detection: 0.01 mg/sample (equals to a limit of detection of 0.02-0.03 mg/m3)
Reliability : (4) not assignable
Documentation insufficient for assesment

22.11.2004 (82)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: calculated with PCKOCWIN v1.66, 2000
Year : 2004

Remark : Calculation is not suitable due to hydrolysis. In water, 4,4'-methylenedicyclohexyl diisocyanate hydrolyzes with a half-life of approximately 2 h
Result : Koc = 3.762E+05
log Koc = 5.575
Test substance : 4,4'-Methylenedicyclohexyl diisocyanate
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
03.11.2005 (28)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: calculated with PCKOCWIN v1.66, 2000

Year : 2005

Result : Koc (estimated): 672
Test substance : 4,4'-Methylenebis(cyclohexylamine)
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
31.10.2005 (94)

3.3.2 DISTRIBUTION

Media : water - air
Method : other (calculation): EPIWIN HENRY (v3.10) Program
Year : 2005

Result : HENRYs LAW CONSTANT at 25 °C:
- Bond estimate: 4.54E-009 atm-m3/mole = 1.86E-007 unitless = 0.00046 Pa-m3/mole
Bond estimation:
22 Hydrogen to carbon (aliphatic) bonds -2.6329
4 Hydrogen to nitrogen bonds 5.1341
14 C-C fragments 1.6283
2 C-N fragments 2.6020
Total 6.731
- Group estimation: Incomplete
- Estimation from vapor pressure/water solubility equation using a vapor pressure of 0.000671 mm Hg and a water solubility of 1146 mg/l: 1.621E-007 atm-m3/mole = 0.016 Pa-m3/mole
Test substance : 4,4'-Methylenebis(cyclohexylamine)
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
03.11.2005 (94)

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2000

Result : Distribution on compartments:
Air: 0.041 %
Soil: 0.880 %
Water: 98.256 %
Sediment: 0.823 %
Biota: 0.001 %
Source : Huels AG, Marl (calculation in IUCLID)
Test condition : Input parameters:
Molar mass: 210.36 g/mol
log Kow: 2.03
Vapour pressure: 0.033 Pa
Water solubility: 5.8 g/l at 20 °C

Equations used for additional data:
log Koc = 0.989 log Kow - 0.346

Volumes used (m3):
Air: 6 000 000 000
Soil: 45 000
Water: 7 000 000

Sediment: 21 000
Suspended Sediment: 35
Biota: 7

Test substance : 4,4'-Methylenebis(cyclohexylamine)
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
22.12.2005 (58)

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year : 2005

Remark : Result is different from the result of the EU PBT Working Group because different (mostly calculated) input parameters were used
Result : Compartment
Water 37.70 %
Air 0.155 %
Sediment 1.350 %
Soil 60.75 %
Suspended sediment 0.042 %
Aerosol <0.001 %
Aquatic biota 0.0033 %
Test condition : Input parameters:
Temperature 25 °C
Vapour pressure 0.089 Pa
Water solubility 1146 mg/l
log Kow 3.26
Melting point 320 °C
Test substance : 4,4'-Methylenebis(cyclohexylamine)
Reliability : (2) valid with restrictions
Accepted calculation method
04.11.2005 (30)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge, domestic, non-adapted
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : 0 (±) % after 28 day(s)
Result : other: not readily biodegradable
Control substance : Benzoic acid, sodium salt
Kinetic : 14 day(s) 87 %
%
Deg. product :
Method : Directive 92/69/EEC, C.4-D
Year : 2000
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : The used concentration of the test substance did not show toxic effects to bacteria (toxicity control)
Test condition : - Activated sludge concentration in test flasks: 30 mg ss/l.

- Test temperature: 20 +/- 1 °C.

Reliability : (1) valid without restriction
GLP guideline study

Flag : Critical study for SIDS endpoint

23.11.2004 (21)

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : 12 mg/l related to Test substance
related to
Contact time :
Degradation : 0 (±) % after 28 day(s)
Result : other: not readily biodegradable
Control substance : Aniline
Kinetic : 28 day(s) 83 %
%
Deg. product :
Method : OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
Year : 1992
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : In a first respirometer test performed with a test substance concentration of 100 mg/l, the test substance showed toxic effects to bacteria. Thereupon a Closed Bottle Test should be conducted with lower test substance concentrations. But at last this test was not feasible because neither a stock solution could be prepared nor a direct weighing of test substance was possible. Therefore the respirometer test was performed with a test substance concentration of 12 mg/l.

Test condition : - Activated sludge was taken from laboratory wastewater treatment system, sludge concentration: 30 mg dry weight/l
- Test temperature 20 +/- 1 °C

Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions (concentration tested was lower than the required by the OECD TG 301 of 100 mg/l, as the toxicity threshold towards bacteria available at the time was lower than the current available peer-reviewed toxicity)

Flag : Critical study for SIDS endpoint

23.11.2004 (14)

Type : aerobic
Inoculum :
Contact time :
Degradation : (±) % after
Result : other: 4 out of 6 estimation methods predict fast biodegradation, with an ultimate biodegradation timeframe of weeks
Deg. product :
Method : other: (calculated) EPIWIN BIOWIN program
Year : 2005
GLP : no
Test substance : other TS: 4,4'-Methylenebis(cyclohexylamine)

Remark : Although EPIWIN is an accepted calculation method for many physical parameters, its reliability for estimation of biodegradation is not clearly proofed

Result : Biowin1 (Linear Model Prediction): Biodegrades fast
Biowin2 (Non-Linear Model Prediction): Biodegrades fast
Biowin3 (Ultimate Biodegradation Timeframe): Weeks
Biowin4 (Primary Biodegradation Timeframe): Days-Weeks

Biowin5 (MITI Linear Model Prediction): Does not biodegrade fast
Biowin6 (MITI Non-Linear Model Prediction): Does not biodegrade fast

Reliability : (4) not assignable
Documentation insufficient for assesment

Flag : Critical study for SIDS endpoint

22.12.2005 (94)

Type : aerobic
Inoculum :
Contact time :
Degradation : 20 (±) % after 28 day(s)
Result : other: 4,4'-Methylenebis(cyclohexylamine) is at least inherently biodegradable
Deg. product :
Method : other: Zahn-Wellens
Year : 2000
GLP : no data
Test substance : other TS: 4,4'-Methylenebis(cyclohexylamine)

Remark : Only short documentation available
Result : Biodegradation tests on 4,4'-methylenebis(cyclohexylamine) show that the substance is at least inherently biodegradable
Reliability : (2) valid with restrictions
Reliable source
Flag : Critical study for SIDS endpoint

02.01.2006 (58)

3.6 BOD5, COD OR BOD5/COD RATIO

01.04.2004

3.7 BIOACCUMULATION

Elimination :
Method :
Year : 2003
GLP :
Test substance : other TS: 4,4'-Methylenedicyclohexyl diisocyanate

Remark : 4,4'-Methylenedicyclohexyl diisocyanate hydrolyzes rapidly in the presence of water with a half life of approximately 2 hours. Therefore a risk estimation regarding the bioaccumulation potential of 4,4'methylenedicyclohexyl diisocyanate on the basis of a log Kow, determined by QSAR, is misleading. A calculated theoretical log Kow value reflects the undissociated molecule without influence of water.
According to the EU Technical Guidance Document a substance is regarded as potentially bioaccumulative if the log Kow exceeds 3 and the half life time in water exceeds 12 hours. This is not the case for 4,4'methylenedicyclohexyl diisocyanate. The substance is not persistent in water due to the rapid hydrolysis. Therefore it is not bio-available. Possible hydrolyzation products are less lipophilous. On the basis of these information it can not be expected that bioaccumulation of 4,4'methylenedicyclohexyl diisocyanate occurs
Reliability : (2) valid with restrictions
Accepted calculation method

Flag	:	Critical study for SIDS endpoint
04.11.2005		(27)
Species	:	
Exposure period	:	at 25 °C
Concentration	:	
BCF	:	7 - 18
Elimination	:	
Method	:	other: (calculated) BCF-equation from EPIWIN BCF Program (v2.15)
Year	:	2005
GLP	:	no
Test substance	:	other TS: 4,4'-Methylenebis(cyclohexylamine)
Result	:	Equation used to make BCF estimate: log BCF = 0.77 log Kow - 0.70 log Kow used by BCF estimates: measured log Kow (OECD 107) of 2.03 log BCF values of 0.863 (BCF = 7) calculated log Kow (CLOGP3 program) = 2.55 Estimated log BCF = 1.264 (BCF = 18). Conclusion: Not bioaccumulative according to EU TGD
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint
22.12.2005		(58)
Species	:	
Exposure period	:	at 25 °C
Concentration	:	
BCF	:	65
Elimination	:	
Method	:	other: (calculated) EPIWIN BCF Program (v2.15)
Year	:	2005
GLP	:	no
Test substance	:	other TS: 4,4'-Methylenebis(cyclohexylamine)
Result	:	Equation used to make BCF estimate: log BCF = 0.77 log Kow - 0.70 log Kow used by BCF estimates: 3.26 Estimated log BCF = 1.814 (BCF = 65.16). Conclusion: Not bioaccumulative according to EU TGD
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint
22.12.2005		(94)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	>= 8.1
Limit test	:	yes
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.1
Year	:	2000
GLP	:	yes
Test substance	:	other TS: Desmodur W, purity: 99.5 % (21.1 % trans,trans-4,4'-methylenedicyclohexyl diisocyanate, 50.2 % trans,cis-4,4'-methylenedicyclohexyl diisocyanate, and 28.2 % cis,cis-4,4'-methylenedicyclohexyl diisocyanate
Remark	:	Before beginning of the study a pretreatment was performed with the test substance according to the recommendation mentioned in the OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures in order to accelerate the solution procedure. For that purpose a five fold amount (30 mg/l) of the maximum water solubility of the test substance in the preliminary test (6 mg/l) was weighed into water, treated for 60 seconds at 8000 rpm with an ultra-turrax, afterwards stirred for 24 hours on a magnetic stirrer and finally filtered. Analysis of the only test substance concentration and the control was performed daily by means of TOC determination. The test result LC0 >= 8.1 mg/l (10 % mortality rate) refers to a concentration of the test substance which was calculated directly from analytically determined TOC values (arithmetic mean). According to relevant product information, 1 mg/l TOC equals to 1.5 mg/l of the test substance (structural formula C15H22N2O2, molecular weight 262.4 g/mol). Deviating from the preliminary test, a mortality rate of 10 % was detected in the main test at the limit tested concentration of 6 mg/l. The validity criteria of the test guideline permit a maximum mortality of 10 % in the control.
Result	:	LC0 >= 8.1 mg/l (10% mortality rate)
Test condition	:	- The test was conducted in a ventilated vessel (300 x 135 x 200 mm) filled with 5 l test medium. - Synthetic fresh water (in accordance with ISO) was used for dilution. The water hardness was 14.1 °dH. - 20 fishes were used for the test (10 fishes for the test vessel and 10 for the control). Length: 2.9-3.5 cm. Fresh weight of 10 fishes: 4.41 g (control) and 4.02 g (test vessel). - The test was performed at the nominal limit test concentration of 6 mg/l. - Photoperiod: 16 hours light/8 hours dark. - Test temperature in the test vessel during the study period was 21.3 to 21.8 °C, pH-value was 7.8 to 8.0 and oxygen concentration varied between 8.1 and 8.6 mg/l (oxygen saturation: 93.8 to 99.5%).
Reliability	:	(1) valid without restriction GLP guideline study
Flag	:	Critical study for SIDS endpoint

04.11.2005 (22)

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)

Unit	:	mg/l
LC0	:	.69
LC50	:	1.2
LC100	:	2.76
Limit test	:	no
Analytical monitoring	:	no
Method	:	
Year	:	1992
GLP	:	yes
Test substance	:	other TS: Desmodur W, purity: 91.6 % (24.38 % trans,trans-4,4'-methylenedicyclohexyl diisocyanate, 43.00 % trans,cis-4,4'-methylenedicyclohexyl diisocyanate, and 24.20 % cis,cis-4,4'-methylenedicyclohexyl diisocyanate
Method	:	German UBA-Proposal "Letale Wirkung beim Zebrabaerbling Brachydanio rerio" (LC 0, LC 50, LC 100; 48-96 Stunden), May 1984 (this proposal is in most parts equivalent to OECD TG 203).
Remark	:	Because of the high reactivity of the test substance in water and the low water solubilty, respectively, no determination of the test substance concentrations in the test vessels was performed during the test. This test has not been taken into account for the assessment of 4,4'-methylenedicyclohexyl diisocyanate. 4,4'-Methylenedicyclohexyl diisocyanate is not a consumer product and may only be released into the aquatic environment from manufacturing or processing. The aquatic half-life of this isocyanate is approximately 2 hours. Possible aquatic emissions would enter a wastewater treatment plant with a hydraulic retention time of several hydrolysis half-lives, which means that virtually all isocyanate would hydrolyze to the corresponding amine during wastewater treatment before it enters environmental waters. The hydrolysis product, 4,4'-methylenebis(cyclohexylamine), is virtually the only form of the test substance in the aquatic environment. Thus, for assessment, not the isocyanate, but its hydrolysis product has to be tested. In the test at issue, the test substance was used immediately after contact with water, and significant concentrations of the unhydrolyzed isocyanate were present at the start of incubation. Thus, these test conditions do not reflect environmental conditions, and were not used for assessment
Test condition	:	- The test was conducted in ventilated vessels (300 x 135 x 200 mm) each filled with 5 l test medium. - Synthetic fresh water (in accordance with ISO) was used for dilution. The water hardness was 12.8 °dH. - 80 fishes were used for the test (10 fishes for each of the seven test vessels and 10 for the control). Length: 2.5-3.5 cm. Fresh weight of 10 fishes: 2.16 g (control) and 2.17 to 3.50 g (test vessels). - To prepare the stock solution an amount of the test substance was weighed into water and treated with an ultra-turrax for 60 seconds at 8000 rpm. - The following nominal concentrations were tested: 0.08, 0.17, 0.35, 0.69, 1.38, 2.76 and 5.53 mg/l. - Test temperature in the test vessels during the study period was between 20.7 and 21.6 °C, pH-value was between 7.5 and 8.1, and oxygen concentration varied between 8.3 and 9.4 mg/l (oxygen saturation: 96.0 to 108.0%)
Reliability	:	(2) valid with restrictions Comparable to guideline study with acceptable restrictions

22.12.2005 (14)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC0	:	>= 8.3
Limit Test	:	yes
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.2
Year	:	2000
GLP	:	yes
Test substance	:	other TS: Desmodur W, purity: 99.5 % (21.1 % trans,trans-4,4'-methylenedicyclohexyl diisocyanate, 50.2 % trans,cis-4,4'-methylenedicyclohexyl diisocyanate, and 28.2 % cis,cis-4,4'-methylenedicyclohexyl diisocyanate
Remark	:	Before beginning of the study a pretreatment was performed with the test substance according to the recommendation mentioned in the OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures in order to accelerate the solution procedure. For that purpose a five fold amount (45 mg/l) of the maximum water solubility of the test substance in the preliminary test (9 mg/l) was weighed into water, treated for 60 seconds at 8000 rpm with an ultra-turrax, afterwards stirred for 24 hours on a magnetic stirrer and finally filtered. Analysis of the only test substance concentration and the control was performed at the start of the test and after 48 hours of exposure by means of TOC determination. The test result EC0 >= 8.3 mg/l refers to a concentration of the test substance which was calculated directly from analytically determined TOC values (arithmetic mean). According to relevant product information, 1 mg/l TOC equals to 1.5 mg/l of the test substance (structural formula C15H22N2O2, molecular weight 262.4 g/mol).
Test condition	:	- The test was conducted in a not ventilated cylindrical test vessel (diameter: 4.0 cm, height: 6.5 cm) filled with 20 ml test medium. - M4-Medium according to Elendt and BGA (1992) was used for dilution. The water hardness was 14.2 °dH. - 20 daphnids, 0-24 hours old, were used for the test (10 daphnids for the test vessel and 10 for the control). - The test was performed at the nominal limit test concentration of 9 mg/l. - Photoperiod: 16 hours light/8 hours dark. - Test temperature in the test vessel after 48 hours was 20.2 °C, pH-value was 7.9 and oxygen concentration was 8.5 mg/l.
Reliability	:	(1) valid without restriction GLP guideline study
Flag	:	Critical study for SIDS endpoint

04.11.2005 (23)

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	:	> 5
Limit test	:	no
Analytical monitoring	:	yes
Method	:	Directive 92/69/EEC, C.3
Year	:	2000

GLP : yes

Test substance : other TS: Desmodur W, purity: 99.5 % (21.1 % trans,trans-4,4'-methylenedicyclohexyl diisocyanate, 50.2 % trans,cis-4,4'-methylenedicyclohexyl diisocyanate, and 28.2 % cis,cis-4,4'-methylenedicyclohexyl diisocyanate

Remark : Results of analytical monitoring (test substance concentration):
- Control at start of incubation < 2 mg/l, after 72 h 4 mg/l
- Incubation solution (nominal 5 mg/l) at start of incubation 4 mg/l, after 72 h 6 mg/l
- Incubation solution without algae (nominal 5 mg/l) at start of incubation 4 mg/l, after 72 h 3 mg/l
As the test concentrations for the determination of the NOEC and LOEC were below the detection limit of the TOC determination (2 mg/l) the test results refer to nominal concentrations. The arithmetic means of the TOC determination of the highest test concentration (5 mg/l) exhibited an expected recovery rate of the test substance based on organic C (4.5 mg/l = 90 % recovery)

Result : Cell number/ml (x10E3)

	24h	48h	72h
Control:	41.1	140	304
0.08:	48.9	157	307
0.16:	50.0	158	450
0.31:	46.7	166	361
0.63:	36.7	142	197
1.3:	27.8	143	165
2.5:	22.2	153	211
5.0:	22.2	150	180

Growth and growth rates at several concentrations:
Control: 0 and 0
0.08: -8.4* and 0
0.16: -32.5* and -18.*
0.31: -19.5* and -9.1*
0.63: 18.2 and 9.1
1.3: 26.0 and 18.2
2.5: 16.9 and 9.1
5: 23.1 and 9.1
*increase
Toxicities:
Endpoint growth: EbC50 > 5 mg/l,
Endpoint growth rate: ErC50 > 5 mg/l,
NOEC (cell density after 72 h): 0.31 mg/l,
LOEC (cell density after 72 h): 0.63 mg/l

Test condition : - Preparation of stock solution according to the recommendation mentioned in the OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures: A 5 fold concentration of (37.5 mg/l) of the maximum water solubility of the test substance in preliminary test (7.5 mg/l) was weighed into water and treated for 60 seconds at 8000 rpm in an ultra turrax. The suspesion was stirred by a magnetic stirrer for 24 h. Undissolved particles were removed by filtration through a folded filter of the pore size of 7-12 µm
- The cultivation of stock cultures, precultures and test cultures was performed in a light chamber at 23 +/- 2 °C and with a quantum flux which equals 120 µE/m2 x s
- The test was conducted in Erlenmeyer flasks (300 ml) with stoppers, each filled with 100 ml of test medium. The test flasks were put in a light chamber with shaker
- Deionised water was used for dilution
- Inoculum: algal suspension taken from an exponentially growing

		preculture which serves to adjust an initial cell density of 10,000 cells per ml - The following nominal concentrations were tested: 0.08, 0.16, 0.31, 0.63, 1.3, 2.5 and 5 mg/l - The pH-value in the test vessels was 8.1 at the beginning of the test and between 9.3 and 10.4 after 72 hours of exposure - Analytical monitoring by TOC measurement (limit of detection 2 mg C/l). Analysis of the highest test concentration and the control was performed at the start of the test and after 72 h of exposure. Additionally analysis of the highest concentration without algal inoculum was performed at the same time intervals
Reliability	:	(1) valid without restriction GLP guideline study
Flag	:	Critical study for SIDS endpoint

18.01.2006 (24)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	activated sludge of a predominantly domestic sewage
Exposure period	:	3 hour(s)
Unit	:	mg/l
EC50	:	= 191
Analytical monitoring	:	no
Method	:	
Year	:	2000
GLP	:	yes
Test substance	:	other TS: Desmodur W, purity: 99.5 % (21.1 % trans,trans-4,4'-methylenedicyclohexyl diisocyanate, 50.2 % trans,cis-4,4'-methylenedicyclohexyl diisocyanate, and 28.2 % cis,cis-4,4'-methylenedicyclohexyl diisocyanate
Method	:	Commission Directive 88/302/EEC, Official Journal of the EC L133, Part C: Biodegradability: Test for inhibition of oxygen consumption (corresponds to the OECD TG 209).
Remark	:	The described method for the preparation of test solution will lead to the nearly complete hydrolysis of 4,4'-methylenedicyclohexyl diisocyanate and to the formation of the hydrolysis product, 4,4'-methylenebis(cyclohexylamine)
Test condition	:	- Before the incubation a pretreatment was performed with the test substance according to the recommendation mentioned in the OECD Guidance Document on aquatic toxicity testing of difficult substances and mixtures. The test substance was added to about 130 ml deionised water, treated 3-4 h by ultrasound and stirred overnight before testing (equilibration phase) - The following nominal concentrations were tested: 56, 100, 180, 320 and 560 mg/l - The test concentration of activated sludge was 320 mg/l - The pH-value of the suspension before application was 6.7 - Incubation time: 3 hours with permanent aeration. - The test temperature was 20 +/- 2 °C
Reliability	:	(1) valid without restriction GLP guideline study
Flag	:	Critical study for SIDS endpoint

22.12.2005 (25)

Type	:	aquatic
Species	:	

Exposure period	:	
Unit	:	mg/l
EC3	:	80
Method	:	
Year	:	2003
GLP	:	
Test substance	:	other TS: Methylene bis(4-cyclohexyldiamine)
Result	:	The hydrolysis product, 4,4'-methylenebis(cyclohexylamine), has a low ecotoxicity
Reliability	:	(2) valid with restrictions Reliable source
Flag	:	Critical study for SIDS endpoint

22.12.2005 (58)

Type	:	aquatic
Species	:	activated sludge of a predominantly domestic sewage
Exposure period	:	3 hour(s)
Unit	:	mg/l
EC50	:	= 19
Analytical monitoring	:	no
Method	:	ISO 8192 "Test for inhibition of oxygen consumption by activated sludge"
Year	:	1992
GLP	:	yes
Test substance	:	other TS: Desmodur W, purity: 91.6 % (24.38 % trans,trans-4,4'-methylenedicyclohexyl diisocyanate, 43.00 % trans,cis-4,4'-methylenedicyclohexyl diisocyanate, and 24.20 % cis,cis-4,4'-methylenedicyclohexyl diisocyanate
Remark	:	The test substance was not completely soluble in water at all tested concentration levels. This test has not been taken into account for the assessment of 4,4'-methylenedicyclohexyl diisocyanate. 4,4'-Methylenedicyclohexyl diisocyanate is not a consumer product and may only be released into the aquatic environment from manufacturing or processing. The aquatic half-life of this isocyanate is approximately 2 hours. Possible aquatic emissions would enter a wastewater treatment plant with a hydraulic retention time of several hydrolysis half-lives, which means that virtually all isocyanate would hydrolyze to the corresponding amine during wastewater treatment before it enters environmental waters. The hydrolysis product, 4,4'-methylenebis(cyclohexylamine), is virtually the only form of the test substance in the aquatic environment. Thus, for assessment, not the isocyanate, but its hydrolysis product has to be tested. In the test at issue, the test substance was used immediately after contact with water, and significant concentrations of the unhydrolyzed isocyanate were present at the start of incubation. Thus, these test conditions do not reflect environmental conditions, and were not used for assessment
Result	:	Test concentration* (mg/l) / resperation rate (mg/l h) / Inhibition (%) 0 / 22.2 / 0 5.6 / 19.5 / 12.2 10 / 16.0 / 27.9 18 / 10.8 / 51.4 32 / 7.0 / 68.5 56 / 4.0 / 82.0 * nominal
Test condition	:	- The following nominal concentrations were tested: 5.6, 10, 18, 32 and 56 mg/l - Type of application: Test substance stock emulsion was prepared by

addition of 1 g/l of test substance into water and treatment with ultra-turrax at 8000 rpm for 60 seconds. The emulsion was used for preparation of test solutions by dilution of aliquots
- The concentration of inoculum was 6 g/l test substance

Reliability : (2) valid with restrictions
Comparable to guideline study with acceptable restrictions

18.01.2006 (14)

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	:	= 9900 mg/kg bw
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	
Number of animals	:	5
Vehicle	:	other: corn oil
Doses	:	6310, 7940, 10000, 12600 mg/kg
Method	:	other: see Test Condition
Year	:	1966
GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity
Result	:	MORTALITY: Number of deaths at each dose: 6310 mg/kg: 0/5, 7940 mg/kg: 1/5, 10000 mg/kg: 3/5, 12600 mg/kg: 4/5 SURVIVAL TIME: One to four days CLINICAL SIGNS: severe diarrhea, loss of appetite and increasing weakness NECROPSY: Liver discoloration and renal hyperemia
Test condition	:	ADMINISTRATION: the test material was administered by stomach tube as 50% solution-suspension in corn oil sex: 5 animals per dose with alternate sex (e.g. 3 females and 2 males or 2 females and 3 males) post observation period: no data EXAMINATIONS: mortality, clinical signs and necropsy of the animals that succumbed CALCULATION OF LD50: According to a modification of the method of E.J. de Beer
Reliability	:	(2) valid with restrictions Limited documentation, no data on purity of test substance
Flag	:	Critical study for SIDS endpoint

22.12.2005 (77)

Type	:	other: ALD
Value	:	> 11000 mg/kg bw
Species	:	rat
Strain	:	other: ChR-CD
Sex	:	male
Number of animals	:	
Vehicle	:	peanut oil
Doses	:	670, 2250, 3400, 5000, 7500, 11000 mg/kg
Method	:	other: no data
Year	:	1963
GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity
Remark	:	ALD = Approximate lethal dose
Result	:	MORTALITY: no mortality CLINICAL SIGNS: Initial weight loss; diarrhea, perineal discoloration,

discomfort at levels of 2250 mg/kg and above
NECROPSY: Slight to moderate changes in kidney and brain at all doses; injury to stomach and small intestine at 11000 mg/kg

Test condition : No. of Animals: no data
ADMINISTRATION: the test material was administered by stomach tube as suspension in peanut oil in single doses
post observation period: 14d
EXAMINATIONS: mortality, clinical signs and necropsy

Reliability : (3) invalid
The documentation of the study is insufficient, i.e. the number of animals is not mentioned

21.10.2004 (46)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	= 434 mg/m³
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	5
Vehicle	:	other: no
Doses	:	151, 388, 418, 552, 730, 865, 1,352 mg/m³
Exposure time	:	4 hour(s)
Method	:	OECD Guide-line 403 "Acute Inhalation Toxicity"
Year	:	1985
GLP	:	yes
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, purity > 99.2 %

Result :
VALUE:
LC50 (male): 456 mg/m3 (95% confidence interval of 313 to 667 mg/m3)
LC50 (female): 431 mg/m3 (95% confidence interval of 363 to 513 mg/m3)
LC50 (male/female): 434 mg/m3 (95% confidence interval of 355 to 533 mg/m3)
MORTALITY:
Number of deaths at each dose (time of death), male rats: 151 mg/m3: 0/5; 388 mg/m3: 2/5 (1d-2d); 418 mg/m3: 2/5 (1d-2d); 552 mg/m3: 5/5 (1d-4d); 730 mg/m3: 4/5 (1d-3d); 865 mg/m3: 2/5 (1d-2d); 1,352 mg/m3: 5/5 (0d-1d)
Number of deaths at each dose (time of death), female rats: 151 mg/m3: 0/5; 388 mg/m3: 2/5 (1d); 418 mg/m3: 2/5 (1d); 552 mg/m3: 4/5 (1d-2d); 730 mg/m3: 5/5 (1d); 865 mg/m3: 5/5 (1d-3d); 1,352 mg/m3: 5/5 (0d-1d)
CLINICAL SIGNS:
Number of animals with clinical signs, male rats: >= 151 mg/m3: 5/5 (due to early death at 1,352 mg/m3 clinical signs were only for 4/5 animals recorded) showed during the exposure and up to 12d after the exposure bradypnea, dyspnea, laboured breathing, rales, irregular breathing pattern, ungroomed coat, piloerection, motility reduced, tremor, hunched posture, highlegged gait, staggered gait, sluggish, cyanosis, vocalization, emaciation, serous discharge from nose, reddish rhinarium, wheezing, nose with red encrustations, nose-Muzzle/red encrustations, prostration (lying on belly); at the end of the post observation period all surviving animals were without symptoms
Number of animals with clinical signs, female rats: >= 151 mg/m3: 5/5 (due to early death at 1,352 mg/m3 clinical signs were only for 4/5 animals recorded) showed during the exposure and up to 9d after the exposure bradypnea, dyspnea, laboured breathing, rales, irregular breathing pattern, ungroomed coat, piloerection, motiltiy reduced, tremor, hunched posture, highlegged gait, staggered gait, sluggish, cyanosis, vocalization,

emaciation, serous discharge from nose, reddish rhinarium, wheezing, nose with red encrustations, nose-Muzzle/red encrustations, prostration (lying on belly); at the end of the post observation period all surviving animals were without symptoms
BODY WEIGHT:
>= 151 mg/m3: body weight retardation
RECTAL TEMPERATURE:
concentration dependent decrease
REFLEX EXAMINATION:
no substance induced effects
NECROPSY:
rats died during the post observation period:
pale liver, spleen and kidneys, lobular pattern of the liver, duodenum was filled with a red mucous mass, trachea was filled with a mucous mass, less collapsed lungs with red foci, pulmonary edema and hydrothorax; lungs were red up to hepatoid changes, red secretions in the nose
rats sacrificed at the end of the post observation period:
>= 151 mg/m3 no specific concentration dependent organ changes

Test condition : ADMINISTRATION:
vapour inhalation under dynamic head-nose only exposure conditions
post observation period: 2 weeks
nominal concentrations: 667, 1,167, 1,333, 1,667, 2,500, 3,333, 6,667 mg/m3
chamber concentration:
Analysis of the test atmosphere:
the chamber samples were taken in the vicinity of the breathing zone and the test-substance concentration was determined by HPLC (test material was collected in a glass tube filled with mineral wool which was impregnated with a nitrocompound to react in situ with the diisocyanate) and by gravimetric analysis (filter: Glass Fibre-Filter)
the analytical values determined by HPLC < the analytical values determined gravimetrically
the analytical values were 20 to 33% of the nominal concentration;
particle size distribution:
90% of the particle mass with an aerodynamic diameter <= 3 µm
mass median aerodynamic diameter (MMAD) » 1.4 µm; geometric standard deviation (GSD) » 1.8 µm
EXAMINATIONS:
mortality; clinical signs; body weight; rectal temperature, reflex, necropsy
CALCULATION OF LC50:
according to A.P. Rosiello et al., J. Tox. and Environ. Health 3, 797-809 (1977) and modified by J. Pauluhn; Bayer Report No. 11845 (1983)

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
14.01.2005 (18)

Type : LC50
Value : 295 - 307 mg/m³
Species : rat
Strain : Sprague-Dawley
Sex : male/female
Number of animals : 10
Vehicle : other: no
Doses : 191, 113, 307, 288, 340, 608 mg/m³
Exposure time : 4 hour(s)
Method : other: see Test Condition
Year : 1985
GLP : yes
Test substance : other TS: see Test substance

Result : VALUE:
LC50 (male): 295 mg/m3 (95% confidence interval of 221 to 380 mg/m3)
LC50 (female): 307 mg/m3 (95% confidence interval of 268 to 327 mg/m3)
NOEL: < 113 mg/m3
the result for 191 mg/m3 was not used in calculating the LC50
MORTALITY:
Number of deaths at each dose (time of death), male rat: 113 mg/m3: 1/10 (1d), 191 mg/m3: 0/10, 288 mg/m3: 5/10 (1d), 307 mg/m3: 3/10 (0-1d), 340 mg/m3: 7/10 (1-2d), 608 mg/m3: 10/10 (0-1d)
Number of deaths at each dose (time of death), female rat: 113 mg/m3: 0/10, 191 mg/m3: 0/10, 288 mg/m3: 3/10 (1-3d), 307 mg/m3: 4/10 (1d), 340 mg/m3: 9/10 (1-2d), 608 mg/m3: 10/10 (0-1d)
CLINICAL SIGNS:
number of animals with clinical signs (male/female): 10/10 >= 113 mg/m3 nasal and ocular irritation during exposure and
post-exposure. Some of the animals exposed to 307, 340 and 608 mg/m3 air showed salivation, lacrimation, decreased activity, occasional tremors and corneal opacity. The clinical signs lasted up to ten days in both male and female animals. Difficulty in breathing was also observed in animals when they were taken out of the tubes. Most of the surviving animals exhibited alopecia of varying degree in areas that were in contact with the compound during the exposure. The alopecia was noticed on day 2 or 3 and lasted until the end of the study. Neck edema observed in animals was related to the mode of exposure and not to the compound.
BODY WEIGHT:
The group mean body weights of male animals exposed to test material were significantly lower than those of the control group on days 2, 3 and 4 at concentrations 113 and 288 mg/m3 air, on days 2 through 7 at concentration 340 mg/m3 air and on days 2 through 14 at concentration 307 mg/m3 air.
The group mean body weights of compound-exposed females were significantly lower on day 2 at exposure concentration 191 mg/m3 air, and on days 2 through 4 at concentrations 288, 307 and 340 mg/m3 air.
NECROPSY and HISTOPATHOLOGY:
Compound-related gross lesions observed in most of the animals sacrificed at term included alopecia of the ear and head skin (the areas directly exposed to test material) and occasional crusty zones. The gross lesions observed in the animals that died during 01: after compound exposure were agonal changes and included lacrimation, dark pink or red lungs, yellow or red nasal discharge, reddened turbinates and gas-filled intestines. Other gross lesions observed in control and compound-exposed animals were incidental and distributed randomly in both groups.
Microscopic examination of the ear and skin lesions showed that the severity of ear lesions was concentration-related (P<O.O5). The lesions consisted of acanthosis, chronic or chronic-active inflammation and Langhan's giant cells with phagocytized hair and foamy cytoplasm. These lesions occurred in the ears and skin of several sacrificed animals at all but the lowest concentration level and probably represent a foreign body reaction initiated by debris contaminating the dermis through overlying ulcers. Exposed animals that died during the study had no ear or skin lesions which might reflect a shorter exposure time to the compound.
Lesions of lung, liver, and kidney were lesions were toxicologically nonsignificant since they were seen in both controls and exposed animals (sacrificed and found dead) or were seen only in control animals.

Test condition : ADMINISTRATION:
Test material was generated as a liquid aerosol by an apparatus that consisted of two concentric nozzles. The test material was conducted into a fine inner nozzle by an infusion pump at a constant rate. Animals were exposed under dynamic conditions in a 60-liter cylindrical chamber. In the middle portion of the chamber were two rows of ten tubes each, which

were attached radially to the chamber. The animals were individually positioned in these tubes so that only their heads were exposed to the test material while their bodies remained within perforated tubes.
post observation period: 14 days
nominal concentrations:
500, 750, 1,000, 1,240, 1,500 and 1,750 mg/m3
chamber concentration:
Analysis of the test atmosphere:
Analytical concentration of the chamber atmosphere was determined by taking samples near the animal breathing zone; 1.5 to 3-liter samples were taken at 15 minute intervals; samples were drawn through Millipore FH (pore size 0.5 um) filters at a rate of 1.5 l/min; the contents of the filter were determined by HPLC.
The analytical values were 23 to 38% of nominal concentration, except for one value (113 mg/m3) which was only 15%.
particle size distribution:
50% of the particle mass had mass median aerodynamic diameter (MMAD) below 2 µm; about 90% of the particle mass had MMAD less than 6.6 µm

EXAMINATIONS:
mortality, clinical signs approximately (three to four times post-exposure (on day of exposure) and then twice daily up to 14 days), body weights (prior to exposure and on days 2, 3, 4, 7 and 14 after exposure), necropsy, histopathology (lungs, liver, kidneys from animals exposed to 113, 119, 288 and 340 mg/m3).
CALCULATION OF LC50:
The LC50 values with 95% confidence limits were calculated by probit analysis. During sampling. higher recoveries (30.7%) were seen at 307 mg/m3 air concentration (nominal 1,000 mg/m3 air) and lower recoveries (23.2%) at 288 mg/m3 air (nominal 1,240 mg/m3 air. This reflected higher mortality at the low concentration and lower mortality at the high concentration, which made it difficult to calculate the LC50. Therefore, the concentrations of 288 and 307 mg/m3 air and their corresponding mortalities were averaged in calculating LC50 values.

Test substance : 4,4´-Methylenedicyclohexyl diisocyanate, technical grade, no further data
Reliability : (2) valid with restrictions
Due to the method applied for the analysis of the test atmosphere the values for the analytical concentrations underestimate the actual exposure concentration because the test sample partly would have been captured by reaction with the filter material and/or humidity; no replicate of the determination using another detection method (e.g. gravimetric analysis) was performed
Flag : Critical study for SIDS endpoint
06.11.2006 (76)

Type : other
Value :
Species : rat
Strain : other: ChR-CD
Sex : male
Number of animals : 4
Vehicle : other: no
Doses :
Exposure time : 4 hour(s)
Method : other: see Test Condition
Year : 1963
GLP : no
Test substance : other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity

Result : MORTALITY RATIO:

0/4 (200 °C); 2/4 (250 °C); 2/4 (300 °C)
OBSERVATIONS:
At the 250 and 300 °C level the rats exhibited gasping, labored respiration, ruffled fur, extremely red extremities, eye irritation and lacrimation. In addition to CO, white fumes were observed in the exposure chamber.
At the 200 °C level the animals showed slightly deep respiration, red extremities, eye irritation and lacrimation. Neither CO nor fumes were detectable in the exposure chamber at 200 °C.

Test condition : approx. 20 grams of material was placed in a flask and heated to and maintained at the required temperature (200, 250, 300 °C) in a heating mantle. A dry air stream passed through the flask to a 8-liter bell jar containing the rats; survivors killed 14 days later;
nominal concentration:
12,1 mg/m3 (300 °C); 11,1 mg/m3 (250 °C); 10,4 mg/m3 (200 °C)
(computed from weight loss of sample and air flow)

Reliability : (3) invalid
Due to the high temperature decomposition of the test material cannot be excluded; nominal exposure was not verified analytically; whole body exposure

14.01.2005 (46)

Type : other
Value :
Species : rat
Strain : other: ChR-CD
Sex :
Number of animals : 4
Vehicle : other: butyl acetate
Doses :
Exposure time : 1 hour(s)
Method : other: see Test Condition
Year : 1968
GLP : no
Test substance : other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity

Result : During exposure no clinical signs of respiratory irritation were seen; immediate reddening of the rat ears followed over a 14-day period by swelling of the ears, sluffing of the outer ear skin and its regeneration. This was accompanied by microscopically identifiable edems and congestion of the ear skin layers which was still midly evident 14 days after exposure, the test material caused tracheitis and brinchitis which was healing 7 days after exposure and had healed 14 days after exposure
nominal isocyanate concentration: 2,85 mg/m3

Test condition : The test material was dissolved in commercial butyl acetate , the test solution was sprayed at the same uniform rate into the exposure chamber throughout the exposure, the solutions were sprayed with stainless steel paint spray nozzle using house air. Control rats were similary exposed to butyl acetate only. Droplet size distribution was measured with Monsanto cascade impactor; 2 rats were sacrified for gross and histopathologic examination at each of 7 and 14 days post-exposure; tissue examined were lung, liver, brain, spleen, kidney, testes, stomach, thymus, thyroid, adrenal, ear and bone marrow.

Reliability : (3) invalid
Due to lack of study documentation and study design and unreliable exposure analysis

14.01.2005 (47)

Type : other: Class B Poison Test
Value :
Species : rat

Strain	:	other: ChR-CD
Sex	:	male
Number of animals	:	10
Vehicle	:	other: no
Doses	:	
Exposure time	:	
Method	:	other: see Test Condition
Year	:	1972
GLP	:	no
Test substance	:	other TS: Hylene W, no data on purity
Result	:	The test material is not a Class B Poison by inhalation as defined by the Department of Transportation
Test condition	:	Exposure No. 1: approx. 100 grams of the test material was maintained at room temperature in a round-bottomed flask. Dry houseline air was passed over the material and into a 20-liter exposure chamber containing the rats. Samples of the chamber atmosphere were taken at least three times during exposure and analyzed using a colorimetric method. Neither gross nor histopathologic examination was performed on any animals tested Exposure No. 2: Procedure same as above with one modification: houseline air was passed into the flask through a stainless steel nobulizer to generate aerosol and test material was heated at 62-75 °C
Reliability	:	(3) invalid Methodological deficiencies, analytical detection method and/or the generation of the test atmosphere are unrealiable because the analytical concentrations ranged from 0.005 -0.514 mg/l for several exposures which were conducted under identical conditions

22.10.2004 (50)

Type	:	other: inhalation hazard test
Value	:	
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	4
Vehicle	:	other: no
Doses	:	no data
Exposure time	:	6 hour(s)
Method	:	other: see Test Condition
Year	:	1966
GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity
Result	:	MORTALITY: All animals survived the exposure as well as the following observation period CLINICAL SIGNS: reduced activity and occasional changes in breathing rate were the only outward evidence of toxicity. Nasal and ocular mucosae were not inflammed and there was no weakness; activity and appearance were normal in 24 hours. No complications developed during the ten day observation period
Test condition	:	The animals (whole body exposure) were exposed to a concentrated atmosphere of vapors produced by passing a stream of air through 100 ml of the compound contained in a 250 ml Erlenmeyer flask, vapors from the flask passed into a one liter bottle to remove droplets and then into the chamber Average temperature inside the chamber: 75oF

Average relative humidity inside the chamber: 63%
post observation period: 10 days

Reliability : (3) invalid
Due to lack of study documentation and exposure analysis; whole body exposure

22.10.2004 (77)

Type	:	other: RD50 (sensory irritation)
Value	:	= 27 mg/m³
Species	:	mouse
Strain	:	CD-1
Sex	:	male
Number of animals	:	4
Vehicle	:	other: acetone
Doses	:	8, 8, 18, 20, 19, 36, 48, 72, 93 mg/m³
Exposure time	:	3 hour(s)
Method	:	other: see Test Condition
Year	:	1984
GLP	:	yes
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, commercial grade, no further data

Result :
VALUE:
RD50 = 27 mg/m3 (95% confidence limits: 18 to 36 mg/m3)
MORTALITY: ¼ at 20, 48 and 93 mg/m3
CLINICAL SIGNS:
Number of animals with clinical signs (duration of symptoms): 8 mg/m3: 0/4, 8 mg/m3: 0/4, 18 mg/m3: 2/4 (during exposure up to 3d), 20 mg/m3: ¼ (during exposure up to 1d), 19 mg/m3: ¼ (during exposure up to 1d), 36 mg/m3: 4/4 (during exposure up to 1d), 48 mg/m3: ¾ (during exposure up to 3d), 72 mg/m3: 4/4 (during exposure up to 1d), 93 mg/m3: 4/4 (during exposure up to 7d)
The signs of toxicity were concentration-related and included difficulty in breathing, decreased activity, tremors and ataxia and lasted from one to three days except at 93 mg/m3 where one mouse showed labored breathing on days 6 and 7 and was found dead prior to necropsy.
BODY WEIGHT: no compound related effect
RESPIRATORY RATE:
The time-response relationships show an increase in the respiratory rate in the beginning of exposure followed by a decrease in the respiratory rate reaching maximum decrease by the end of the three-hour exposure. This pattern of response was more clear at the lower concentration (8 mg/m3) where only an increase in the respiratory rate was observed. An increase in the respiratory rate is indicative of deep lung irritation (pulmonary irritation), whereas a decrease in respiration rate indicates irritation of the upper respiratory tract (sensory irritation). The animal responses to the test material exhibited irritation of both the upper and lower respiratory tract.
NECROPSY:
No compound-related gross lesions were observed in any of the animals. A random lesion noted was gas and fluid filled intestines in one animal exposed to 20 mg/m3.

Test condition :
ADMINISTRATION:
Test material was generated as liquid aerosol. Desired concentrations of aerosol atmosphere were generated by using 0.3 to 4.85% (w/w) solution of Desmodur W in acetone, head-only exposure chambers were used; no concurrent acetone or air control groups were used during the study. The acetone and air control data used is from a similar study using the same strain of mice. The data show that no significant effect on the respiratory rate of animals was observed due to the use of acetone as the solvent or to the method of exposure (air control).

post-observation period: 7 days
nominal concentrations: 23, 37, 51, 75, 90, 100, 160, 245, 388 mg/m3
EXAMINATIONS:
mortality, clinical signs, body weight, body plethysmography, necropsy

Reliability : (3) invalid
Unsuitable test for aerosols because the generation of the test atmosphere (-> particle size distribution) determines the pattern of the test material deposit in the respiratory tract and thus the response, therefore no reliable conclusion is possible; test (RD50 determination) is restricted to vapours (upper tract irritant)

14.01.2005 (75)

Type : other: RD50 (sensory irritation)
Value : = 4 mg/m³
Species : mouse
Strain : Swiss Webster
Sex : male
Number of animals : 4
Vehicle : other: acetone
Doses : 16.7, 288 , 379, 505, 669 mg/m³
Exposure time : 4 hour(s)
Method : other: see Test Condition
Year : 1985
GLP : no data
Test substance : other TS: 4,4´-methylenedicyclohexyl diisocyanate, purity 99.3 % minimum

Remark : To confirm the pulmonary irritation properties mice were exposed via tracheal cannula (414 mg/m3) which will eliminate sensory irritation and pulmonary irritation can be studied alone. A decrease in respiratory frequency was observed, indicating that the test material acts as pulmonary irritant.

Result : VALUE:
RD50 = 40 mg/m3
RESPIRATORY RATE: decline dependence on both the duration of exposure and the exposure concentration
LUNG WEIGHT: increase with exposure concentration

Test condition : ADMINISTRATION:
The test material was generated as liquid aerosol. Desired concentrations of aerosol atmosphere were generated by using 0.25 to 1.5% solution of test material in acetone; the chamber concentrations were determined gravimetrically
post-observation period: all animals were killed 24 hr postexposure
EXAMINATIONS:
body plethysmography, lung weight

Reliability : (3) invalid
Limited documentation; test system unsuitable for aerosols because the generation of the test atmosphere (-> particle size distribution) affects the pattern of test sample deposit in the respiratory tract and thus the response; therefore no reliable conclusion is possible; test (RD50 determination) is restricted to vapours (upper tract irritants)

14.01.2005 (95)

Type : LC50
Value : 51 mg/m³
Species : guinea pig
Strain : other: English smooth-haired
Sex : male/female
Number of animals : 5
Vehicle : other: no
Doses : 0, 17, 44, 55, 90 mg/m³

Exposure time	:	1 hour(s)
Method	:	other: see Test Condition
Year	:	1982
GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity
Result	:	VALUE: LC50 (male/female): 51 mg/m3 (95% confidence interval = 36 to 72 mg/m3) MORTALITY: Number of deaths at each dose (time of death), male rats: 17 mg/m3: 0/5, 44 mg/m3: 0/5, 55 mg/m3: 3/5 (2-3d), 90 mg/m3: 5/5 (1-3d) Number of deaths at each dose (time of death), female rats: 17 mg/m3: 1/5 (4d), 44 mg/m3: 1/5 (2d), 55 mg/m3: 2/5 (3d), 90 mg/m3: 4/5 (1-2d) CLINICAL SIGNS: The most frequent clinical signs, observed during the first three days of the study, consisted of pallor of the skin or cyanosis, respiratory distress, weakness or lethargy, and nasal discharge (no information on number of animals with clinical signs per concentration and sex) BODY WEIGHT: body weight losses occurred in all treated groups except for males exposed to the lowest concentration. Body weight losses were made good by the end of the first week of the observation period ANTIBODY ANALYSIS: no information available NECROPSY: marked gross changes in the lungs such as rubbery texture, swelling and reddening were observed in the animals that died.
Test condition	:	ADMINISTRATION: The test material was generated as a liquid aerosol by using a concentric jet glass atomizer supplied with predried compressed air. The animals were positioned in plexiglas whole-body exposure chambers. post observation period: 14 days nominal concentrations (calculated from the weight loss from the generator and the total airflow through the chamber during the 1-hour exposure period): 70, 90, 140, 240 mg/m3 EXAMINATIONS: mortality, clinical signs, body weights, antibody analysis, necropsy CALCULATION OF LC50: The LC50 value and the 95% confidence interval were calculated using the method of Litchfield and Wilcoxon, Journal of Pharamacology & Experimental Therapeutics, 1949, 96 (2), 99-113.
Reliability	:	(3) invalid Significant methodological deficiencies (i.e. whole body exposure) and limited documentation

14.01.2005 (3)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	other: skin absorption MLD
Value	:	> 10000 mg/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	1
Vehicle	:	other: corn oil
Doses	:	1000, 1580, 2510, 3980, 6,310, 10000 mg/kg
Method	:	other: see Test Condition
Year	:	1966

GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity
Result	:	no mortality up to 10000 mg/kg; activity and appetite were reduced for several days after 6130 and 10000 mg/kg, there was moderate weakness but no paralysis
Test condition	:	The undiluted sample (6130 and 10000 mg/kg) and diluted sample (50% solution/suspension in corn oil) was applied to the closely clipped intact skin of a male or female rabbit. The treated areas were covered with plastic strips and the animals placed in wooden stocks for 24 hours; observations were made for toxic symptoms and since there were no deaths, no autopsies were performed post observation period: no data
Reliability	:	(2) valid with restrictions Limited documentation, only one animal per dose with alternate sex, no data on purity of test substance
Flag	:	Critical study for SIDS endpoint

22.10.2004 (77)

Type	:	other: Class B Poison Test
Value	:	
Species	:	rabbit
Strain	:	no data
Sex	:	male
Number of animals	:	6
Vehicle	:	other: no
Doses	:	200 mg/kg
Method	:	other: see Test Condition
Year	:	1972
GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity
Result	:	After a 24-hour exposure of 200 mg/kg b.w. 0/6 animals died; no clinical signs were observed
Test condition	:	The test material was applied to the intact clipped dorsal skin. The rabbits trunks were then wrapped with a layer of Saran wrap, stretch gauze bandage and elastic adhesive tape. After 24-hour exposure period, the wrapping were removed and the skin was washed with water and dried. The animals were observed for a further 48 hours.
Reliability	:	(3) invalid Limited documentation and only one dose group tested

22.10.2004 (49)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	500 other: ul
Exposure	:	Occlusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	other: no
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"

Year	:	1981
GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate liquid sample, no data on purity
Result	:	A primary irritation value of 4.2 was calculated (3.1 - 5.0 = moderately irritating); retrogression after 8d to the level of a slight irritation (surface, parchment-like skin scaling)
Test condition	:	test substance was applied on the flank skin on both sides of the body of each animal; the determination of findings followed immediately after removal of the cloths and washing (water) of the application site (4 h value), then after 24, 48 and 72 h and after 8 d. The 24 and 72 h values are the basis for the irritancy index; the 24 and 72 h levels of erythema and edema formation in both test areas were averaged for the test animals; the eight average values were divided by four, to yield the primary skin irritation index
Reliability	:	(2) valid with restrictions No data on purity of test substance
Flag	:	Critical study for SIDS endpoint
20.11.2004		(8)
Species	:	rabbit
Concentration	:	500 other: mg
Exposure	:	Occlusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1981
GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, solid sample, no data on purity
Result	:	A primary irritation value of 3.6 was calculated (3.1 - 5.0 = moderately irritating); retrogression after 8d to the level of a slight irritation (surface skin scaling)
Test condition	:	test substance (moistened in oil) was applied on the flank skin on both sides of the body of each animal; the determination of findings followed immediately after removal of the cloths and washing (water) of teh application site (4 h value), then after 24, 48 and 72 h and after 8 d. The 24 and 72 h values are the basis for the irritancy index; the 24 and 72 h levels of erythema and edema formation in both test areas were averaged for the test animals; the eight average values were divided by four, to yield the primary skin irritation index
Reliability	:	(2) valid with restrictions No data on purity of test substance
Flag	:	Critical study for SIDS endpoint
20.11.2004		(9)
Species	:	rabbit
Concentration	:	500 other: ul
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	1
Vehicle	:	
PDII	:	

Result	:	
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1994
GLP	:	yes
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, purity > 99.2 %
Result	:	RESULT: "severely irritating to the skin" On the exposed skin strong erythematous and exsudative reactions were observed. From day 7 on a white to yellowish squamous coat (on day 14 the coat was white) and eschar formation were seen. On day 14 on the exposed skin area the epidermis was partly removed. SCORE: Erythema (observation time): 2 (1h, 72h, 7d)); 3 (24h, 48h, 14d) Edema (observation time): 2 (1h, 24h); 1 (48h, 72h, 7d), 0 (14d) mean value "erythema": 2.7 mean value "edema": 1.3
Test condition	:	For reasons of animal welfare, due to the expected irritant potency of the test substance on the skin, in the test only one animal was used. The scores at the reading times 24, 48, 72 hours for an effect were used in calculating respective mean values.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint
06.11.2006		(17)
Species	:	rabbit
Concentration	:	500 other: ul
Exposure	:	Semiocclusive
Exposure time	:	
Number of animals	:	3
Vehicle	:	
PDII	:	
Result	:	irritating
Classification	:	
Method	:	other: see Test Condition
Year	:	1996
GLP	:	yes
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, purity: 99.89%
Result	:	There was no evidence of corrosion observed at any of the test sites for any of the exposure periods (3-minutes, 1 -hour, and 4-hours). Dermal irritation was observed sporadically from the 4-hour observations (for the 4-hour exposure sites) through the 72-hour observations and at most exposure sites from the 96-hour observations through the Day 14 observations. This dermal irritation was characterized by very slight to well-defined erythema (scores of l to 2) and very slight to slight edema (scores of 1 to 2). On Day 21, all signs of edema had subsided and only one animal was noted with very slight erythema at all exposure sites. However, on Day 21, areas of thickened skin were observed at the exposure sites for two animals (all exposure sites for Animal No. 4022 and the 3-minute exposure site for Animal No. 4023). There were no remarkable signs of clinical toxicity and/or ill health noted during the course of this study. All animals gained weight over the course of the study.
Test condition	:	TEST ANIMALS: strain: New Zealand White albino sex: male EXPOSURE TIME: 3 minute, 1-hour and 4-hours ADMINISTRATION/EXPOSURE: The undiluted test material was applied to three separate test areas on the

intact skin on each animal's back. Each area of application was covered with a 2.5-cm x 2.5-cm gauze patch secured with Paper tape, loosely overwrapped with Gran Wrap, and secured with Elastoplast tape to provide a semiocclusive dressing. The wrappings applied to each test site were independent of the other sites. Each animal was exposed to the test material for 3-minute, 1 -hour, and 4-hour periods of time. At the end of the 3-minute, 1 -hour, or 4-hour exposure periods, the patches were removed and the test sites were washed using tap water. The test material was removed from the test sites as thoroughly as possible without irritating the skin.
EXAMINATIONS:
At the end of the 3-minute, 1 -hour, or 4-hour exposure periods, one patch from each animal was removed and the treated area was examined for evidence of corrosion. Corrosion is characterized by irreversible alterations at the site of contact which may include ulceration and necrosis; changes such as edema, erythema, sloughing of the epidermis, and tissuring alone do not constitute corrosion. After the initial corrosion examination, the residual test material was removed using tap water to prevent further test material exposure. After removal of the patches, each application site was examined for erythema and edema reactions according to the Draize technique (recorded as the 3-minute, 1 -hour, or 4-hour Score). Subsequent examinations were made at 24,48,72, and 96 hours and days 7, 14, and 21. Each site per animal (3-minute, 1-hour, and 4-hour exposure sites) was scored independently at these timepoints. The untreated skin of each animal was used for comparison. Photographs were taken of all exposure sites for each animal and all exposure times for each animal, and a sample of untreated skin, were preserved for future possible microscopic evaluation.
Animals were also observed for signs of clinical toxicity and/or ill health at each interval of dermal irritation scoring; these observations were recorded by exception.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
22.10.2004 (26)

Species : rabbit
Concentration : 500 other: ul
Exposure : Semiocclusive
Exposure time : 4 hour(s)
Number of animals : 6
Vehicle :
PDII :
Result : corrosive
Classification :
Method : other: see Test Condition
Year : 1973
GLP : no
Test substance : other TS: Hylene W, no data on purity

Result : According to the regulation of the Department of Transportation (Department of Transportation, Hazardous Materials Regulations Board, Docket No. HM-57, Federal Register, Vol. 38, no.28, section 173.240, February 12, 1973) Hylene W is considered a corrosive material
4/6 rabbits with corrosion (no further information)
Test condition : the test material was applied to intact skin of 6 animals; after 4 hours the wrapping and gauze pads were removed and any skin reactions were evaluated; the test sites were washed, readings were again made 24 and 48 hours after initial application
Reliability : (4) not assignable
Individual animal data are not reported, no data on primary skin irritation

indices, exposure sites were only observed at 24 and 48 hours
22.10.2004 (51)

Species : guinea pig
Concentration :
Exposure :
Exposure time : 24 hour(s)
Number of animals : 10
Vehicle : other: yes
PDII :
Result :
Classification :
Method : other: the test material was applied to intact skin of 10 animals as a solution in aceton: dioxane (1:1) containing 13% guinea pig fat (f.a.d.)
Year : 1963
GLP : no
Test substance : other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity

Result : 24-hour reaction: strong erythema and edema (5%), strong erythema (0,5%), no irritation (0,05%)
Reliability : (3) invalid
Unsuitable test system
25.10.2004 (46)

Species : guinea pig
Concentration : 50 other: ul
Exposure :
Exposure time : 24 hour(s)
Number of animals : 3
Vehicle : other: acetone
PDII :
Result :
Classification :
Method : other: see Test Condition
Year : 1977
GLP : no
Test substance : other TS: Hylene W, no data on purity

Result : 24 hour reaction: moderate irritation (50%, 25%) and mild irritation (10%, 5%)
Test condition : TEST ANIMALS:
strain: albino
sex: male
ADMINISTRATION/EXPOSURE:
One drop (= 0.05 ml) each of a 50%, 25%, 10% and 5% acetone solution was applied and lightly rubbed into the shaved intact back skin.
EXAMINATIONS:
Readings were made 24 hours after the topical applications.
Reliability : (3) invalid
Unsuitable test system
25.10.2004 (55)

Species : guinea pig
Concentration : 50 other: ul
Exposure : no data
Exposure time :
Number of animals : 10
Vehicle : other: acetone
PDII :
Result :

Classification	:	
Method	:	other: see Test Condition
Year	:	1977
GLP	:	no
Test substance	:	other TS: Hylene W, no data on purity
Remark	:	A range-finding study was done on 3 animals with 50%, 25%, 10% and 5 % testmaterial in acetone, after 24 hours 3/3 animals showed mild (5% and 10%) or moderate (25% and 50%) erythema
Result	:	24 and 48 hour reaction: slight (8/10 and 6/10) to no reaction (0,5%), no irritation (0,05%)
Test condition	:	TEST ANIMALS: strain: albino sex: male ADMINISTRATION/EXPOSURE: One drop (= 0.05 ml) each of a 0.5% and 0.05% solution of test material in acetone was applied and lightly rubbed into the shaved intact shoulder skin. EXAMINATIONS: Readings were made 24 and 48 hour(s) after application
Reliability	:	(3) invalid Unsuitable test system

25.10.2004 (54)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	3
Vehicle	:	
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	other: see Test Condition
Year	:	1966
GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity
Result	:	The compound was classed as a moderate irritant; the average maximum score was 4.3 out of a possible 8 in 24 hours, within 7 days edema disappeared but mild redness remained.
Test condition	:	TEST ANIMALS: strain: albino sex: 1 male, 2 females ADMINISTRATION/EXPOSURE: The undiluted compound was applied to the clipped, intact skin and removed after 24 hours. The application was covered with plastic strips EXAMINATION: observations were made at the end of 1 hour, 24, 48, 72, 120 and 168 hours; the data were scored according to the method of Draize.
Reliability	:	(4) not assignable Limited documentation, e.g. no data on applicated volume, no individual scores are reported

25.10.2004 (77)

5.2.2 EYE IRRITATION

Species	:	rabbit

Concentration	:	undiluted
Dose	:	100 other: ul
Exposure time	:	
Comment	:	other: rinsed after 30 sec./not rinsed
Number of animals	:	6
Vehicle	:	
Result	:	irritating
Classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1981
GLP	:	no
Test substance	:	other TS: 4,4´-methylenedicyclohexyl diisocyanate liquid sample, no data on purity

Result :

A primary irritation value of 3.0 was calculated (0 - 10 = not irritating); with regard to the results the test material was classified "not irritating", however there were slight effects on the conjunctivae (grade 1-2) in 3/6 animals at the end of the observation period; there was no difference between "with rinsing" and "without rinsing"

INDIVUDUAL SCORES, with rinsing (1, 24, 48, 72h, 8d/animal)
-Cornea: 0, 1, 0, 1, 1, 0; 0 (all further timepoints)
- Iris : 1, 0, 0, 0, 0, 0; 0 (all further timepoints)
- Conjunctivae (redness): 3, 2, 2, 2, 2, 2;
1, 0, 1, 0, 1, 1;
1, 0, 1, 0, 1, 1;
1, 0, 1, 0, 0, 1;
1, 0, 2, 0, 0, 1;
- Conjunctivae (chemosis): 2, 2, 2, 1, 3, 1;
0, 2, 1, 0, 1, 1;
0, 2, 1, 0, 1, 1;
1, 1, 1, 0, 1, 1;
1, 0, 2, 0, 0, 1;

INDIVUDUAL SCORES, without rinsing (1, 24, 48, 72h, 8d/animal)
-Cornea: 0 (all timepoints evaluated)
- Iris : 1, 0, 0, 0, 0, 0; 0 (all further timepoints)
- Conjunctivae (redness): 2, 2, 2, 2, 3, 2;
2, 0, 1, 0, 1, 1;
1, 0, 1, 0, 1, 1;
0, 0, 1, 0, 0, 1;
0, 0, 2, 0, 0, 1;
- Conjunctivae (chemosis): 2, 2, 2, 1, 3, 1;
1, 2, 1, 0, 1, 1;
1, 2, 1, 0, 1, 1;
0, 1, 1, 0, 0, 1;
0, 1, 2, 0, 0, 1;

Test condition :

TEST ANIMALS:
strain: New Zealand Wight
sex: male
ADMINISTRATION/EXPOSURE:
the test material was applied into the conjunctival sac of the lower lid of both eyes; the lids were gently held together for one second. The right eye was flushed 30 s after the application (physiol. saline solution; 3 min.) the left was not flushed
EXAMINATION:
The findings were determined 1 (only for the flushed eyes), 24, 48 and 72 hours and 8d after application.
EVALUATION:
The scoring system of Draize was applied to calculate the irritation index; the 24, 48 and 72 hours values are the basis for the irritation index; the

levels of damage to cornea (0-80), iris (0-10) and conjunctiva (0-20), together 0-110, are added for all six animals after 24, 48 and 72 hours. the total is divided by 18, and yields the level of primary irritation to the eye.

Reliability : (2) valid with restrictions
The text of the summary and the individual scores are contradictory, the reasons why the effects on the conjunctivae at the end of the observation period have no biological relevance are not given

Flag : Critical study for SIDS endpoint

20.11.2004 (10)

Species : rabbit
Concentration : undiluted
Dose : 100 other: ul
Exposure time :
Comment : other: rinsed after 30 sec/not rinsed
Number of animals : 6
Vehicle :
Result : irritating
Classification :
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1981
GLP : no
Test substance : other TS: 4,4´-methylenedicyclohexyl diisocyanate solid sample, no data on purity

Result : A primary irritation value of 0.4 was calculated for the flushed eyes (0 - 10 = not irritating); a primary irritation value of 6,3 was calculated for the unflushed eyes (0 - 10 = not irritating); the slight irritation of the conjunctiva (score 1-2 for redness and chemosis) has almost subsided after 24 hours with rinsing, and after 72 hours without rinsing; total recovery was documented after 72 hours (with rinsing) and 8 days (without rinsing); corneal opacity was restricted to 3/6 (with rinsing) and 2/6 (without rinsing) animals, respectivily and it was reversible within 24 (with rinsing) and 72 hours (without rinsing), respectivily.
INDIVUDUAL SCORES, with rinsing (1, 24, 48, 72h, 8d/animal)
-Cornea: 1, 1, 0, 0, 0, 1; 0 (all further timepoints)
- Iris : 0 (all timepoints)
- Conjunctivae (redness): 2, 2, 2, 1, 1, 2;
0, 1, 1, 0, 0, 0;
0, 1, 1, 0, 0, 0;
0, 0, 0, 0, 0, 0;
0, 0, 0, 0, 0, 0;
- Conjunctivae (chemosis): 1, 1, 1, 1, 0, 1;
0, 0, 0, 0, 0, 0;
0, 0, 0, 0, 0, 0;
0, 0, 0, 0, 0, 0;
0, 0, 0, 0, 0, 0;
INDIVUDUAL SCORES, without rinsing (1, 24, 48, 72h, 8d/animal)
-Cornea: 1 h was not evaluated
4, 0, 0, 0, 0, 1
1, 0, 0, 0, 0, 0
0, 0, 0, 0, 0, 0
0, 0, 0, 0, 0, 0
- Iris : 0 (all timepoints)
- Conjunctivae (redness): 2, 2, 2, 1, 2, 2;
2, 1, 1, 1, 2, 2;
2, 1, 1, 1, 1, 2;
2, 0, 0, 1, 0, 0;
0, 0, 0, 0, 0, 0;
- Conjunctivae (chemosis): 2, 1, 2, 2, 1, 2;

2, 0, 0, 0, 1, 1;
2, 0, 0, 0, 1, 1;
0, 0, 0, 0, 0, 0;
0, 0, 0, 0, 0, 0;

Test condition : TEST ANIMALS:
strain: New Zealand Wight
sex: male
ADMINISTRATION/EXPOSURE:
the test material was applied into the conjunctival sac of the lower lid of both eyes; the lids were gently held together for one second. The right eye was flushed 30 s after the application (physiol. saline solution; 3 min.) the left was not flushed
EXAMINATION:
The findings were determined 1 (only for the flushed eyes), 24, 48 and 72 hours and 8d after application. The 24, 48 and 72 hours values are the basis for the irritation index; the levels of damage to cornea (0-80), iris (0-10) and conjunctiva (0-20), together 0-110, are added for all six animals after 24, 48 and 72 hours. the total is divided by 18, and yields the level of primary irritation to the eye.

Reliability : (2) valid with restrictions
No data on purity of test substance

Flag : Critical study for SIDS endpoint

20.11.2004 (11)

Species : rabbit
Concentration : undiluted
Dose : 100 other: ul
Exposure time : 24 hour(s)
Comment : rinsed after (see exposure time)
Number of animals : 3
Vehicle :
Result :
Classification :
Method : other: see Test Condition
Year : 1966
GLP : no
Test substance : other TS: 4,4´-methylenedicyclohexyl diisocyanate, no data on purity

Result : The compound was classed as a severe eye irritant; the average maximum score was 63.3 out of a possible 110 in 24 hours; no reversibility within 168 hours
Copious discharge, partial eversion of the lids, moderately severe erythema, and moderate corneal cloudiness produced an average score of 44.3 in one hour. The lids were closed ovenight and swelling extended for a considerable distance around the eye. The iris was visible and continued to react to light. Individual vessels of the conjunctivae were not easily discernible. Gradual improvement followed
irrigation. The lida were still nearly closed after five days but corneal clarity had improved markedly leading to the conclusion that eyesight would not be permanently damaged.

Test condition : TEST ANIMALS:
strain: albino
sex: 1 male, 2 females
ADMINISTRATION/EXPOSURE:
The undiluted compound was placed in the conjunctival sac of the right eye; the eyes were rinsed with isotonic saline solution after 24 hours
EXAMINATION:
observations were made at the end of 1 hour, 24, 48, 72, 120 and 168 hours; the data were scored according to the method of Draize.

Reliability : (4) not assignable

No individual scores are reported

25.10.2004 (77)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	100 other: ul
Exposure time	:	
Comment	:	other: rinsed after 20 sec (6 rabbits), not rinsed (2 rabbits)
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: see Test Condition
Year	:	1979
GLP	:	no
Test substance	:	other TS: Hylene W (composition: 99.3%)
Remark	:	This test was done to determine the most effective eye wash for removal of Isocyanic acid, Methylenebis-(4-cyclohexyl) ester from eyes
Result	:	The two rabbits, which served as positive controls (dosed with Hylene W and not washed) showed mild conjunctivitis and irritation of the outer lids (hair loss and occasional necrotic spots); no corneal or iritic effects occured and the eyes were normal at 15 days except the hair loss on the outer lids which was returning to normal at 28 days
Test condition	:	TEST ANIMALS: strain: no data sex: no data ADMINISTRATION/EXPOSURE: The undiluted compound was placed in the conjunctival sac of the right eye; the treated eye of 2 animals was not washed; after 20 seconds the treated eyes of the other rabbits were washed as follows: - 2 eyes washed 1 minute with tape water - 2 eyes washed 15 minutes with tape water - 2 eyes washed 1 minute with 25% aqueous propylene glycol with 0.01% thimerosal EXAMINATION: observations of the cornea, iris and conjunctiva were made with a hand-slit lamp at 1 and 4 hours, 1, 2, 3, 7, 14 or 15, and 28 days
Reliability	:	(3) invalid Unsuitable test system (for further explanation see "remark")

25.10.2004 (56)

5.3 SENSITIZATION

Type	:	other: Modified Guinea pig maximization test
Species	:	guinea pig
Number of animals	:	20
Vehicle	:	other: paraffin oil
Result	:	not sensitizing
Classification	:	
Method	:	other: modified OECD TG 406
Year	:	1984
GLP	:	no
Test substance	:	other TS: 4,4´-Methylenedicyclohexyl diisocyanate (liquid), mixed isomers, no further data
Remark	:	In a pilot study with 4 animals the skin irritation was examined for the challenge with 0.03, 0.1, 0.3% and 1% (24 hours, occlusive); the animals

were treated with FCA and paraffin oil like the control animals
0.03%: 3 of 4 animals showed mild or moderate erythema;
>= 0.1%: all animals showed mild up to pronounced signs of irritation which were still evident after 72 hours.

Result : 1/20 treated animals died after the second induction, because none of the remaining animals showed clinic signs the death seemed to be not substance related.
1. challenge:
0.01%: 0/19 (2/10 in the control group) with a positive reaction
0.03%: 0/19 (6/10 in control group) with a positive reaction
2. challenge:
0.01%: 0/19 (5/10 in the control group) with a positive reaction
0.03%: 1/19 (6/10 in control group) with a positive reaction
The reason why there were more positive responses in the control groups with both concentrations is not entirely understood but local irritant effects seemed to be involved.

Test condition : Animals are acclimatised to the laboratory conditions for approx. 1 week prior to the test.
Before the test, animals are randomised and assigned to the treatment groups; Number of animals: 20 test and 2 x 10 control guinea pigs have been used; removal of hair is by shaving and chemical depilation (challenge). The animals are weighed before the test commences and every week during the study. All skin reactions and any unusual findings, including systemic reactions were observed twice a day and recorded.

Induction: Intradermal Injections

Day 0 - treated group
Three pairs of intradermal injections of 0.1 ml volume are given in the shoulder region which is shaved.
Injection 1: a 1:1 mixture (v/v) Freunds Complete Adjuvans (FCA)/water
Injection 2: the test substance in paraffin oil
Injection 3: the test substance formulated in FCA

Day 0 - control groups
Three pairs of intradermal injections of 0.1 ml volume are given in the same sites as in the treated animals.
Injection 1: a 1:1 mixture (v/v) FCA/water
Injection 2: paraffin oil
Injection 3: FCA

Induction: Intradermal injections

Day 7 - treated group
Three pairs of intradermal injections of 0.025 ml volume of the undiluted test material are given in the same sites as in the induction.

Day 7 - control groups
no treatment

Challenge: Topical Application

Day 21 - treated and first control group
A patch with the test substance is applied to the opposed flanks of the animals. The patches are held in contact by an occlusive dressing for 6 hours.

Day 35 - treated and second control group
A patch with the test substance is applied to the opposed flanks of the animals. The patches are held in contact by an occlusive dressing for 6

hours.

Observations - treated and control groups

After removing the patch (1 hour before the first evaluation) the challenge area is cleaned and
depilated to facilitate the evaluation of the skin reaction;
- approximately 8 hours from the start of the challenge application the skin reaction is observed and recorded according to MAGNUSSON AND KLIGMAN GRADING SCALE FOR THE EVALUATION OF CHALLENGE PATCH TEST REACTIONS
0 = no visible change
1 = discrete or patchy erythema
2 = moderate and confluent erythema
3 = intense erythema and swelling

- approximately 16 hours after this observation a second observation (24 hours), a third (48 hours) and fourth (72 hours) is made and once again recorded.

Skin reactions which are observed at two observation times are evaluated "positive". An animal is evaluated as sensitized if the treated animal showes a positive response without any evidence of irritation.

1st: Induction (day 0): 10% intradermal
2nd: Induction (day 7): undiluted intradermal
3rd: Challenge (day 21 and 35): 0.01 and 0.03% occlusive (6 hours);

Reliability : (2) valid with restrictions
Restrictions: no standard protocol; no range finding for the induction; slightly irritating concentration for the challenge

Flag : Critical study for SIDS endpoint

22.12.2005 (12)

Type : Guinea pig maximization test
Species : guinea pig
Number of animals : 20
Vehicle : other: paraffin oil
Result : not sensitizing
Classification :
Method : other: similar to OECD TG 406
Year : 1985
GLP : yes
Test substance : other TS: 4,4´-Methylenedicyclohexyl diisocyanate (liquid), mixed isomers, no further data

Remark : In a pilot study for the challenge the skin irritation was examined with 4 animals with 0.01, 0.03, 0.1 and 0.3% (24 hours, occlusive); the animals were treated with FCA and paraffin oil like the control animals; only one animal showed skin irritation with all applied concentration and at every examination time (48 and 72 hours after application)

Result : 0.001%: 1/20 (1/10 in the control group) with a positive reaction
0.01%: 1/20 (5/10 in control group) with a positive reaction
The reason why half of the control animals showed a positive reaction towards 0.01% is not entirely understood but local irritant effects seemed to be involved.

Test condition : Animals are acclimatised to the laboratory conditions for approx. 1 week prior to the test.
Before the test, animals are randomised and assigned to the treatment groups; Number of animals: 20 test and 10 control guinea pigs have been used; removal of hair is by shaving and chemical depilation (challenge).

The animals are weighed before the test commences and every week during the study. All skin reactions and any unusual findings, including systemic reactions were observed twice a day and recorded.

Induction: Intradermal Injections

Day 0 - treated group
Three pairs of intradermal injections of 0.1 ml volume are given in the shoulder region which is shaved.
Injection 1: a 1:1 mixture (v/v) Freunds Complete Adjuvans (FCA)/water
Injection 2: the test substance in paraffin oil
Injection 3: the test substance formulated in paraffin oil/FCA (1:1)

Day 0 - control group
Three pairs of intradermal injections of 0.1 ml volume are given in the same sites as in thetreated animals.
Injection 1: a 1:1 mixture (v/v) FCA/water
Injection 2: paraffin oil
Injection 3: paraffin oil in a 1:1 mixture (v/v) FCA/water

Induction: Topical Application

Day 7 - treated group
A adhesive tape (2.5 x 2.5 cm) is fully-loaded with test substance in paraffin oil and applied to the test area and held in contact by an occlusive dressing for 48 hours.

Day 7 - control group
Paraffin oil only is applied in a similar manner to the test area and held in contact by an occlusive dressing for 48 hours.

Challenge: Topical Application

Day 21 - treated and control groups
A patch with the test substance is applied to the opposed flanks of the animals. The patches are held in contact by an occlusive dressing for 24 hours.

Observations - treated and control groups

After removing the patch the challenge area is cleaned and depilated to facilitate the evaluation of the skin reaction;
- approximately 48 hours from the start of the challenge application the skin reaction is observed and recorded according to MAGNUSSON AND KLIGMAN GRADING SCALE FOR THE EVALUATION OF CHALLENGE PATCH TEST REACTIONS
0 = no visible change
1 = discrete or patchy erythema
2 = moderate and confluent erythema
3 = intense erythema and swelling

- approximately 24 hours after this observation a second observation (72 hours) and third (96 hours) is made and once again recorded.

An animal is evaluated as sensitized if the treated animal showes a skin reaction graded >=1 without any evidence of irritation at 2 observation times.

CONCENTRATION:

1st: Induction (day 0): 1% intradermal
2nd: Induction (day 7): 10% topical (occlusive; 48 hours)
3rd: Challenge (day 21): 0.001 and 0.01% topical (occlusive ; 24 hours)

Reliability : (2) valid with restrictions
No range finding for the induction. Slightly irritating test concentrations for the challenge

Flag : Critical study for SIDS endpoint

22.12.2005 (13)

Type : Buehler Test
Species : guinea pig
Concentration : 1st: Induction 2 %
2nd: Challenge .5 %
3rd:
Number of animals : 20
Vehicle : petrolatum
Result : sensitizing
Classification :
Method : Directive 96/54/EC, B.6
Year : 1998
GLP : no data
Test substance : other TS: Desmodur W, purity: > 99.5%

Result : 19/20 showed a positive reaction
Test condition : Strain: Dunkin-Hartley
Sex: female
Dose: 0.5 ml for induction and challenge
Histopathological examination was carried out to clarify doubtful reactions, and the results were interpreted as positive only if they were confirmed as sensitization reactions of experimental eczema; the sensitivity and realiability of the test were assessed by the use of reference substance (neomycin sulfate)

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint

05.11.2004 (100)

Type : Buehler Test
Species : guinea pig
Number of animals : 15
Vehicle : other: olive oil and anhydrous acetone (1 : 1)
Result :
Classification :
Method : other: see Test Condition
Year : 1984
GLP : yes
Test substance : other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity

Remark : An irritation range-finding study was performed in order to select a vehicle and doses for the induction and challenge applications.
Six animals were treated topically with 1.0, 0.3, 0.1, 0.03, 0.01 and 0.003 Molar of the test material in 100% olive oil or in a 1 : 1 mixture of olive oil and anhydrous acetone under occlusive conditions. The patches were left in place for 6 hours. Observations for irritation were made 24 and 48 hours after application and again at day 4, 5 or 6.

Result : Author´s conclusion: Under conditions of this study 4,4´-methylenedicyclohexyl diisocyanate exhibited the potential to produce dermal sensitization in guinea pigs.

Concentrations selected for induction were only non-irritating for all low-

and mid-dose animals 24 hours after the first induction exposure; subsequently almost all animals developed skin reactions; for the high dose group the induction concentration was irritating upon initial administration; responses generally increased in incidence and severity after subsequent induction exposures; this type of response to repeated exposures may represent a cumulative irritant effect and/or may be indicative of sensitization.
With the high challenge concentration (60 milliMolar = mid-dose for induction) 9//15 animals of the low dose for induction; 13/15 animals of the mid-dose for induction and 15/15 animals of the high dose for induction showed scores greater than 0.
With the mid-high challenge concentration (20 milliMolar = low-dose for induction) 1/15 animals of the low dose for induction; 5/15 animals of the mid-dose for induction and 5/15 animals of the high dose for induction showed scores greater than 0.
With the other challenge concentrations (0.06-6 milliMolar) no skin reactions were observed in any animal of dose groups for induction.
2/6 irritation controls ad high dose had minimal scrores at 48 hours only.
cross-reactivity to structurally related materials (e.g. TDI, MDI, IPDI) was less pronounced.

Test condition **:** Number of animals: 15/concentration; 6 control animals (did not receive induction exposures)

Dose levels
induction exposure: 20, 60, 200 milliMolar
challenge exposure: 60, 20, 6, 0.6, 0.06 milliMolar/dose level

Induction: Topical application

Treated group:
One flank is cleared of hair (closely-clipped). The test material was adiministered in a volume of 50 microliters beneath an adhesive-backed gauze patch. The test patch was covered by ovelapping, impermeable plastic and firmly secured by an elastic adhesive bandage wound around the torso of the animal. The patch was held in contact with the skin for 6 hours after which it was removed . This was repeated at the same site once weekly for 3 weeks, for a total of 3 applications.

control group: not used

Challenge

Treated groups:
Fourteen days after the last induction exposure the untreated flank of treated animals is cleared of hair (closely-clipped). Five different concentrations (25 microliters) were administered as described for the induction. The patch was held in contact for 6 hours. In order to differentiate possible dermal reactions produced by irritation from those produced by sensitization, 6 additional animals (= control group) were subjected to the same challenge procedure

Cross-Challenge

Single concentrations of 4 different materials were applied to the high dose test animals upon recovery from challenge (7 days after challenge). Cross-challenge control animals were also treated with these materials and concentrations.

Observations - treated and control groups

Induction sites: prior to dosing and approximately 24 hours after each induction application

Challenge sites: prior to dosing and approximately 24 and 48 hours after challenge application

GRADING SCALE FOR THE EVALUATION OF CHALLENGE PATCH TEST REACTIONS
0 = no visible change
1 = discrete or patchy erythema
2 = moderate and confluent erythema
3 = intense erythema and swelling

Reliability : (2) valid with restrictions
Only 15 animals/dose group, no control animals during induction exposure; pronounced skin reaction during induction exposure, slightly irritating test concentrations for the challenge

Flag : Critical study for SIDS endpoint

22.12.2005 (2)

Type : Mouse ear swelling test
Species : mouse
Number of animals :
Vehicle : other: acetone
Result : sensitizing
Classification :
Method : other: see Test Condition
Year : 1987
GLP : no data
Test substance : other TS: 4,4´-Methylenedicyclohexyl diisocyanate, purity > 99.3%

Result : The dose response curve has a nearly vertical direction (single data were not reported); this suggests that this compound may effect threshold response rather than a dose-dependent one; the steep dose-response curve suggested a threshold-type response occuring at 0.24 mg/kg; Crossreaction was observed to HDI and MDI

Test condition : NUMBER OF ANIMALS: groups 4 - 5 animals were used per dose with many replicate determinations (no further data).
Mice were sensitized and challenged using the method described by Stadler and Karol (Toxicol. Appl. Pharamacol. 78, 445-450, 1985) adapted from that of Asherson and Ptak (Immunology 15, 405-410, 1968). 100 ul acetone containing the specified amount of diisocyanate (no further information available) was applied to the shaved and depilated abdomen of the test animals. After 4 days the mice were challenged on the right ear with acetone and on the left ear with acetone containing a nonirritating dose isocyanate.Challenge doses were determined in separate experiments in which groups of mice were administered 40, 100, 200, 400 ug isocyanate to the ear and measurements of ear thickness were taken at 24 h. A dose below that which caused an increase in ear thickness was selected. Based on these tests, 40 ug 4,4´-methylenedicyclohexyl diisocyanate were used for challenge.
Cross-reactivity studies were performed with diphenylmethane-4,4´-diisocyanate (MDI), toluene diisocyanate (TDI) and hexamethylene diisocyanate (HDI); the dose for sensitization was 0.75 mg 4,4´-methylenedicyclohexyl diisocyanat/kg

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint

22.12.2005 (91)

Type	:	Mouse local lymphnode assay
Species	:	mouse
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: an alternative endpoint (production of interleukin 6) was measured (in vivo and in vitro experiments)
Year	:	
GLP	:	no data
Test substance	:	other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity
Remark	:	The objective of the studies published in the cited papers was to evaluate the potential of a molecular (IL-6 production), rather than a cellular (lymphocyte proliferation), endpoint for determing the extent of lymph node activation induced by topical exposure to a chemical allergen; for this special purpose the experiments were done with chemicals known to cause contact sensitization
Result	:	3 days after initiation of exposure the test material induced at all lymph node cells (LNC) concentrations vigorous proliferative response and significant levels of IL-6 production
Reliability	:	(2) valid with restrictions Limited documentation

22.12.2005 (43) (63) (65)

Type	:	Mouse local lymphnode assay
Species	:	mouse
Number of animals	:	
Vehicle	:	other: acetone : olive oil (4 : 1)
Result	:	
Classification	:	
Method	:	other: see Test Condition
Year	:	1992
GLP	:	no data
Test substance	:	other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity
Remark	:	The objective of the studies published in the cited papers was to evaluate the potential of a molecular (IL-6 production), rather than a cellular (lymphocyte proliferation), endpoint for determing the extent of lymph node activation induced by topical exposure to a chemical allergen; for this special purpose the experiments were done with chemicals known to cause contact sensitization
Result	:	While a lymphocyte proliferative response in lymph nodes draining was observed, the test material did not induce a change in serum IgE concentration. With regard to the author´s opinion this result is consistent with the differential immune response for contact and respiratory sensitizer. The test material appears not to cause respiratory allergy but causes contact sensitization.
Test condition	:	A combination of local lymph node assay (Groups of mice (n = 4) received 25 ul of various concentrations (0.1 - 5%) of the test material or an equal volume of vehicle alone on the dorsum of both ears. Three days later all mice received [3H]methylthymidine iv via the tail vein. Mice were killed 5 hr later and draining auricular lymph nodes isolated and pooled for each experimental group.) and measurement of serum IgE concentration in mice (n= 10) which recieved the test material (50 ul, 2 or 1%) on each shaved flank and seven days later the same test material (25 ul of a 1:1 dilution) was applied to the dorsum of both ears.
Reliability	:	(2) valid with restrictions Limited documentation

Flag : Critical study for SIDS endpoint
22.12.2005 (42) (44)

Type : other
Species : other: mouse and guinea pig
Number of animals :
Vehicle : other: methylethyl ketone
Result :
Classification :
Method : other: See Test Condition
Year : 1985
GLP : no data
Test substance : other TS: Desmodur W, no data on purity

Result : Application of high doses of each chemical resulted in extensive erythema and a large proportion of animals became sensitzed. Lower doses produced less sensitivity. In mice, as well as in guinea pigs, a dose-response relationship was apparent between the sensitizing dose and both severity of response and number of animals responding. For mice, comparison of the dose of chemical required to sensitize 50% of the animals (SD5O) yielded 0.40 mg/kg for PiCl and approximately 0.20 mg/kg for 4,4´-Methylenedicyclohexyl diisocyanate (using probit analysis).

Test condition : The study was undertaken to determine if the dose-response relationship could be used to assess the sensitizing potencies. Picryl chloride (PiCl) was selected because the extensive literature describing its ability to cause delayed dermal sensitivity.
Groups (4-8) of BALB/cBy mice and English smooth-haired guinea pigs (8) were exposed to 4,4´-Methylenedicyclohexyl diisocyanate or PiCl by topical exposure. Mice were challenged 5 days later using an ear swelling assay (20 ul 0.5% PiCl, 0.1% 4,4´-Methylenedicyclohexyl diisocyanate) and the thickness of each ear was measured 6, 24 and 48 hours postchallenge. Guinea pigs were challenged 7 days later by patch testing (25 ul of 0.5% PiCl or 0.1% 4,4´-Methylenedicyclohexyl diisocyanate) and responses graded at 1, 2, 4, 6, 8,24 and 48 hr postchallenge.

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint
09.11.2006 (87)

Type : other
Species : guinea pig
Number of animals :
Vehicle :
Result :
Classification :
Method : other: see Test Condition
Year : 1982
GLP : no data
Test substance : other TS: 4,4´-Methylenedicyclohexyl diisocyanate, purity: 99,3%

Remark : The study utilize a recently developed animal model (Karol et al., Toxicol. Appl. Pharmacol. 53, 260-270 (1980) and 58, 221-230 (1981)) to evaluate 4,4´-methylenedicyclohexyl diisocyanate as a sensitizing agent and to compare its respiratory and dermal sensitizing abilities with that of TDI.

Result : antibody response:
with the double-diffusion assay, no antibodies were detected in sera tested of any HMDI treated animal; few sera demonstrated antibodies when applying the more sensitive passive cutaneous anaphylaxis technique, but antibody titers were extremely low.
cutaneous reactions:

- contact sensitivity was observed in the animals exposed by topical application (12/12) and toepad inoculation
- dermal sensitivity was observed in the animals exposed by topical application (9/12) and i.p. injection (3/4)
- pulmonary sensitivity was only elicited with HMDI in acetone in 2/11 animals which have been sensitized with toepad inoculation of test material in Freund´s complete adjuvant; challenge with HMDI-GSA did not produce any pulmonary response in these animals. No pulmonary sensitivity using HMDI-GSA was detected in any of 12 guinea pigs sensitized by topical exposure.

Test condition : Guinea pigs were exposed by topical application, intradermal and intraperitoneal injection, as well as toepad inoculation of test material in Freund´s complete adjuvant; subsequent the animals were examined for antibody body response (sera taken on days 15 and 22), contact sensitivity (0,1% test material onto clean depilated dorsal area), dermal sensitivity (intradermal injection of 0.1% HMDI-GSA) and pulmonary sensitivity (bronchial provocation challenge with 0.1% HMDI in acetone and HMDI - GSA)

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint

22.12.2005 (67)

Type : other
Species : other: mouse and guinea pig
Number of animals :
Vehicle : other: acetone
Result :
Classification :
Method : other: see Test Condition
Year : 1984
GLP : no data
Test substance : other TS: Desmodur W, no data on purity

Result : Guinea pig: skin sensitivity following inhalation of
> 3 ug/l, no sensitization after 1,25 ug/l;
mice: contact sensitivity was detected following inhalation
of > 17 ug/l, no reaction after < 7 ug/l;
dermal contact of the head, as would occur during inhalation exposures, also resulted in contact sensitization

Test condition : INDUCTION:
guinea pig: inhalation for 2h/day on 3 consecutive days; head only exposure to an aerosol (1, 3, 17, 32, 44, 53 mg/m3); 4 animals/concentration
mice: exposure was similiar to that described for guinea pigs, however mice were expoed nose onyl exposed
mice: direct application to the noses of mice to cover an area comparable to that which extended into the "nose-only" inhalation chamber; the application was performed over a period of 2h on 3 consecutive days

CHALLENGE:
7 days following the initial inhalation exposure guinea pigs were challenged by topical application (25 ul, 0.1% = nonirritating concentration) onto the flank area and all mice (inhalation and dermal application) by application (20 ul, 0.1% = nonirritating concentration) to each side of the right ear (ear swelling test)

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint

14.01.2005 (86)

Type	:	other: lung sensitization following intradermal induction
Species	:	guinea pig
Number of animals	:	8
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: see Test Condition
Year	:	1995
GLP	:	yes
Test substance	:	other TS: Desmodur W; purity: > 99.2 %
Result	:	Following induction, slight skin reactions at the injection sites occurred. During or following test material-challenges, the incidence of immediate-onset respiratory reactions was roughly the same in vehicle controls and test substance-induced animals. No deaths or anaphylactic reactions were observed during challenge, and no clinical signs or specific abnormalities were observed at necropsy. The histopathological evaluation of lungs revealed a marked influx of eosinophils in test material-sensitized guinea-pigs, a characteristic feature of asthma and airway hypersensitivity. The study provides evidence that the testsubtance is weak respiratory sensitizer in guinea pigs.
Test condition	:	ADMINISTRATION: Groups of eight female guinea-pigs were intradermally induced once on day 0 (injection volume: 100 ul/, 0.13 % solution in olive oil). Eight female controls received vehicle alone under otherwise identical conditions. Following a recovery period of approximately four weeks (starting on day 28) a test material-hapten challenge (mean concentration: 68 ± 3.6 mg/m3 air) was performed (challenge duration: 30 min). The technical exposure criteria specified in OECD TG 403 were fulfilled insofar as these are applicable to this study. The aerosolized test material proved to be of adequate respirability. EXAMINATIONS: During and after challenge exposures with the hapten, immediate-onset respiratory reactions were evaluated by measurement of respiratory rate, tidal volume, respiratory minute volume, inspiratory and expiratory times, and peak expiratory flow rate. Additional parameters were derived mathematically. During sacrifice the trachea, lung, and lung associated lymph nodes were fixed and subjected to histological evaluation.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

14.01.2005 (19)

Type	:	Patch-Test
Species	:	human
Number of animals	:	
Vehicle	:	petrolatum
Result	:	
Classification	:	
Method	:	other: no further data
Year	:	1976
GLP	:	no data
Test substance	:	other TS: Prepolymers consisting of 4,4´-methylenedicyclohexyl diisocyanate (no further infomation available)
Result	:	2/2 contact dermatitis patients showed a positive reaction in a patch test with prepolymers consisting of 4,4´methylenedicyclohexyl diisocyanate
Test condition	:	8/12 employees of a small polyurethane moulding plant who worked as plastic molders developed contact dermatitis; the case history of 3 patients is described in details; patch testing was performed with 2 of these 3

patients with nonirritating concentrations (1%) and 4 healthy volunteers served as control

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint

22.12.2005 (57)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : other: toluene
Result :
Classification :
Method : other: no further data
Year : 1980
GLP : no data
Test substance : other TS: Hylene W, no data on purity

Result : A case report about a student with contact sensitivity developed during a project on manufacture of polyurethane foam; the student showed a positive reaction when patch tested with 1% Hylene W; control patch tests were performed on a member of staff who showed no response

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint

15.11.2004 (70)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other: no further data
Year : 1977
GLP : no data
Test substance : other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity

Result : A case report about a chemical engineer who began investigative work with various polyester and isocyanates sufferd from itchy polymorphic dermatitis; he was patch tested with the substances of the international standard tray and with 32 substances he has used in his research; the only substance to which he clearly reacted was 4,4´diisocyanatodicyclohexyl methane (1%).

Reliability : (2) valid with restrictions
Limited documentation

Flag : Critical study for SIDS endpoint

22.12.2005 (73)

Type : Patch-Test
Species : human
Number of animals :
Vehicle : petrolatum
Result :
Classification :
Method : other: no further data
Year : 1997
GLP : no data
Test substance : other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity

Result	:	A case report about a textile worker with pruritic, papulovesicular eruption on the dorsum of her hands, forearms, axillae, sternum and anterior neck. Patch testing to work related chemicals revealed strong positive reactions to 4,4´-methylenedicyclohexyl diisocyanate (0.5, 0.1 and 0.05%) and triethylenetetramine.
Reliability	:	(2) valid with restrictions Limited documentation
Flag	:	Critical study for SIDS endpoint
22.12.2005		(90)

Type	:	Patch-Test
Species	:	human
Number of animals	:	
Vehicle	:	petrolatum
Result	:	
Classification	:	
Method	:	other: no further data
Year	:	
GLP	:	no data
Test substance	:	other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity

Result	:	In a factory where 4,4´-methylenedicyclohexyl diisocynate was used to form a surface-coating polyurethane 7 females operatives suffered from contact dermatitis, 2/7showed a positive reaction in the patch with 4,4´-methylenedicyclohexyl diisocyanate (1%); no reaction was observed for the 50 control patients.
Reliability	:	(2) valid with restrictions Limited documentation
Flag	:	Critical study for SIDS endpoint
22.12.2005		(96) (97)

Type	:	Patch-Test
Species	:	human
Number of animals	:	
Vehicle	:	petrolatum
Result	:	
Classification	:	
Method	:	other: no further data
Year	:	1982
GLP	:	
Test substance	:	other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity

Result	:	A woman woman who began working with 4,4´-methylenedicyclohexyl diisocyanate and a poly-type catalyst suffered from pruritic, erythematous dermatitis after one week. Patch testing were performed with the diisocyanate (1%), the polyether glycol blend, a previously used epoxy resin and hardener and to the standard American Academy of Dermatology tray of patch test substances; there was a reaction (3+) to 4,4´-methylenedicyclohexyl diisocyanate; all other patch tests were negative
Reliability	:	(2) valid with restrictions Limited documentation
Flag	:	Critical study for SIDS endpoint
22.12.2005		(64)

Type	:	Patch-Test
Species	:	human
Number of animals	:	
Vehicle	:	petrolatum

Result	:	
Classification	:	
Method	:	other: see Test Condition
Year	:	2003
GLP	:	no data
Test substance	:	other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity
Result	:	13/17 contact dermatitis patients working at a factory manufacturing medical equipment showed a positive reaction with 4,4´-methylenedicyclohexyl diisocyanate (0.1 and 1%) and the isocyanate glue, while none reacted to the other constituent, TDI. 5 patients showed simultaneous reactions to 4,4´-methylenedicyclohexyl diisocyanate and 4,4´-methylenebis(cyclohexylamine). In several cases, the patients also showed multiple reactions to 1 or more preparations of the isocyanate series. 9 patients also reacted to 1.6-hexamethylenediisocyanate (HDI), 4 to isophoronediisocyanate (IPDI), 1 to isophorone diamine (IPDA) and 5 to MDA. 5/12 showed positive reaction with 0.01% 4,4´-methylenedicyclohexyl diisocyanate.
Test condition	:	Patch testing was performed using the Finn Chamber on Scanpor tape technique lixed with Scanpor or Medipore tape. Patch tests were removed after 2 days by the patient and read after 1 day, according to International Contact Dermatitis Research Group criteria. In 7 cases, a 2nd reading was done 7 days after the initial application of patches.
Reliability	:	(2) valid with restrictions Limited documentation
Flag	:	Critical study for SIDS endpoint
22.12.2005		(59)
Type	:	Guinea pig maximization test
Species	:	guinea pig
Number of animals	:	20
Vehicle	:	other: olive oil and acetone/olive oil (2. challenge)
Result	:	
Classification	:	
Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1993
GLP	:	no
Test substance	:	other TS: Desmodur W, purtiy: 99.2 %
Remark	:	A pilot study for the induction (intradermal: 1, 2, 2.5 and 5%; topical: 12, 25, 50 and 100%) was performed. In a pilot study with 5 animals the skin irritation was examined for the challenge with 0.25, 0.5, 1 and 3% (24 hours, occlusive); the animals were treated with FCA and olive oil like the control animals; skin effects were noticed in 2/5 animals >= 0.25% 3/5 animals >= 0.5% 4/5 animals with 1%
Result	:	Under these testing conditions it can not be excluded that the testsubstance has a sensitizing potential 1. challenge: 0.25%: 20/20 (10/10 in the control group) with a positive reaction 1%: 20/20 (7/10 in control group) with a positive reaction 2. challenge: 0.25%: 17/20 (8/10 in the control group) with a positive reaction 1%: 20/20 (9/10 in control group) with a positive reaction
Test condition	:	CONCENTRATION:

1st: Induction (day 0): 5% intradermal
2nd: Induction (day 7): 3% occlusive (48 hours)
3rd: Challenges (day 21 and 35): 0.25 and 1% semiocclusive (24 hours); vehicle: acetone/olive oil (1:1)

Reliability : (3) invalid
Clearly irritating concentration for the two challenges; irritating vehicle

27.10.2004 (15)

Type : Intracutaneus test
Species : guinea pig
Number of animals : 10
Vehicle :
Result : sensitizing
Classification :
Method : other: see Test Condition
Year : 1977
GLP : no
Test substance : other TS: Hylene W, no data on purity

Result : One animal died from noncompound related causes.
1. challenge (by error only 5 of the 9 test animals were treated):
positive response in 5/5 animals with 0.5% solution;
positive response in 2/5 with 0.1% solution; no response with 0.05% and 0.01% solution
2. challenge:
positive response in 5/9 with 0.1% and 1/9 with 0.05% solution

Test condition : A series of four sacral intradermal injections was given, one each week over a three week period, which consisted of 0.1 ml of a 1% solution of test material in dimethyl phthalate; following a 2 weeks rest period, the test animals were challenged by applying and lightly rubbing in, 0.05 ml of a 0.5%, 0.1%, 0.05% and 0.01% solution of test material in acetone on the shaved intact shoulder skin. A group of previously unexposed animals received similar applications at the time of challenge. After a two week rest period the test animals were rechallenged by applying and lightly rubbing in one drop of a 0.1% and 0.05% solution in acetone. A new group of ten previously unexposed animals were treated in the same fashion.

Reliability : (3) invalid
Unsuitable test system

27.10.2004 (54)

Type : other
Species :
Number of animals :
Vehicle :
Result : sensitizing
Classification :
Method : other: mouse ear swelling test (published elsewhere and local lymph node assay, unpublished)
Year : 1994
GLP : no data
Test substance : other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity

Remark : In this article the development and validation of the murine local lymph node assay are described and comparisons with guinea pig predictive test methods discussed. In addition we examine the advantages and limitations of the method and consider new opportunities and applications of the assay in the context of the toxicological evaluation of sensitizing potential.
Result : both test results are cited as positive in this review article
Reliability : (4) not assignable
Secondary literature

22.12.2005 (69)

Type	:	other
Species	:	guinea pig
Number of animals	:	6
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: see Test Condition
Year	:	1974
GLP	:	no
Test substance	:	other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity
Result	:	During sensitization period a small but statistically significant increase in airway resistance; in the recovery period animals returned to within baseline level after a short period of time; after challenge exposure no increase in airway resistance
Test condition	:	Animals were exposed (whole body) to an average of 6.70 ug/l 4 hours/day fo 5 days; 2 weeks after the last exposure the animals received a single challenge exposure of 1.6 ug/l for 4 hours; isocyanate aerosol was obtained by heating at 75-120 °C in an apparatus and dry house-air ears passed through; 3 animals were sacrificed immediately after the challenge exposure and another 3 were killed seven days later for pathological examination, blood was collected from the heart at the time of the sacrifice in order to obtain anti-isocyanate immune serum; lungs were fixed and prepared for miscroscopic slides
Reliability	:	(3) invalid Unsuitable test system

22.12.2005 (52)

Type	:	other
Species	:	mouse
Concentration	:	1st: 2 % 2nd: 3rd:
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: see Test Condition
Year	:	2004
GLP	:	no data
Test substance	:	other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity
Result	:	there were no change in total or differential cell counts at any time; significant hyperresponsiveness at 2 weeks; these differences were greater at 4 weeks
Test condition	:	BALB/c mice received 5 dermal exposure over a period of 2 weeks; mice were then challenged with increasing doses of methacholine and responsiveness was assessed using whole body plethysmorgraphy; half of the group was killed and serum, bronchoalveolar lavage fluid and lymph nodes were collected for total IgE, cell counts and cytokine profiling; the remaining mice were exposed for additional 2 weeks and reassessed
Reliability	:	(4) not assignable Abstract

22.12.2005 (83)

Type	:	other
Species	:	mouse

Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: see Test Condition
Year	:	2002
GLP	:	no data
Test substance	:	other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity
Result	:	induction of cytokines which are characteristic of a Th2T cell response
Test condition	:	Previous studies have shown that RNA message levels for the Th2T cell cytokines IL4, IL10 and IL 13 are elevated in response to respiratory sensitizer trimellitic anhydride and these increases may be detected by ribonuclease protection assay (RPA). Female BALB/c mice were topically exposed to the test material and total mRNA was isolated from draining lymph nodes 14 days post challenge.
Reliability	:	(4) not assignable Abstract

22.12.2005 (80)

Type	:	other
Species	:	guinea pig
Number of animals	:	6
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: see Test Condititon
Year	:	1971
GLP	:	no
Test substance	:	other TS: Hylene W, no data on purity
Result	:	1/6 elicited sensitization response, no cross-sensitization with TDI and MDI (polymer)
Test condition	:	Animals were exposed to the aerosol mist (0.22 ppm x 4 hous x 3 days), following a one-week rest period, the animals were challenged via the skin route (0.5% and 0.1% Hylene W in 13% guinea pig fat in a 1:1 solution of acetone and dioxane)
Reliability	:	(3) invalid Unsuitable test system

29.10.2004 (48)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	inhalation: aerosol
Exposure period	:	5 days
Frequency of treatm.	:	6 h/day on 5 consecutive days
Post exposure period	:	2 days
Doses	:	0, 1, 6, 36 mg/m³ (target concentration) - 1.7, 5.86, 34.18 mg/m³ (actual concentration)
Control group	:	other: conditioned air
Method	:	other: pilot dose-range finding study according OECD Guide-line 412
Year	:	2002
GLP	:	yes
Test substance	:	other TS: Desmodur W, purity 99.3%

Remark	:	pilot dose-range finding study (main study: Bayer MaterialScience AG; Report No. AT01057 (2004))
Result	:	Mortality: none Rats exposed to 1 and 6 mg/m3 did not elaborate any test substance-induced clinical signs, neurological effects, changes in rectal temperatures or changes on body weights. Rats exposed to 36 mg/m3 and above experienced a mild and transient decrease in body weights and signs of respiratory tract irritation (salivation, bradypnea, stridor). At 36 mg/m3 the lung (m=12%;f=14%) and heart (m=17%; f=3%) weights were significantly increased. Gross necropsy findings (less collapsed lungs with red foci and red secretions in the nose) were observed only at this exposure level.
Test condition	:	TEST ORGANISMS - Age: 2 month - Number of animals: 5/dose/sex ADMINISTRATION / EXPOSURE - Type of exposure: nose-only exposure - Particle size: MMAD range: 0.947-1.02µm (geometric standard deviation: approx. 2) CLINICAL OBSERVATIONS AND FREQUENCY: - Clinical signs: twice daily (exposure days) - Mortality: twice daily - Body weight: days 0, 4, 7 - Rectal Temperature: days 0 and 4 ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC): - Gross Pathology - Organ Weights: Brain, Heart, Kidneys, Liver, Lungs, Spleen, - Microscopic: none STATISTICAL METHODS: Dunnett Test, Adjusted Welch Test, Kruskal-Wallis Test
Conclusion	:	Author concluded: Taking all findings into account 6 mg/m3 constitutes a no-observed adverse effect-level.
Reliability	:	(2) valid with restrictions A pilot dose-range finding study
Flag	:	Critical study for SIDS endpoint

14.01.2005 (33)

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	inhalation: aerosol
Exposure period	:	4 weeks
Frequency of treatm.	:	6 hours per day (5 days/week)
Post exposure period	:	none
Doses	:	0, 1, 6, 36 mg/m³ (target concentration); 1.06, 6.02, 33.8 mg/m³ (actual concentration)
Control group	:	other: conditioned air
NOAEL	:	= 1 mg/m³
Method	:	OECD Guide-line 412 "Repeated Dose Inhalation Toxicity: 28-day or 14-day Study"
Year	:	2003
GLP	:	yes

Test substance : other TS: Desmodur W, purity 99.3%

Result : Mortality: none
Clinical signs:
Group 1 and 2 (controls and 1 mg/m3):
all rats tolerated the exposures without any clinical signs.
Group 3 (6 mg/m3): 7/10 male and 7/10 female animals with signs after exposure; e.g. nasal discharge (most rats recovered during the exposure-free weekends).
Group 4 (36 mg/m3):
Bradypnea, labored breathing patterns, irregular breathing patterns, stridor, tachypnea, nasal discharge, nostrils: red encrustations.

A gender-specific susceptibility could not be ascertained. Most signs suggestive of respiratory tract irritation were observed from the second exposure week onwards.
Nasal discharge and reddened nostrils were observed throughout the study period.

Rectal temperature:
In comparison to the control group, there the body (rectal) temperatures of rats of the 36 mg/m3 group were mildly, although significantly decreased on days 0 (both sexes) and 21 (males).

Body weights:
no toxicologically consistent effect on body weights up to and including the 36 mg/m3 group.
1 mg/m3:
no significant different body weights compared to control animals (except an increase on day 14 in females)
6 mg/m3:
significant increase on days 4, 11, 14, 18, 21, 25, 28 in females,
36 mg/m3:
no significant different body weights compared to control animals (except an increase on day 11 in females)

Hematology and Clinical Pathology:
no effects considered to be of pathodiagnostic relevance

Ophthalmology: no changes

Gross Pathology:

Absolute Organ Weights:

1 mg/m3:
male: no changes
female: elevated spleen and thymus weights
6 mg/m3:
male: no changes
female: elevated spleen and liver weights
36 mg/m3:
male: no changes
female: elevated lung weights (approx. 12%)

Relative Organ Weights (vs. body weights):

1 mg/m3:
male: no changes
female: decreased brain and kidney weights

6 mg/m3:
male: no changes
female: decreased brain weights
36 mg/m3:
male: elevated lung weights (approx. 12%)
female: elevated lung weights (approx. 12%) and decreased liver weights

Relative Organ Weights (vs. brain weights):

1 mg/m3:
male: no changes
female: elevated spleen and thymus weights
6 mg/m3:
male: no changes
female: elevated spleen weights
36 mg/m3:
male: no changes
female: elevated lung weights (approx. 12%)

During necropsy, no findings were seen which have to be assessed as treatment-related.

Histopathological findings:

NASAL CAVITY:
In the anterior level of the nasal cavity (nasal location 1) squamous epithelial metaplasia occurred in all high concentration (36 mg/m3) males and females, in most rats together with mucus and/or cells in lumen (10/10 males; 8/10 females), with inflammatory infiltrates (8/10 males, 7/10 females) and some males (3/10) in combination with focal epithelial necrosis.In these animals, in the nasal locations 2 to 4 (posterior level) epithelial changes were detectable in some rats (max. 2-4 animals per sex) indicating beginning metaplasia.
In mid dose (6 mg/m3) animals epithelial changes were only seen in the anterior level of the nasal cavity in some rats (3/10 males, 3/10 females).
In low dose (1 mg/m3) animals no epithelial changes were seen in the nasal cavity.

PHARYNX:
In the pharynx, epithelial metaplasia occurred in almost all high concentration (36 mg/m3) males (9/10) and females (9/10) and in only one mid concentration male.

LARYNX
In the larynx, all test substance exposed animals showed epithelial metaplasia (30/30 males and 30/30 females) together with increased inflammatory infiltrates. Focal inflammatory infiltrates were also detectable in control animals.

Focal inflammatory infiltrates:

controls:
10/10 males with grade 1; 9/10 females with grade 1

1 mg/m3:
2/10 males with grade 1 and 8/10 males with grade 2;
5/10 females with grade 1 and 5/10 females with grade 2

6 mg/m3:
10/10 males with grade 2; 10/10 females with grade 2

36 mg/m3:
10/10 males with grade 2; 10/10 females with grade 2

Epithelial metaplasia:

controls:
0/10 males and 0/10 females

1 mg/m3:
10/10 males with grade 2
2/10 females with grade 1 and 8/10 females with grade 2

6 mg/m3:
5/10 males with grade 3 and 5/10 males with grade 4
5/10 females with grade 3 and 5/10 females with grade 4

36 mg/m3:
3/10 males with grade 3 and 7/10 males with grade 4
1/10 females with grade 3 and 9/10 females with grade 4

TRACHEA:
In the trachea, epithelial changes indicating beginning epithelial metaplasia were seen in about half of the high concentration (36 mg/m3) males (6/10) and females (5/10) and in each one low and mid concentration male, respectively.

LUNG:
In the lungs, inflammatory lesions in the bronchiolo-alveolar region occurred in the majority of high concentration males (8/10) and females (9/10). These inflammatory lesions consisted of an increased cellularity in the terminal bronchioles and alveolar ducts with more alveolar macrophages and a focally increased septal thickening.
Furthermore, intraalveolar macrophages, mainly enlarged and with a foamy cytoplasm, were obvious in almost all high concentration rats (10/10 males, 9/10 females) and in some animals from the other groups (6 mg/m3: 4/10 males, 3/10 females; 1 mg/m3: 2/10 in both sexes; control animals: 0/10 males, 1/10 females)).

Comparable to the epithelial changes in the upper airways, similar lesions indicating beginning metaplasia occurred in the bronchi (36 mg/m3: 10/10 males, 9/10 females; 6 mg/m3: 5/10 males, 4/10 females; 1 mg/m3 and control animals of both sexes: no changes), predominantly at the main airway bifurcations.

In the other organs/tissues evaluated, no findings could be detected which have to be assessed as treatment related. All the other findings were known from controls of previous studies to be of spontaneous nature.

Test condition **:** TEST ORGANISMS
- Age: 2 month
- Number of animals: 10/dose/sex
ADMINISTRATION / EXPOSURE
- Type of exposure: dynamic directed-flow nose-only exposure
- Doses:
mean actual analytical concentrations of 1.057, 6.022, 33.83 mg/m3; nominal concentration of 4.8, 19.8 and 118.9 mg/m3
- Particle size: MMAD range: 1.0-1.2µm (geometric standard deviation approx. 2); highly respirable to rats

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: twice daily (exposure days)
- Mortality: twice daily
- Body weight: twice weekly
- Rectal Temperature: days 0 and 21
- Reflexes: days 3 and 21
- Ophthalmoscopic examination: prior the first exposure, towards the end of the exposure period

CLINICAL PATHOLOGY at the end of study
- Haematology
- Biochemistry
- Urinalysis

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Gross Pathology:
Fixed organs: Adrenals, aorta, brain (cerebrum, cerebellum, ponslmedulla), epididymides, esophagus, eyes, eyelids, extraorbital lachrymal glands, femur, harderian glands, head (with nasal and paranasal cavities), heart, intestine (duodenum, jejunum, ileum, cecum, colon, rectum and remaining intestine), kidneys, larynx, liver, lymph nodes (mandibular, bronchial/hilus, and mesenteric), lung, mamma, optical nerves, ovaries, oviducts, pancreas, pharynx, pituitary, prostate, salivary glands, sciatic nerve, seminal vesicles (incl. coagulating glands), skeletal muscle (thigh), skin (mammary and muzzle), spinal cord (cervical, thoracic, lu,mbar), spleen, sternum, stomach (forestomach and glandular stomach), testes, thymus, thyroids (including parathyroid glands), tongue, trachea, ureter, urethra, urinary bladder, uterus with uterine cervix, vagina, Zymbal's glands and all organs or tissues with macroscopic findings.
Organ Weights: Adrenals, brain, heart, kidneys, Liver, Lungs, Ovaries, Spleen, Testes, Thymus

- Microscopic: From the respiratory tract (nasal cavity, pharynx, larynx, trachea, lungs and lung associated lymph nodes) slides from all animals were evaluated. From the other organs/tissues assigned for histopathological
evaluation, slides were prepared from the first five animals of all groups and evaluated from the control and the high concentration group.

STATISTICAL METHODS: Dunnett Test, Adjusted Welch Test, Kruskal-Wallis Test

Conclusion **:** The test substance was tolerated without any systemic adverse effects at all exposure levels (1, 6, 36 mg/m3). At 36 mg/m3, evidence of respiratory irritation existed which also occurred at 6 mg/m3 in borderline intensity. With regard to histopathological changes, all changes observed were related to portal-of-entry, local irritant effects (nasal passages, larynx, airways and alveoli), i.e, changes that occurred at anatomical structures, to some extent rat specific, favoring focal deposition of irritant particulates. No changes of pathodiagnostic relevante occurred at 1 mg/m3, except the laryngeal findings. The laryngeal squamous epithelial metaplasia is considered to be a rather rat-specific response. In the rat, the layout of the upper respiratory structures is tandem such that the air could travel in nearly linear fashion from the nose to the bifurcation of the trachea. The linear arrangement of the upper airways allows the larynx of rats to lie close to the posterior edge of the oral and nasal cavities. In the condition, the epiglottis lies against the soft palate. The apposition of the epiglottis to the soft palate in the resting condition isolates the oral cavity from the respiratory airways and makes the rat an obligatory nose breather (virtually

no oropharynx). Thus, the direction of flow in rats is almost linear whereas in humans it is rectangular (for more details see DeSesso, Quality assurance Good Practice, Regulation, and Law 2, 213-231,1993). Apart from these dosimetric issues a concentration dependent increase in the extent of cell infiltration in the larynx, as indirect evidence of local irritation, did not occur. Therefore, the metaplastic changes observed at this location are considered to be causally related to adaptive (differentiation of cells to become more resistant) rather than adverse effects.
Taking all findings into account, 1 mg/m3 constitutes a no-observed-adverse-effect-level (NOAEL) for effects governed by respiratory tract irritation.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
14.01.2005 (34)

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : inhalation: aerosol
Exposure period : two weeks before mating until day 19 of gestation
Frequency of treatm. : 7 x 6 hours/week
Post exposure period : 4-6 days (females)
Doses : 0, 1, 6, 36 mg/m³ (target concentration)
Control group : other: conditioned air
Method : other: see Test Condition
Year : 2004
GLP : yes
Test substance : other TS: purity 99.5%

Remark : For the results on Reproduction/Developmental Toxicity see chapter 5.8.3
Result : MORTALITY:
<= 6 mg/m3: no deaths
36 mg/m3: 2/24 deaths; one male was found dead during premating period and one female has to be killed in moribund condition.
CLINICAL SIGNS:
at 6 mg/m3: serous nasal discharge; nostrils with red encrustation
at 36 mg/m3 breathing symptoms and/or serous nasal discharge and nostrils with red encrustation
BODY WEIGHT:
at 36 mg/m3 body weight retardation in both sexes
FOOD CONSUMPTION:
at 36 mg/m3 transient reduction in males
ORGAN WEIGHT:
at 36 mg/m3 increased lung (absolute/relative) weights in males (14%/18%).
Test condition : According to OECD Guideline No. 421

ADMINISTRATION/EXPOSURE:

Type of exposure: nose-only exposure
Analytical concentrations: 0.00106, 0.00595, 0.03404 mg/l
Nominal concentrations: 0.005, 0.020, 0.119 mg/l
Particle size: mass median aerodynamic diameter: approx 1 um (geometric standard deviation: approx. 2)
Reliability : (2) valid with restrictions
A study according to OECD TG 421 primarily examines the effects on reproduction and development
Flag : Critical study for SIDS endpoint
22.12.2005 (35)

Type	:	Sub-acute
Species	:	rat
Sex	:	no data
Strain	:	no data
Route of admin.	:	inhalation
Exposure period	:	4 hours/day
Frequency of treatm.	:	5 days/week during 2 weeks
Post exposure period	:	no data
Doses	:	120 mg/l and 40 mg/m³
Control group	:	other: no data
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	no data
Result	:	Clinical signs of marked respiratory irritation and decreased growth rates were observed in rats exposed to 120 mg/m3. At 40 mg/m3 only an initial weight loss was observed
Reliability	:	(4) not assignable Onyl an abstract available

14.01.2005 (61)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Bacterial gene mutation assay
System of testing	:	S. typhimurium TA 1535, TA 1537, TA 98, TA 100, TA 102
Test concentration	:	up to 50 µg/plate
Cycotoxic concentr.	:	1.6 µg/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471
Year	:	2005
GLP	:	yes
Test substance	:	other TS: Desmodur W; purity 99.5%
Remark	:	Appropriate reference mutagens (sodium azid, nitrofurantoin, 4-nito-1,2-phenylene diamine, mitomycin C, cumene hydroperoxide and 2-aminoanthracene) were used as positive controls and showed the expected results.
Result	:	GENOTOXIC EFFECTS: Evidence of mutagenic activity was not seen. No biologically relevant increase in the mutant count, in comparison with the negative controls, was observed. CYTOTOXIC CONCENTRATION: Doses up to and including 0.5 µg/plate did not cause any bacteriotoxic effects. Total bacteria counts remained unchanged and no inhibition in growth was observed. At higher doses, the substance had a strain-specific bacteriotoxic effect. Nevertheless this range could partially be used up to 50 µg/plate for assessment purposes.
Test condition	:	SYSTEM OF TESTING: 1. experiment: Plate incorporation assay 2. experiment (= independent repeat): preincubation test Metabolic activation system: S9 liver microsomal fraction of male Sprague Dawley rats which received a single i.p. injection of Aroclor 1254

ADMINISTRATION:
concentration tested:

1. and 2. experiment
without S9 mix:0.05, 0.16, 0.5, 1.6, 5.0, 16.0 µg/plate
with S9 mix: 0.16, 0.5, 1.6, 5.0, 16.0, 50 µg/plate

SOLVENT:
ethylene glycol dimethylether (EDGE) for the test substance and the positive controls
deionized water for mitomycin C

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
22.12.2005 (38)

Type : Ames test
System of testing : S. typhimurium TA 1535, TA 1537, TA 1536, TA 98, TA 100
Test concentration : up to 250 ug/plate
Cycotoxic concentr. : Pretest results are not reported
Metabolic activation : with and without
Result : negative
Method : other: see Test Condition
Year : 1977
GLP : no
Test substance : other TS: 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity

Result : GENOTOXIC EFFECTS:
- without metabolic activation: no significant increase of revertants in any strain (individual test results specified)
- with metabolic activation: no significant increase of revertants in any strain (individual test results specified)
PRECIPITATION CONCENTRATION: no data
CYTOTOXIC CONCENTRATION: "Prior to testing for mutagenicity, the compound was tested for toxicity to the tester strains." (no further information available)

Test condition : SYSTEM OF TESTING:
Plate incorporation assay
Metabolic activation system: S9 liver microsomal fraction of rats
One experiment with one test plate (no replicates)
ADMINISTRATION:
concentrations tested:
without S9 mix: 0.1, 0.2, 0.4, 0.6, 0.8 and 1 ug/plate;
with S9 mix: 50, 100, 150, 200 and 250 ug/plate;
SOLVENT: aceton
- Positive and negative control groups and treatment
negative control: solvent
positive control: without metabolic activation
TA1535, TA100: N-Methyl-N-nitro-N-nitrosoguanidine
TA1537: 9-Aminoacridine
TA1538, TA98: 2-Nitrofluorene
with metabolic activation
for TA100: 2-Aminoanthracene (5 ug/plate)
TA98, TA1538, TA1535: 2-Aminoanthracene (10 ug/plate
TA1537: 2-Aminoanthracene (100 ug/plate)

Reliability : (2) valid with restrictions
The test design does not comply with the current guideline with regard to the number and kind of applied strains; no independend repeat experiment was performed, limited documenation (i.e. no data on S9-mix preparation, no details of the pretest on toxicity to the tester strains)

Flag : Critical study for SIDS endpoint

22.12.2005 (53)

Type	:	Chromosomal aberration test
System of testing	:	Chinese Hamster V79 Cells
Test concentration	:	1.5, 3, 4.5, 6, 8 and 7.5 µg/ml without S9 mix and 6, 12, 20, 24 and 28 µg/ml with S9 mix (see also freetext TC)
Cycotoxic concentr.	:	4.5 µg/ml without S9 mix and 12 µg/ml with S9 mix (see also freetext RS)
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 473
Year	:	2004
GLP	:	yes
Test substance	:	other TS: Desmodur W, no data on purity
Remark	:	The positive controls mitomycin C and cyclophosphamide induced clastogenic effects and demonstrated the sensitivity of the test system and the activity of the used S9 mix.
Result	:	Without S9 mix cytotoxic effects were observed at 4.5 µg/ml and above after 4 hours treatment and at 8 µg/ml and above after 18 hours treatment. With S9 mix cytotoxic effects were observed at 12 µg/ml and above. Precipitation in the medium was not observed. Therefore, concentrations of 4.5, 6 and 7.5 µg/ml test substance (4 hours treatment) and 2.5, 5 and 8 µg/ml (18 hours treatment) were chosen for reading in the absence of S9 mix. In the presence of S9 mix 6, 12 and 20 µg/ml of test substance were employed. All of these cultures harvested 18 hours after the beginning of the treatment were included. In addition, cultures treated in the absence of S9 mix with 7.5 µg/ml and harvested 30 hours after the beginning of the treatment were used. The same was true for cultures treated in the presence of S9 mix with 20 µg/ml. None of the cultures treated with test substance in the absence and in the presence of S9 mix showed biologically relevant or statistically significant increased numbers of aberrant metaphases.
Test condition	:	METABOLIC ACTIVATION: S9 mix - from liver homogenates of with Aroclor 1254 induced male Spargue Dawley rats. The S9 mix contained 40% S9 fraction. CONTROLS: Vehicle: DMSO positive controls: mitomycin C (0.1 and 0.03 µg/ml); cyclophosphamide (2 µg/ml) Initially Chinese hamster V79 cells were exposed in the absence of S9 mix for 4 hours to concentrations of 1.5, 3, 4.5, 8 and 7.5 µg/ml of test substance. Cultures of all concentrations were harvested 18 hours after the beginning of the treatment. In addition, cells treated with 4.5, 6 and 7.5 µg/ml were harvested 30 hours after the beginning of the treatment. In the presence of S9 mix cells were exposed for to concentrations of 6, 12, 20, 24 and 28 µg/ml of test substance. Cultures of all concentrations were harvested 18 hours after the beginning of the treatment. In addition, cells treated with 20, 24 and 28 µg/ml were harvested 30 hours after the beginning of the treatment. Without S9 mix an additional experiment was performed using continuous treatment for 18 hours, harvest at the same time, and test substance-concentrations of 2.5, 5, 8, 1O and 12 µg/ml. Based on their cytotoxicity, which was also determined 8 hours after the beginning of the treatment, concentrations were selected for reading of metaphases. 100 metaphases were scored for structural chromosome aberrations.
Conclusion	:	Based on this test, the test substance is considered not to be clastogenic for mammalian cells in vitro.

Reliability : (1) valid without restriction
Guideline Study
Flag : Critical study for SIDS endpoint
13.01.2005 (36)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	other: nose only inhalation: aerosol
Exposure period	:	6 hours
Frequency of treatm.	:	daily
Duration of test	:	from day 6 up to day 19 p.c.
Doses	:	0, 1, 6, 36 mg/m³ (target concentration)
Control group	:	other: conditioned air
NOAEL maternal tox.	:	= 1 mg/m³
NOAEL teratogen.	:	= 6 - mg/m³
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	2003
GLP	:	yes
Test substance	:	other TS: Desmodur W, purity 99.5%

Result : MATERNAL DATA:

Appearance, behavior, and mortality of the females were unaffected at the 1 mg/m3 level, while increased or decreased respiratory rates, labored breathing, irregular
respiration, and sounds consistent with rhinitis occurred each before and after inhalation at the 36 mg/m3 level. Furthermore, rough fur, piloerection (one female,
one day only), serous nasal discharge, and reddish encrusted nostrils each before and after inhalation, and reddish encrusted nose (one female, one day only) occurred in the 36 mg/m3 group.
Labored breathing after inhalation, piloerection before and after inhalation, paleness before and after inhalation and and reddish encrusted nostrils after inhalation occurred in single females at the 6 mg/m3 level; several females had serous nasal discharge before (9 females) and after inhalation (17 females) at this dose level.

Decreased feed intake (days 6-9 p.c.: approx. 22%; days 9-12 p.c.: approx. 8%), statistically significant transient body weight loss (approx. 5%) after start of treatment (days 6-7 p.c.), resulting in a decreased body weight gain during the treatment period (days 6-19 p.c., approx. 24%) and during gestation (days 0-20 p.c., approx. 15%) occurred at the 36 mg/m3 level. Mean corrected body weight gain was also marginally decreased (approx. 14%) at this dose level.

No treatment related gross pathological findings occurred at levels up to and including 36 mg/m3.

The gestation rate, appearance of placentas, placental weights, postimplantation loss, number of live fetuses, fetal sex distribution, and fetal weights were unaffected by treatment with the test material up to and including the dose level of 36 mg/m3.

GENERAL REPRODUCTION DATA

The mean number of implantation sites were lower at 36 mg/m3, and a slight increased preimplantation loss occured in this group, whereas the mean number of corporalutea did not differ to meaningful extent, indicating a homogeneous distribution regarding this parameter. The values in the 36 mg/m3 dose group were comparable to the normal range of scattering for the rat strain used, and statistical significance was not evident for these findings, so that treatment related unobserved early postimplantation loss (which would not be detectable by staining the uterus, and would appear as preimplantation loss) is unlikely.

Dose mg/m3: 0/ 1/ 6/ 36
Females with implantations in % of those inseminated: - 77.8 / 96.3/ 74.1 / 71.9
mean values per female with implantation sites
- corpora lutea: 15.0 / 14.4 / 14.1 / 14.7
- preimplantation loss: 1.8 / 1.4 / 1.7 / 2.8
- implantations: 13.2 / 13.0 / 12.4 / 11.8

FETAL DATA

Dose mg/m3: 0/ 1/ 6/ 36
Means per female
- post implantation loss: 0.7 / 0.8 / 1.3 / 1.0
- Number of live fetuses: 12.6 / 12.2 / 11.2 / 10.8
- fetal weights g: 3.51 / 3.53 / 3.40 / 3.55
- sex of live fetuses (% males): 55.3 / 51.8 / 50.5 / 51.8

FETAL MALFORMATIONS

A treatment related effect cannot completely be excluded for the marginally increased incidence (1.2% versus 0.9% in historical controls) in of ventricular septal defects of the heart (common finding) at the level of 36 mg/m3, despite of a lower overall number of fetuses with malformations at this dose level, as this dose showed clear maternal toxicity.

Dose mg/m3: 0/ 1/ 6/ 36

- Number of fetuses per group: 264 / 317 / 224 / 248
- Number of fetuses with malformations: 9 / 5 / 5 / 4
- malformed fetuses per group (%): 3.4 / 1.6 / 2.2 / 1.6
- Number of litters per group: 21 / 26 / 20 / 23
- Number of litters with malformations: 6 / 4 / 5 / 4
- malformed litters per group (%): 28.6 / 15.4 / 25.0 / 17.4
- ventricular septal defect of the heart: 1 / 1 / 1 / 3
- number of litters affected by this malformation:
1 / 1 / 1 / 3

FETAL EXTERNAL AND VISCERAL DEVIATIONS

Meaningful external or visceral deviations of fetuses were not assumed at dose levels up to and including 6 mg/m3. A treatment related effect for the significantly increased incidence of slight dilation of lateral brain ventricle(s) (11.3% affected fetuses, 56.5% affected litters) at the 36 mg/m3 level is unlikely, as the value lay within the range of historical control data and data of different unaffected study groups used (up to 12.7% affected fetuses, up to 65.5% affected litters).

Dose mg/m3: 0/ 1/ 6/ 36

- Number of fetuses per group: 264 / 317 / 224 / 248
- Number of fetuses with deviations: 59 / 60 / 48 / 53
- fetuses with deviations per group (%): 22.3 / 18.9 / 21.4 / 21.4
- Number of litters per group: 21 / 26 / 20 / 23
- Number of litters with deviations: 18 / 20 / 18 / 20
- litters with deviations per group (%): 85.7 / 76.9 / 90.0 / 87.0
- slight dilation of lateral brain ventricle (s):
11 / 14 / 17 / 28
- number of litters affected by this deviation:
5 / 7 / 8 / 13

Test condition **:** TEST SYSTEM:
inseminated Wistar rats
age: 13 - 15 weeks
body weight by study initiation: 201 - 245 g
no. of animals: 27 / dose (dose group 36 mg/m3 32 femals were treated)

CHARACTERIZATION OF TEST ATMOSPHERE:

Particle size determination of the aerosol yielded MMADs within the respirable range (» 1 mm, the geometric standard deviation (GSD) » 2)

PARAMETERS ASSESSED DURING STUDY:
- Clinical observations: daily
- Body weights: day 0 p.c., daily (day 6-20 p.c.)

EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- gross pathological examination at the time of
cesarean section on day 20 p.c. without knowledge of treatment groups.
Investigations at Cesarean Section:
- Number of corpora lutea
- Number of implantations
- Uterine weights
- Number of early resorptions
- late resorptions
- dead fetuses
- Number of live fetuses
- Sex of live fetuses
- Individual weights of live fetuses
- External malformations
- Visceral malformations
- Skeletal malformations
- External and visceral deviations

STATISTICAL METHODS:
Dunnett-Test with a variance analysis; Fisher's exact CHI-SQUARE (positive ANOVA probability test with a
significance levels of alpha=5%)

Reliability **:** (1) valid without restriction
Flag **:** Critical study for SIDS endpoint
14.01.2005 (37)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

Type	:	other: Reproduction/Developmental Toxicity Screening
In vitro/in vivo	:	In vivo
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	inhalation
Exposure period	:	two weeks before mating until day 19 of gestation
Frequency of treatm.	:	7 x 6 hours / week
Duration of test	:	9 weeks
Doses	:	0,1, 6, 36 mg/m3 (= target concentrations)
Control group	:	yes, concurrent no treatment
Result	:	NOAEL - General Toxicity: 1 mg/m3 NOAEL - Reproduction/Developmental Toxicity: 6 mg/m3
Method	:	other: according OECD guide-line 421
Year	:	2003
GLP	:	yes
Test substance	:	other TS: Desmodur W, purity 99.5%

Result :

At 36 mg/m3 changes in breathing behavior and/or serous nasal discharge (nostrils with red encrustation) were noted in the majority of F0 rats. At 36 mg/m3 in single animals also signs of poor general conditions occurred and slightly increased (2 of 24 rats) mortality was observed. One male of the high dose group was found dead during the premating period and one female of the high dose group has to be killed in moribund condition. At 6 mg/m3 only serous nasal discharge and red encrusted nostrils were noted in F0 rats.
No toxic effect was seen on body weights of F0 rats up to 6 mg/m3. At 36 mg/m3 reduced body weight gain was noted at some time points in both sexes (males: week 5-6: 2.8g vs. 9.8g in controls, week 4-5: 10.2g vs. -1.2g in controls; females: week 1-2: -11.2g vs -4.7g in controls).
The food intake of 36 mg/m3 F0 males was transiently reduced.
The absolute (14%) and relative (18%) weights of the lungs were increased in 36 mg/m3 F0 male rats.

PARAMETERS OF REPRODUCTION

At 36 mg/m3 a slightly reduced fertility index was noted.
No other reproduction parameter was affected.

Dose mg/m3: 0/ 1/ 6/ 36

Insemination index %: 100.0/ 91.7/ 100.0/ 100.0
Fertility index %: 91.7/ 81.8/ 83.8/ 66.7 ($p > 0.05$)
Gestation index %: 90.9/ 100.0/ 100.0/ 100.0
Gestation length Days: 22.11/ 22.25/ 22.22/ 22.00
Co-housed females n: 12/ 12/ 12/ 12
Number of implantation sites (per litter): 10.8 / 10.56 / 11.50 / 9.88
Litters alive n: 10/ 9/ 10/ 8
Live birth index %: 98.57 / 99.07 / 97.22 / 96.36
Viability index %: 99.00 / 100.0 / 92.17 / 98.96

SPERM ANALYSIS

Results of sperm analysis were excluded from the study evaluation,

because mechanical stress on the epididymides and testes caused by the narrowness of exposure restrainers had induced untypical and test-compound independent low sperm motility (below 30%) and increase in sperm abnormalities (higher than 50%) in all groups which corroborate with testicular and epididymal changes seen histologically.

Dose mg/m3: 0 / 1 / 6 / 36

Sperm motility, (first min) %: 21 / 7 / 26 / 16
Sperm motility (fifth min) %: 18 / 6 / 25 / 15
Abnormal sperms %: 59.4 / 87.4 / 60.9 / 66.4
Mean number of spermatids per mg testis:
52773 / 41767 / 41989 / 49707
Mean number of sperms per mg epididymis:
490037 / 138194 / 347913 / 323042

HISTOPATHOLOGY

No test compound-related effects were seen in the testes and epididymides of F0 rats.
In the testes of both groups evaluated (control and high dose) tubular degeneration (mainly multi/focal) was seen in the majority of animals:

dose mg/m3: 0 ; 36

Focal tubular degeneration: 5/12 ; 8/12
Dif. tubular degeneration: 2/12 ; 0/12

In the epididymides, spermatic debris and oligospermia occurred in almost all rats.

dose mg/m3: 0 ; 36

Spermatic debris: 12/12 ; 11/12
Oligospermia: 11/12 ; 10/12

The morphology of the ovaries of F0 females was not affected.

Data On PUPS (F1):

dose mg/m3: 0 / 1 / 6 / 36

- Live birth index %: 98.57 / 99.07 / 97.22 / 96.36
- Viability index %: 99.00 / 100.0 / 92.17 / 98.96
- Males %: 54.31 / 50.56 / 49.23 /53.90

No remarkable clinical signs were observed during the four day lactation period up to 36 mg/m3. No effect on body weights and no macroscopical alterations were noted at pup necropsies up to 36 mg/m3.

Test condition **:** ANIMALS:

12 male and 12 male Wistar rats /dose and control group

ADMINISTRATION / EXPOSURE

Type of exposure: nose-only exposure of an aerosol
Analytical concentrations: 1.06, 5.95, 34.04 mg/m3
Nominal concentrations: 5, 20, 119 mg/m3
Particle size: mass medien aerodynamic diameter: approx 1 um (geometric

standard deviation: approx. 2)

- Treatment: The test substance was administered to parental (F0) animals two weeks prior to and during their mating, during the resultant pregnancy up day 19 p.c. Males were dosed 28 days at a minimum. For technical reasons (to avoid withdrawal from their pups) females were not treated during lactation.

MATING PROCEDURES: The F0 animals were pretreated with the compound for 2 weeks up to the cohabitation period. During the following mating period the first F0 male was cohoused
with the first female F0 animal within the group and so on over night at a maximum of 12 times during the two-week mating period. As a rule inseminated females were not further co-housed. Insemination was established by investigating vaginal smears prepared in the morning.

PARAMETERS ASSESSED DURING STUDY F0:
- Clinical observations: daily, detailed recordering at least once weekly
- Body weights: weekly; females additionally on day 0 and 4 after birth of their pups

- Sperm examination: motility and viability, spermatozoa density per mg epididymis, no of spermatid heads per mg testis

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Organ weights F0: lungs with trachea, left epididymis and testes
- Histopathology F0: testes, epididymides and ovaries of controls and high dose

OTHER EXAMINATIONS:
- Indices:
insemination, fertility, gestation, live birth, viability

PARAMETER ASSESSED ON F1:

- Number of live and dead pups
- Sex of the pups
- body weights
- clinical signs
- apparent malformations

were determined shortly after birth and on day 4 p.p..

STATISTICAL METHODS:
Dunnett-Test with a variance analysis; Fisher's exact CHI-SQUARE (positive ANOVA probability test with a
significance levels of alpha=5%)

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
12.01.2005 (35)

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Remark : For information on human experience see also chapter 5.3
Flag : Critical study for SIDS endpoint
22.11.2004

Remark : There is a second reference on the same subject: Smirnov V, Sculsky M, Israeli R (1981) Acute intoxication by organic iso cyanates. Harefuah 100 (11): 520-522, 551. It is published in Hebrew (study not available).
Result : To prevent glass injuries among onsumers glass bottles were coated with polyurethane. 4,4´-Methylenedicyclohexyl diisocyanate was polymerized to polyurethane for this purpose. 11/15 workers who were first exposed to 4,4´-Methylenedicyclohexyl diisocyanate (no airborne concentration determined but insufficient ventilation was admitted) showed allergic and non-allergic skin reaction. 6 suffered from vertigo with and without headaches and 4 developed a decrease of the obstructive lung function, tachycardia and hypotension (EKG normaly); the symptoms appeared 4-7 days after the exposure and were reversible within 10-14 days
Test substance : 4,4´-Methylenedicyclohexyl diisocyanate, no data on purity
Reliability : (2) valid with restrictions
Limited documentation
Flag : Critical study for SIDS endpoint
06.11.2006 (66)

5.11 ADDITIONAL REMARKS

Remark : An overall perspective of the sensitization potential of Methylene bis(4-cyclohexylisocyanate) is given
Reliability : (2) valid with restrictions
Data from a collection of data which was reviewed by an expert panel
23.11.2004 (68)

Remark : An overall perspective of acute animal and human studies with Methylene bis(4-cyclohexylisocyanate) is given
Reliability : (2) valid with restrictions
Data from a collection of data which was reviewed by an expert panel
23.11.2004 (1)

Remark : An retrospective analysis of acute inhalation studies which shows for 4,4´-methylenedicyclohexyl diisocyanate among each other that for irritant aerosols both the concentration and the particle size are equally important for the outcome of the test, independent of whether the endpoint chosen is lethality or the protein in bronchoalveolar lavage fluid (BAL-protein).
Reliability : (2) valid with restrictions
Limited documentation; 4,4´-methylenedicyclohexyl diisocyanate is one of a number of different diisocyanates for which a retrospective analysis is performed
09.09.2004 (79)

Remark : A short description of the results from several toxicological studies (acute

oral, repeated oral, skin/eye irritation, skin sensitization) without any information on details of study performance (incl. dosage).

Reliability : (4) not assignable
no study details are reported

06.11.2006 (72)

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